Some approaches to the synthesis of dendritic polyamides

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SOME APPROACHES TO THE SYNTHESIS OF DENDRITIC POLYAMIDES

By

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A thesis submitted for the degree of Master of Science

UNIVERSITY OF DURHAM

1991

To Minerva who helped me throughout.

ſtælgiert ne pær
pihte þy glenna
þe he þam porðum ſpealg

(*Anglo-Saxon riddle 47*)

ABSTRACT

This thesis describes some approaches to the synthesis of dendritic polyamides, a novel class of macromolecules. A brief overview and general introduction to dendritic polymers is given in chapter one. The synthesis of model compounds based on benzoyl, isophthaloyl and trimesoyl chlorides is described in chapter two. The synthesis of the monomer, di-t-butyl-5-aminoisophthalate, and its use in a divergent synthesis is described in chapter three. The employment of a convergent approach to the synthesis of three second generation dendrimers is discussed in chapter four. The final chapter contains a brief summary of the results plus some suggestions for further work.

MEMORANDUM

The work described in this thesis was carried out in the Durham Laboratories of the Interdisciplinary Research Centre in Polymer Science and Technology, the University of Durham, between October 1989 and September 1991. This work has not been submitted for any other degree and is the original work of the author, except where acknowledged by reference.

ACKNOWLEDGEMENTS

First and foremost I would like to express my thanks to my supervisor Professor W.J. Feast for his support and persistent browbeating without which I would not have taken on this project. I am grateful to my colleagues in the polymer group, especially the ex-inmates of lab. 3, for their friendship and good humour. Special thanks go to Dr. A.M. Kenwright and Mrs. J. Say for recording the NMR spectra, Mr. P. Dounis for help with presentation, Dr. P.M. Bayliff for proofreading and Mr. D.H. Cadd for many helpful discussions (some of which concerning Chemistry), humorous banter and the occasional pint of ale. I would also like to express my gratitude to the technical staff of both the Chemistry Department and the IRC, particularly the tea room card school! Last but not least I would like to acknowledge my friends in the Vikings for helping to keep things in perspective and preserving sanity.

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CHAPTER ONE

INTRODUCTION AND HISTORICAL BACKGROUND

1.1 Introduction

The rising demand for speciality polymers that possess novel properties has led to an interest in the synthesis of polymers which have highly controlled molecular architectures [1]. The ability to control the occupation of a microenvironment as a function of size, shape and disposition of desired organic functionality opens the door to a wide range of potential applications [2]. It is precisely these factors which have led to the development of polymers with unusual topologies amongst which are the class of macromolecules known as hyperbranched or starburst dendrimers.

1.2 Definitions

The class of macromolecules known as dendrimers is characterized by molecules having a central polyfunctional core from which emanate two or more identical branches, each branch containing further branch sites. This results in a cascade structure of symmetrical, self-replicating branches with geometries akin to that of fractal sets [3]. The related cascade structures known as arborols can be unidirectional, in which case the polyfunctional core is replaced by a monofunctional trunk [4]. The growth of an ideal dendrimer is shown in simplified form below (figure 1.1). This shows the assembly of branches around a tetrafunctional core (C), terminating in some moiety (f) with a functionality of two.

The tree-like structures (B-E) of figure 1.1 are described by physicists and mathematicians as Bethe lattices or Cayley trees. These simplified dendrimers may be viewed as a number, depending on the functionality of the core, of trees rooted to a common core. Each of these trees is referred to as an ideal dendron [5].

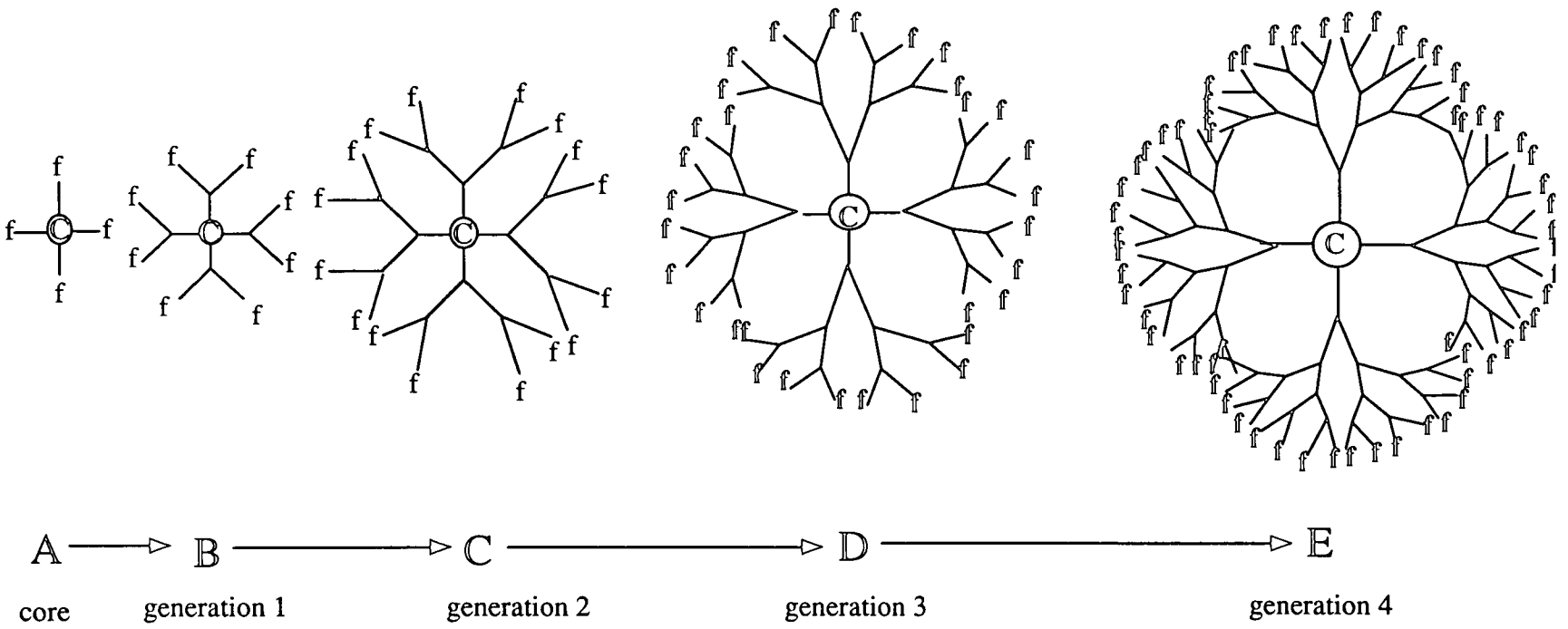


Figure 1.1 Two dimensional projections of tetradendron dendrimers

The novel architecture of dendritic systems distinguishes them from classical macromolecules. Three main architectural features may be identified [6];

i) Dendrons branch out from a central polyfunctional core (or monofunctional trunk in the case of some arborols).

ii) Dendrimers possess interior layers, or generations, of self replicating branch cells extending outwards from the core.

iii) End groups are situated in an exterior or surface region of terminal functionalities attached to the outermost generation.

Some of these features are illustrated below (figure 1.2).

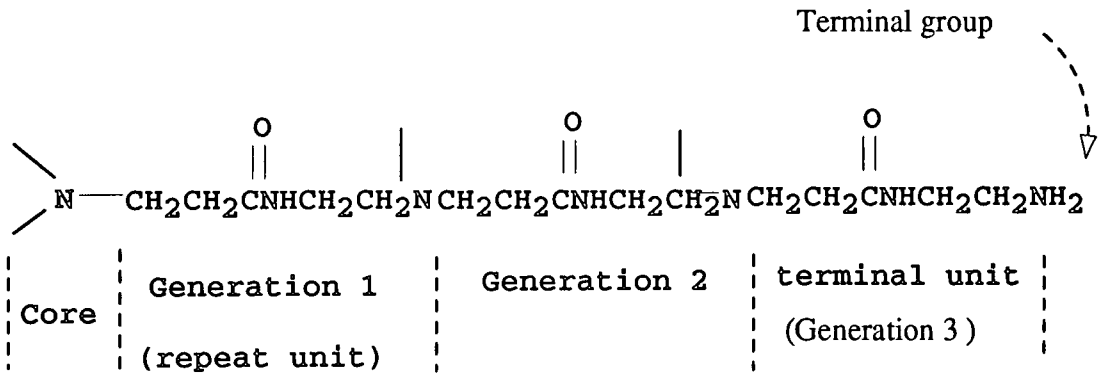
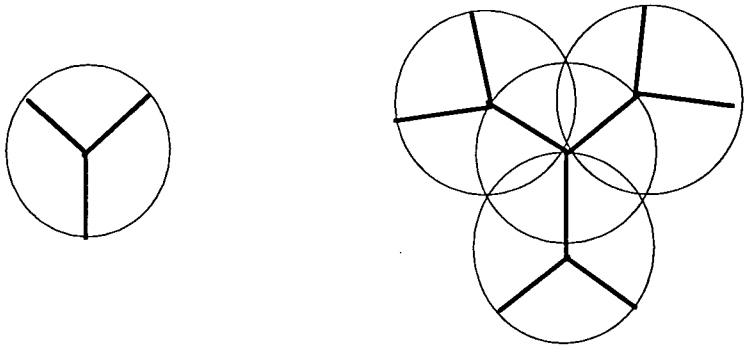


Figure 1.2 A Dendrimer Branch - Polyamidoamine

The architecture of dendrimers has been described in terms of branch cells. This is an extension of the terminology coined by Flory to describe networks. As defined by Flory a network cell is the recurring branch juncture in a network system as well as the excluded volume associated with this branch juncture [7]. Assemblies of these network cells have been termed micronetworks [8]. Whilst this is the terminology of Gaussian coil networks for open branched organizations such as dendritic systems the analogous species have been termed branch cells and branch cell assemblies respectively [5] (figure 1.3).



Branch cell **Branch cell assembly**

Figure 1.3 , Two dimensional representation of a branch cell assembly

A general structure notation has been proposed, by Tomalia [6], in which a dendrimer can be described in terms of the structure of the end group, the structure and multiplicity of the core, the structure and multiplicity of the repeat unit and its degree of growth or generation. A monodisperse dendrimer with core multiplicity N_c, repeat unit multiplicity N_r, and generation G can be described by the following expression:

$$[\text{Core}]\left[(\text{Repeat unit})\frac{N_r^G-1}{N_r-1}(\text{Terminal unit})N_r^G\right]_{N_c}$$

The number of both the branching units and end groups are defined by a geometric progression as a function of generation. Hence, not only is the structure of the dendrimer readily apparent from the above expression but using the terms of the expression the number of repeat units, number of end groups and the theoretical molecular weight can be calculated, using the following relationships [6];

Number of terminal units = $N_c N_r^{G-1}$

Number of repeat units = $N_c\left(\frac{N_r^G - 1}{N_r - 1}\right)$

Molecular weight = $M_c + N_c\left(M_r\left(\frac{N_r^G - 1}{N_r - 1}\right) + M_t N_r^G\right)$

Where M_c, M_r and M_t are the molecular weights of the core, repeat units and terminal groups respectively

Using this notation the dendrimer shown in figure 1.2 would be described as:

$$[N]\left[(CH_2CH_2CONHCH_2CH_2N)\,2^2\text{-}1\,(CH_2CH_2CONHCH_2CH_2NH_2)\,2^2\right]_3$$

However, it should be noted that dendrimer branch cell hierarchies are subject to two differing numbering systems in the literature. The reaction of an initiator core to give the first tier of terminal functionality or branch junctures defines a core cell referred to as generation zero by some authors [5,9-11]. If this terminology is used the term G must be replaced by G + 1 in the above expressions. However, the work presented here will refer to the first branch cell or core cell as a first generation dendrimer. This is in accord with branching theory which denotes the root of a tree as the zero generation and the first set of branch junctures as the first generation [12].

1.3 Historical Background

Present day branching concepts, in polymer science, can be traced to the introduction of infinite network theory by Flory [13-15]. Subsequent statistical modelling by Gordon *et al.* [16-18] attempted to formulate polymer statistics in terms of the theory of branching processes. These dendritic models were combined with cascade theory mathematics to give a statistical treatment for network forming events [19].

However, the dendritic species used for these models were purely conceptual and it was not until 1978 that the first synthetic example in this field was reported by Vögtle *et al.* [20], who introduced the idea of 'cascade' synthesis. As defined by Vögtle, 'cascade' syntheses are reaction sequences which can be carried out repeatedly whereby a functional group is made to react in such a way as to appear twice in the subsequent molecule. The approach adopted by Vögtle was a protection \ deprotection scheme involving Michael addition of an amine to acrylonitrile, followed by reduction of the nitrile group to an amine group (figure 1.4).

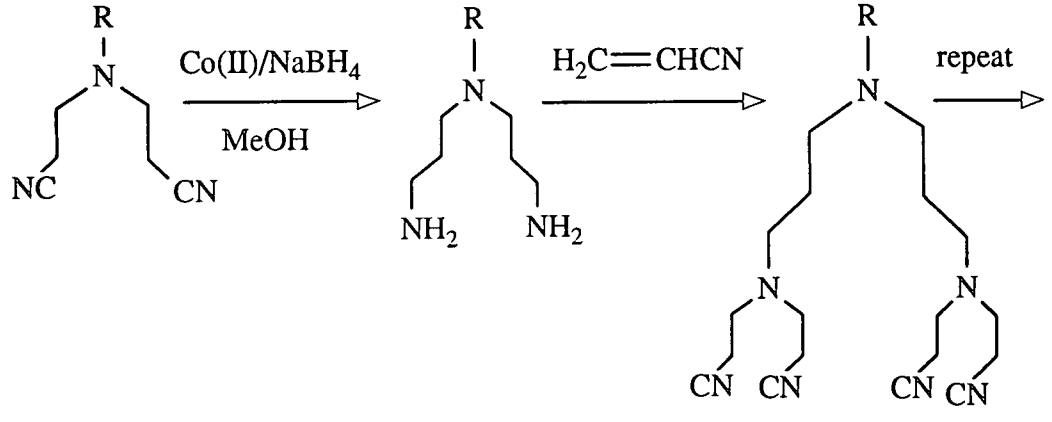


Figure 1.4 Cascade Synthesis

The cascade molecules so produced were of relatively low molecular weight

and it was not until the work of Tomalia, in the early 80's, that truly macromolecular hyperbranched systems were produced [6]. Tomalia introduced a family of hyperbranched polymers prepared by multiplicative growth from a central core which have come to be known as 'starburst dendrimers'. The nomenclature of these macromolecules being in deference to their branched (dendritic = tree-like (Greek)) as well as oligomeric nature [2]. Controlled concentric 'starburst growth' around various amine initiator cores was produced by addition of amines to methyl acrylate and the subsequent amidation of the products with diaminoalkanes (figure 1.5). This

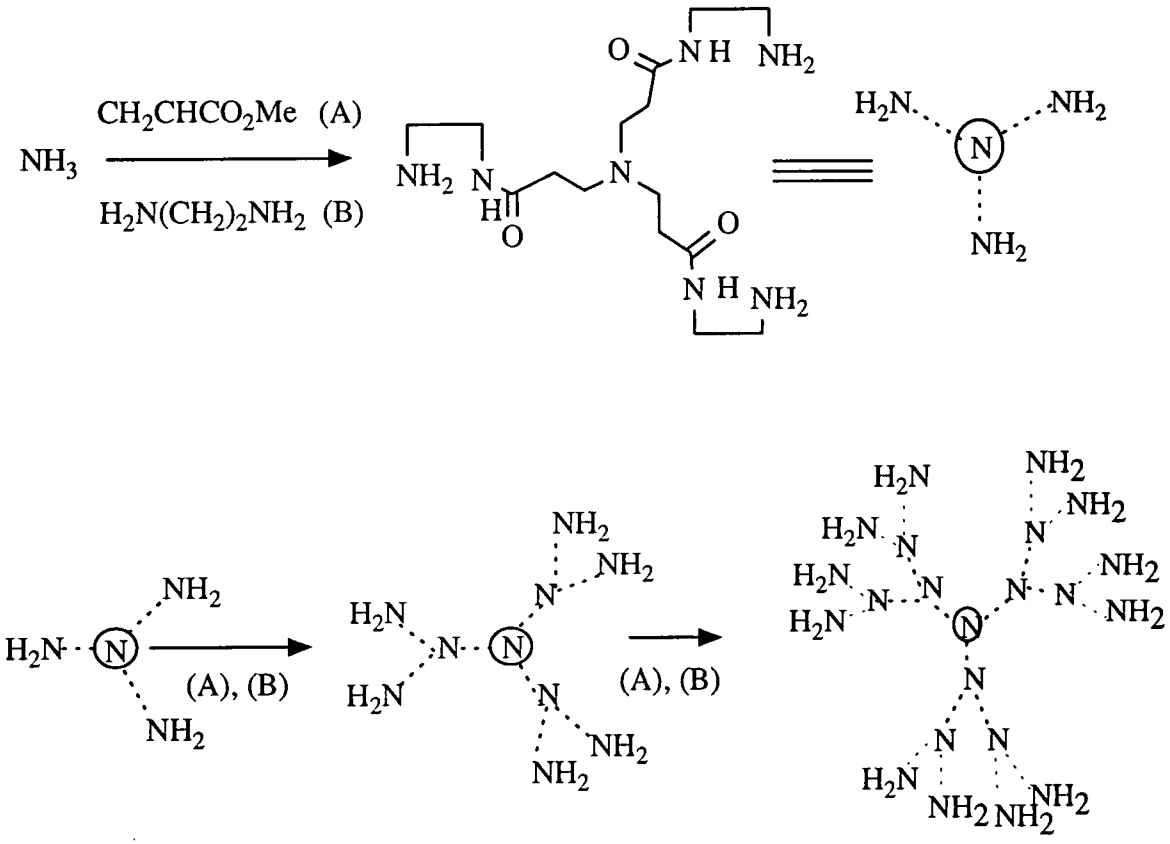


Figure 1.5 Synthesis of starburst polyamidoamines

reiterative reaction sequence was used to produce dendrimer growth over a number of generations to give molecular weights typically in the region of tens of thousands [2, 6, 21].

Theoretical predictions by de Gennes *et al.* [22], in 1983, showed that dendrimer growth should eventually reach a so called starburst limited generation beyond which branching cannot occur in an ideal manner. Later studies on starburst polyamidoamines [23, 24] showed that higher generation dendrimers exhibit a critically branched state which has been termed starburst dense packing. At this critically branched generation the dendrimers exhibit sphere-like topologies with solvent filled interior hollows connected by channels that run the length of the molecule. Such morphologies had been suggested in a theoretical paper by Maciejewski [25], in 1982, where they were referred to as 'shell topologies'. In 1983 a series of monodisperse dendritic macromolecules possessing unsymmetrical branch lengths was reported, in the patent literature. by Denkewalter *et al.* [26]. These poly(α,ϵ-L-lysine) macromolecules were synthesized using the protection / deprotection methods of polypeptide chemistry. The topology of these unsymmetrically branched macromolecules has been shown to differ dramatically from symmetrical starburst dendrimers, such as polyamidoamines. Unlike starburst polyamidoamines they have been shown to be constant density, non-hollow macromolecules with non-draining character [27].

Since 1985, Newkome and co-workers have reported the synthesis of symmetrically branched macromolecules which they call arborols. Examples of uni [4], di[28, 29], tri [30] and tetradirectional [31] arborols have been reported. However, only the tetradirectional arborol synthesis possesses the reiterative chemistry necessary for advancing concentric growth. The two directional arborols have been shown to have 'barbell-like' architectures which self-assemble into rod type structures. Further dendrimer examples have been introduced by Tomalia with rod-shaped dendrimers [32] and polyether [33, 34] and polythioethers [35]. The synthesis of rod shaped dendrimers used poly(ethyleneimine) as an initiator core for the growth of polyamidoamine branches around the linear backbone. The construction

of starburst polyethers was achieved using bicyclic ortho esters in a protection / deprotection scheme involving Williamson ether synthesis around a pentaerythritol core. This produced high density, highly functionalized polyether dendrimers.

Since the mid 80's other research groups have produced dendritic systems such as polyarylamines [36], polysiloxanes [37-39] and iptycenes [40,41]. Although with these systems growth to higher generations has not been demonstrated. The first cascade structure to bear a formal charge was reported by Engel *et al.* [3, 53] in 1990. This utilizes phosphonium cascades in which the initiator core and subsequent branch points are quaternary phosphonium ion sites.

A new approach to dendrimer synthesis was introduced in 1990 by Fréchet *et al.* [42, 43]. Dendritic polyethers were synthesized, using what has been termed, convergent synthesis, a methodology which has also been used by Miller and Neenan [44] in the synthesis of polyphenylenes and aromatic polyamides. In the convergent approach construction of the macromolecule is started at what will ultimately be the periphery of the molecule. The dendritic 'wedges' or dendrons so created being coupled to a suitable core molecule in the last step. A 'double-stage' convergent approach has also been developed in which dendron fragments are coupled to a 'hypercore' consisting of a preformed dendrimer with reactive surface functionalities [45]. The use of the convergent approach has since been used to demonstrate the control of surface functionality in dendritic systems [1, 46].

Recently Tomalia has introduced further novel topologies to the dendrimer field with the advent of 'comb-burst' dendrimers [11]. These involve the reiterative grafting of reactive telechelic polymer chains to form dendritic graft polymers.

1.4 Synthetic Approaches

At present, successful dendrimer synthesis can be divided into two categories, depending upon whether they employ a divergent or convergent methodology.

The divergent approach, exemplified by the work of Tomalia *et al.* on starburst polyamidoamines [2, 6, 21] and polyethers [33-35] (figure 1.6), involves the addition of monomer units to a polyfunctional core molecule. Modification or activation of the

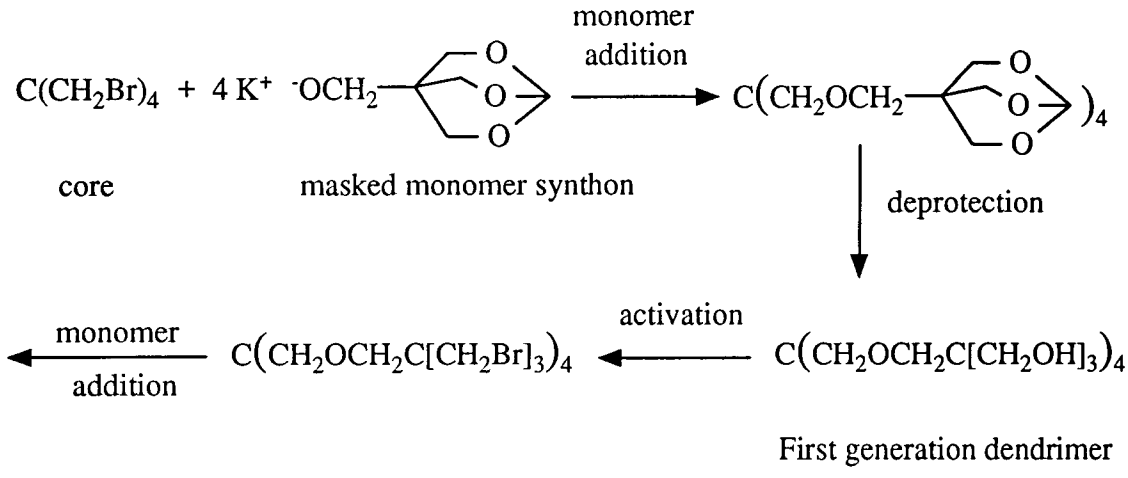


Figure 1.6 Divergent polyether synthesis

resulting first generation dendrimer is followed by exhaustive addition of a second layer of monomer units. Repetition of the above sequence allows growth to proceed outwards from the central core to produce concentric generations of repeat units and branch junctures.

Recently, some interest has been shown in dendrimer growth by one-step methods [38,54,55]. These are essentially one-step divergent syntheses from ABn type monomers, such as 3,5-Bis(trimethylsiloxy)benzoyl chloride [55]. However,

unlike the lengthy and demanding protecting group strategies, dendrimer growth is uncontrolled and leads to non ideal branching. Nevertheless, the approach does provide access to large amounts of material with potentially unusual properties resulting from a hyperbranched structure.

The convergent approach to dendrimer synthesis, exemplified by the work of Fréchet *et al.* on hyperbranched polyethers [42, 43], as mentioned above (1.3), involves creation of preformed dendrons or 'wedges' . These dendritic 'wedges' are grown 'backwards' from what will eventually be the outermost layer of terminal groups (figure 1.7). Coupling of preformed dendrons to an appropriate core molecule

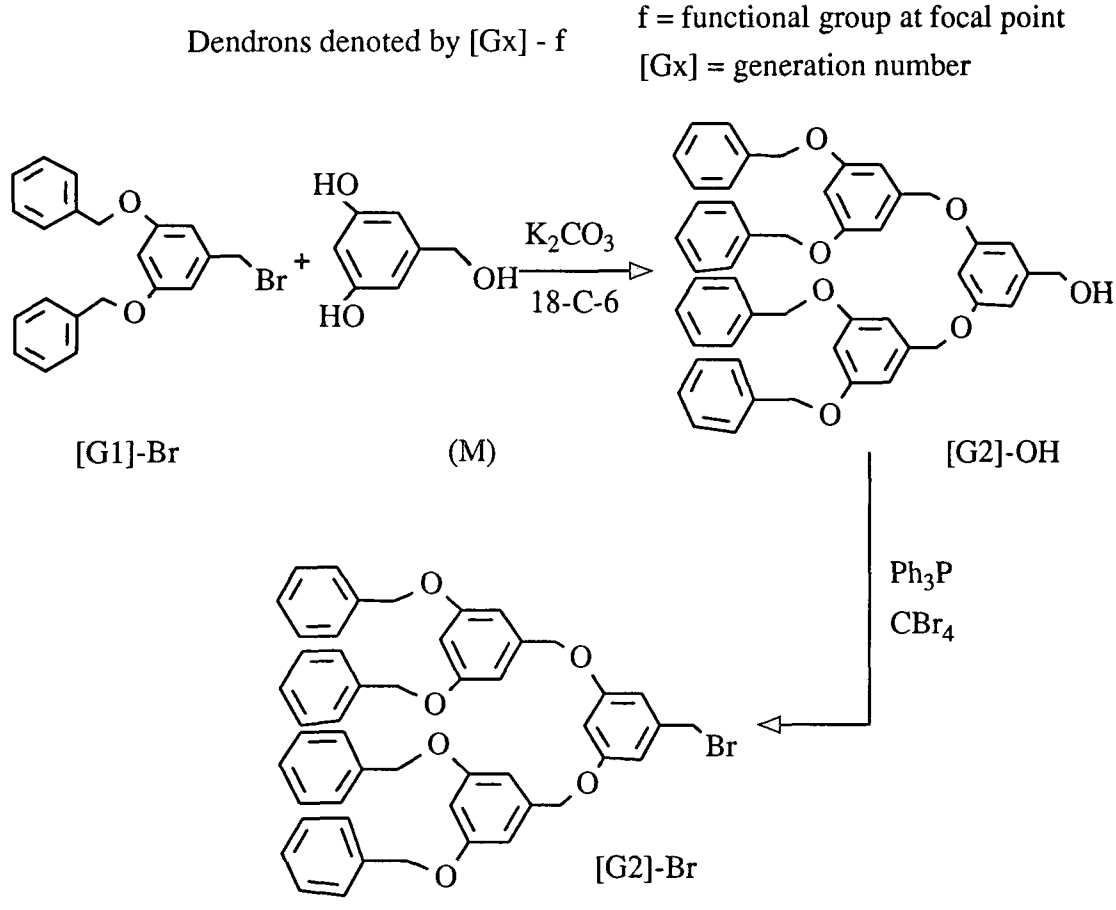
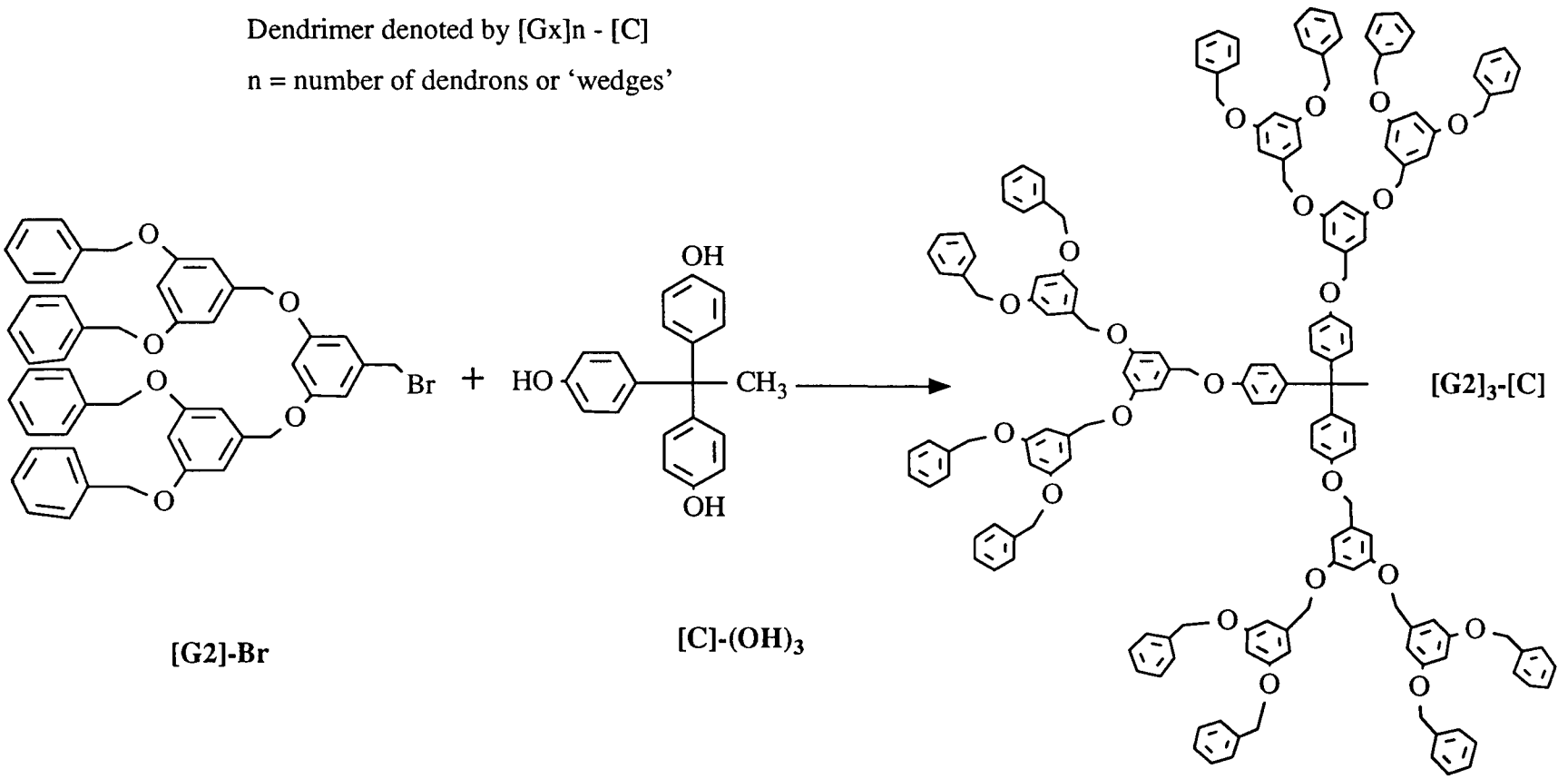


Figure 1.7 Synthesis of polyether dendrons

produces the desired dendrimer (figure 1.8).

Dendrimer denoted by [Gx]n - [C]

n = number of dendrons or 'wedges'



[G2]-Br **[C]-$(OH)_3$**

Figure 1.8

Convergent polyether synthesis

Coupling of preformed dendrons to a core molecule

These approaches are similar in that they both require a reiterative branch cell assembly scheme which is necessary for advancing the starburst architecture. Thus it is necessary for either a protection / deprotection strategy to be used or to employ reaction sequences which allow modification / activation of functional groups to allow growth to continue. Although the divergent approach has been most widely used, with a high degree of success, there are a number of advantages conferred by the convergent approach. A feature of divergent synthesis is the rapid increase in the number of reactive groups at the chain ends of the growing molecule. This may lead to problems as growth is pursued. Any incomplete reaction of the terminal groups leads to non ideal dendrimer growth and deviation from monodispersity [5, 43]. The probability of this occurring increases with the size of the growing macromolecule. Purification problems may arise due to the large excesses of reagents required to force the reactions to completion in the latter stages of growth. By contrast the convergent approach has the advantage that each generation growth step requires the same limited number of reactions, reducing the chances of incomplete reaction or side reactions. It is also possible to control both the number and placement of terminal functional groups using the convergent approach [1, 46].

A further technique of note, relating to divergent dendrimer growth, is the use of 'extender' or 'spacer' groups. As dendrimer growth advances through progressive generations the terminal functionalities can become subject to steric crowding (i.e. growth approaches the starburst limited generation) which limits ideal growth. This can be overcome by the introduction of extender groups to relieve crowding of the terminal moieties and allow outward growth to continue. This technique has been successfully employed in the synthesis of arborols [4] (figure 1.9).

A similar problem can arise during convergent synthesis. A particular limitation of the convergent approach is that, as the sizes of the dendrimers increase, they are increasingly more susceptible to steric inhibition at the focal point group. This

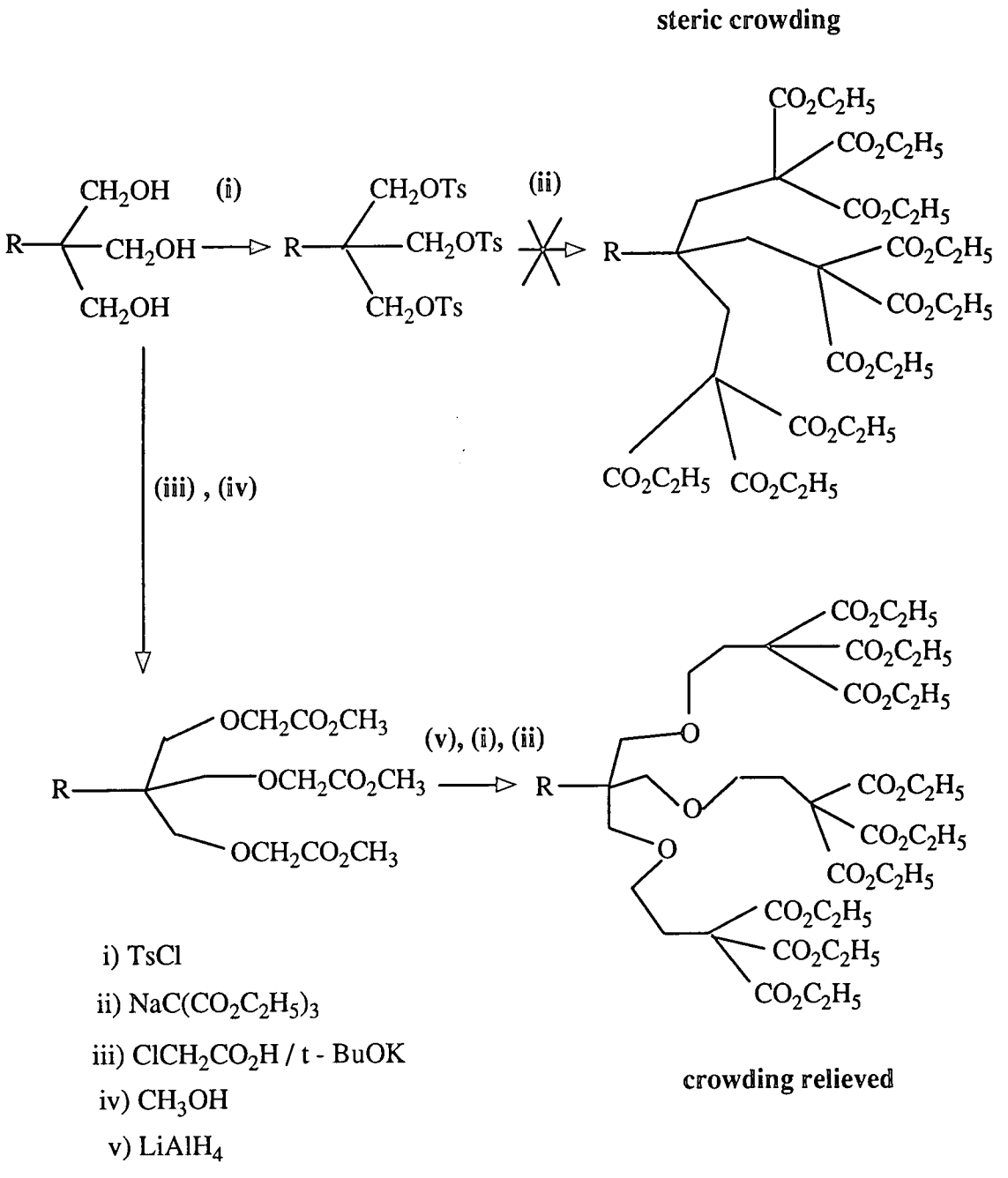


Figure 1.9 The use of extender groups in arborol synthesis

effectively limits the size of the macromolecules that can be prepared in this fashion. Nevertheless, the synthesis of higher molecular weight spherical dendrimers has been achieved using a 'double-stage' convergent approach [45]. This technique employs a preformed dendrimer, bearing reactive surface functionalities (at least one functional group per chain end), as a core molecule to which other preformed dendron fragments can be attached through their single focal point reactive group (figure 1.10). The inner hyperbranched core or 'hypercore' may be composed of flexible segments, allowing for ample spacing between the reactive groups at each chain end. Thus coupling of preformed dendron fragments to the loose hypercore is less subject to the steric constraints encountered with the small, compact core molecules usually employed. A further advantage of the double-stage convergent approach is that the hypercore and outer dendritic layers may be built up using very different chemistries which could conceivably lead to globular structures with unusual chemical or physical properties.

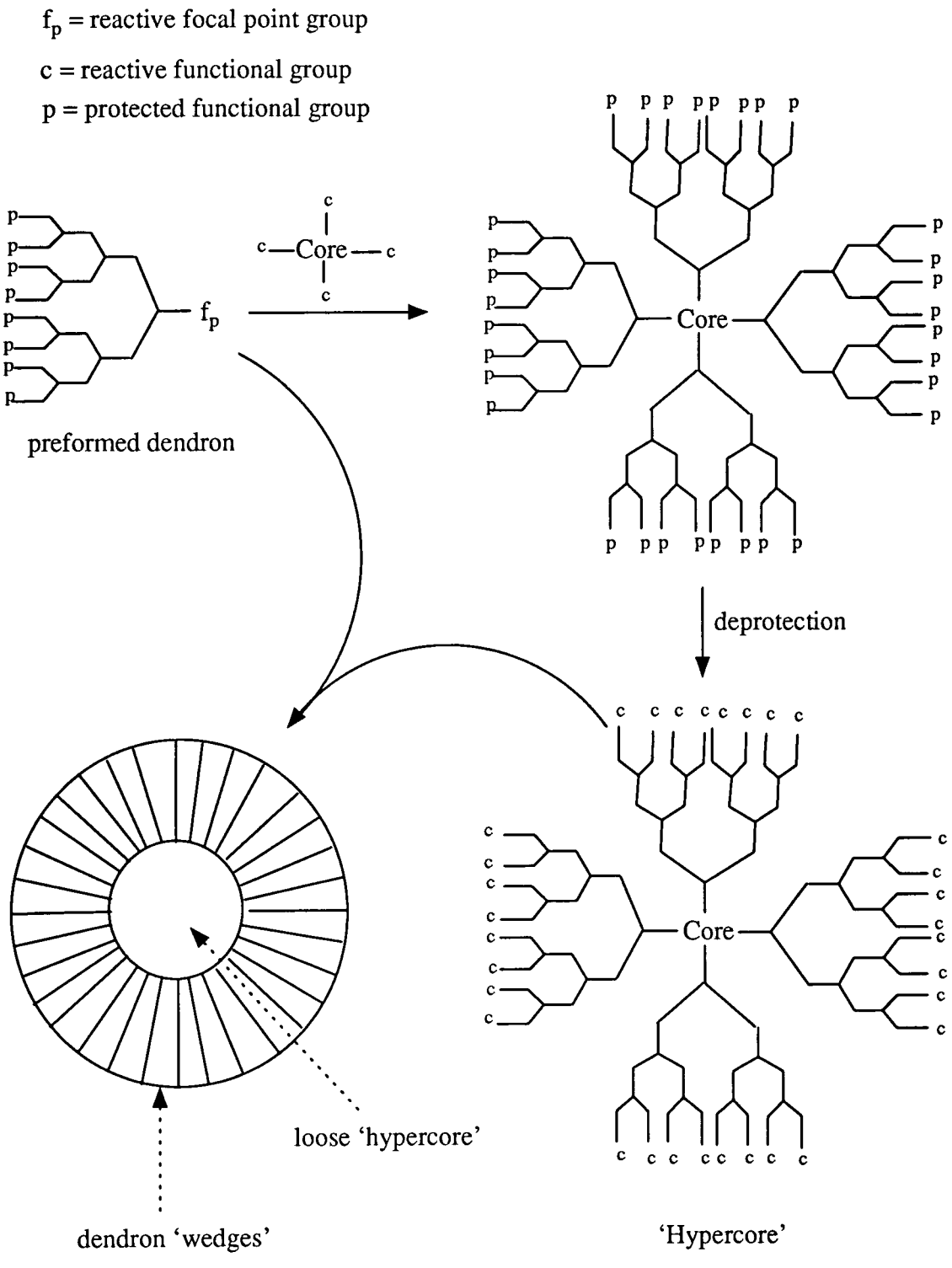


Figure 1.10 Schematic representation of double stage convergent synthesis

1.5 Characterization of dendrimers

The complete elucidation of the complex architecture of dendritic systems requires a wide range of analytical techniques. As yet only the series of polyamidoamines has been extensively studied, nevertheless, some of the techniques used and the information available is shown below (Table 1).

Information available	Techniques used	References
Elemental composition	C, H, N analysis Mass Spectrometry	[5, 6]
Molar Mass	low angle laser light scattering (LALLS) Mass Spectrometry (CI, FAB) Vapour phase osmometry	[5, 6, 33, 35] [5, 6, 21]
Homogeneity	size exclusion chromatography coupled with low-angle laser light scattering electron microscopy	[5, 6]
End groups	infra - red spectroscopy ^{15}N, ^{13}C, ^{1}H nuclear magnetic resonance spectroscopy titration	[5, 6]
Structural information	^{13}C, ^{1}H N.M.R. spectroscopy rheology studies electron microscopy computer assisted molecular simulations fluorescence spectroscopy photo induced electron transfer reactions	[5, 6, 21, 47] [5, 6] [5, 6, 21] [4, 8, 24] [10] [9]
Dimensions	electron microscopy size exclusion chromatography computer assisted molecular simulations	[5, 6, 21] [5, 6, 33, 35] [24]

Table 1.1 Characterization of dendrimers

Of particular note is the importance of ^{1}H and ^{13}C NMR spectroscopy in the

study of these systems. These techniques not only provided support for the proposed dendrimer structures but also yielded information pertaining to branching ideality and the types of branch defects present. Examination of ^{13}C relaxation times (T_1) indicates that the interior carbons of dendrimers are considerably less mobile than the exterior carbons. This is in accord with a tiered structure for dendrimers with the core carbons being the least mobile and mobility increasing towards the exterior layers of the dendrimer. Investigation of host-guest interactions, by NMR relaxation times, has led to the prediction of internal voids at higher generations.

Electron microscopy has proved particularly useful for the examination of polyamidoamines. Co-ordination of group I elements with the terminal functionality of the dendrimers allowed direct observation and measurement of not only aggregates but single dendrimer molecules. This has afforded information relating to dendrimer dimensions and homogeneity.

A variety of probes have been used to examine the surfaces of dendrimers, including photoinduced electron transfer reactions and fluorescence spectroscopy utilizing a pyrene probe. These have successfully confirmed the structural dependence of starburst dendrimers on generation that had previously been suggested from computer modelling [24, 48].

1.6 Properties and uses of dendrimers

1.6a properties

Starburst dendrimers are, as yet, a relatively new class of macromolecules and as such only the properties of the polyamidoamine series have been studied extensively. Nevertheless, the discovery of new phenomena or new properties may be expected from the study of these uniquely shaped macromolecules. The current interest in dendritic systems stems from their highly controlled molecular architectures which may reasonably be expected to influence their properties. As

mentioned previously (1.2), starburst dendrimers possess distinctive and unusual architectures consisting of three basic features. These are a core molecule from which the branches emanate, an interior region of tiered generations and an outermost layer or surface region of terminal functionalities.

The general shape of a dendrimer, and ultimately its overall size, is influenced by the shape, multiplicity and flexibility of both the core molecule and the repeat units [21]. This in turn may have a marked effect upon physical properties. For example, the two-directional arborols, of Newkome, have been shown to possess barbell-like architectures which may self-assemble into rod like structures [28, 29] (figure 1.11). In contrast, the polyamidoamines dendrimers are open, hemispherical,

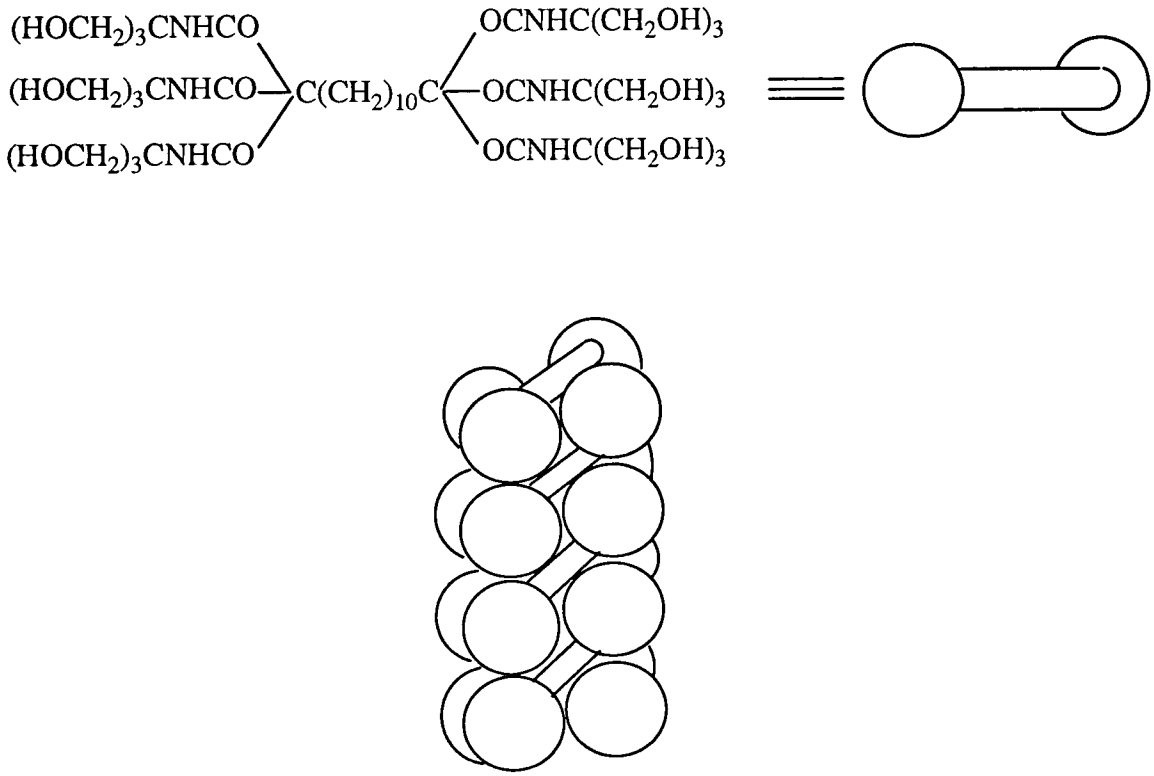


Figure 1.11 Rod - like packing of two - directional arborols

'dome-like' structures at lower generations but closed spheres at higher generations [5, 21, 48]. As mentioned previously (1.3), the higher generation polyamidoamines exhibit sphere-like architectures with interior, solvent filled, hollows referred to as shell topologies [23, 24, 48]. Hence polyamidoamine dendrimers have a great deal of internal surface area and solvent filled volume. This is a direct result of the influence of the size, flexibility and multiplicity of the repeat units. By comparison, Tomalia's polyether dendrimers, which have compact cores and repeat units with high multiplicities (4 and 3 respectively), are high density structures with very little internal surface area or solvent filled volume [5, 21]. Similarly, the Denkewalter series of polylysines have been shown to be constant density, non hollow spheres with non-draining character [27]. This is believed to be due to the increased packing efficiency possible with the unsymmetrical branch lengths associated with these molecules. Hence it would seem that steric bulk and packing efficiency may be key parameters for induced hollowness. Examination of the variation in branch segment densities as a function of molecular weight (or generation) demonstrates the differences between the topology of symmetrically and unsymmetrically branched dendrimers, on one hand, and classical many armed starbranched macromolecules, on the other [5]. With traditional star polymers the branch segment density is greatest at the initiator core and decreases in concentration in a radial fashion. In contrast, symmetrically branched starburst dendrimers have increased branch segment densities (ie more congestion) as higher generations are reached. Whereas, starburst dendrimers with unsymmetrical branch cells exhibit constant branch segment densities as a function of generation.

In summary then, it would seem that symmetrical branch junctures favour shell topologies if branch segment lengths are of an adequate length and core / repeat unit multiplicities are not too high [5].

As a consequence of the controlled step growth assembly of starburst

dendrimers, an ideal dendrimer should be essentially monodisperse. However, several factors can be envisaged that would lead to introduction of polydispersity [5]. These can be a consequence of the experimental procedure, such as the incomplete removal of propagating reagents between growth stages. These can then act as centres for subsequent growth of 'regressed' dendrimers. Defects in the branch cell assembly may also contribute to polydispersity. Such defects can include incomplete reaction of functional groups, intra-dendrimer looping and inter-dendrimer bridging or looping (figure 1.12). The major contributors to polydispersity appear to be excess reagents

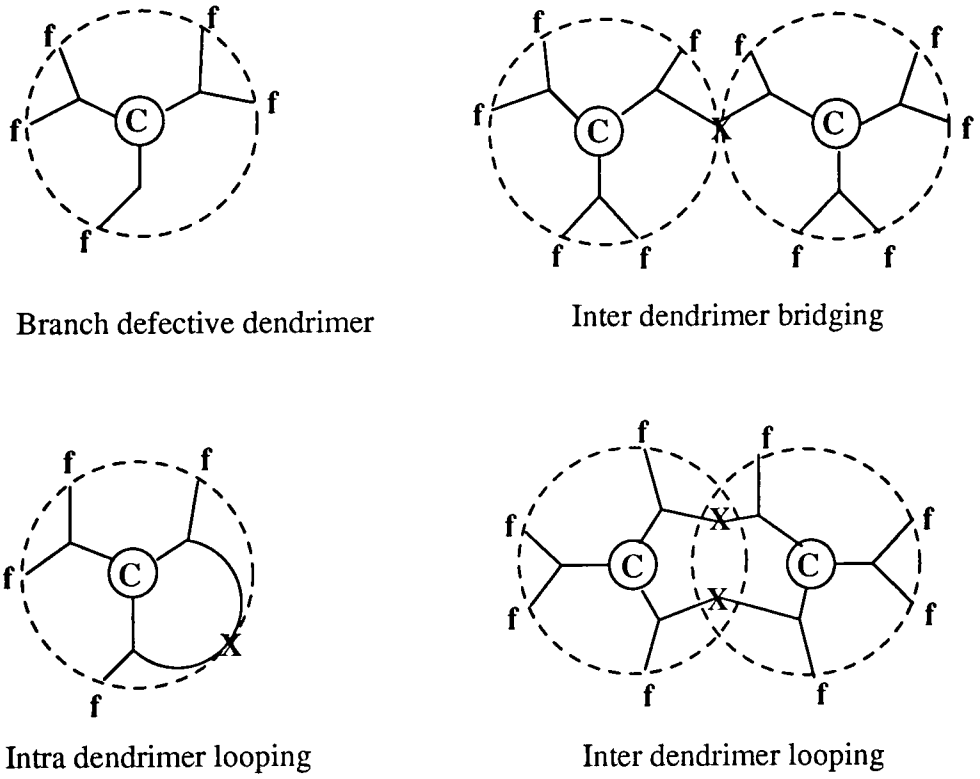


Figure 1.12 Potential branch cell defects

and bridged dendrimers. Nevertheless, monodispersed dendrimers are possible if bridged forms and fragments deriving from excess reagents are removed between

growth stages. This is possible by the use of ultrafiltration techniques [5].

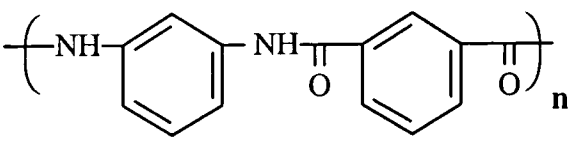
An intrinsic property of starburst dendrimers is that there are a large number of end groups which are situated in an exterior or surface region attached to the outermost generation [6]. If divergent synthesis has been employed, the end groups may well be reactive functionalities. This leads to the possibility of a wide variation in surface chemistry and has been used to provide sites for surface complexation, vary the hydrophobic or hydrophilic character of the dendrimer and produce dendrimers with chiral surfaces [5].

1.6b Potential uses of dendrimers

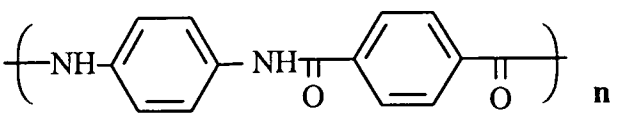
As dendrimers are a relatively new, if expanding, class of macromolecules they have as yet few applications. Their utility as yet seems to be as vehicles for research, particularly in fields where control of molecular size, shape and disposition of organic moieties is desired [2]. They have already been used as models of covalently fixed micelles [21,54] and great interest has been shown in their similarities to many biological systems [5]. Dendrimers have been used as 'nanoscopic reactors' or tiny vessels for studying how space constraints affect chemical reactions [49]. Charge transfer and free radical reactions have been studied in this way. Nevertheless, dendrimers are attracting the interest of some industrial concerns and polyamidoamines are being marketed as sizing kits, where, because of their precise size, they are ideal for calibrating sieves. Other areas in which they are being assessed for potential applications are as constituents of polymer blends, potential catalyst carriers or as vehicles for drug delivery. Thin films of cross-linked dendrimers have been studied as potential separation membranes.

1.7 Aims of this work

Dendrimer growth requires successive additions of monomer units to dendrons in a controlled and well defined manner. Hence, in designing a dendrimer synthesis with a viable scale up potential, it was deemed necessary to choose reactions known to proceed in high yield so that the required reiterative chemistry would not result in diminishing material recovery. To avoid the possibility of uncontrolled step growth the chosen system must also be amenable to a protective group strategy. The possibility of good purification between growth stages was deemed necessary if the introduction of polydispersity, via dendron growth initiated by excess reagents, was to be avoided. The above criteria would seem to be admirably satisfied by the types of reactions well known in conventional step growth polymerizations. Hence a polyamide, and in particular an aromatic polyamide, was chosen as a target molecule. Wholly aromatic linear polyamides, known as aramids, are already of commercial importance in the form of poly(m-phenyleneisophthalamide) [Nomex (Du Pont) or Conex (Teijin)] and poly(p-phenyleneterephthalamide) [Kevlar (Du Pont) or Twaron (Akzo)] [50] (figure 1.13).



poly(m-phenyleneisophthalamide) (Nomex)



poly(phenyleneterephthalamide) - (Kevlar)

Figure 1.13 Commercial linear aramides

More recently Aharoni and Edwards have investigated networks incorporating

aromatic polyamides [51, 52] using monomers such as tris(p-carboxyphenyl)-1,3,5-benzenetriamide (figure 1.14) as the branch points. Hence it should be feasible to incorporate trifunctional aromatic moieties into a regular dendritic network. More

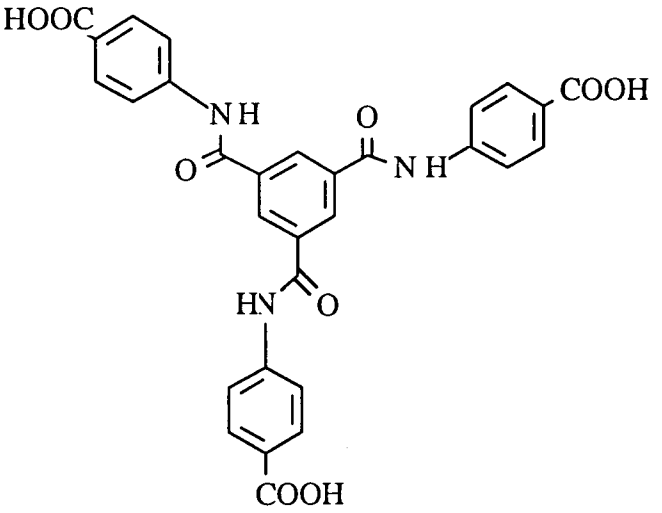


Figure 1.14 Aromatic triamide used as network branch point

specifically, the use of a p-aminoisophthalic acid based repeat unit in combination with various aromatic acid chloride initiator cores could result in a family of dendritic polyamides. In particular a dendritic structure based on a trimesic acid core would parallel the types of branch points employed by Aharoni *et al.* (figure 1.15).

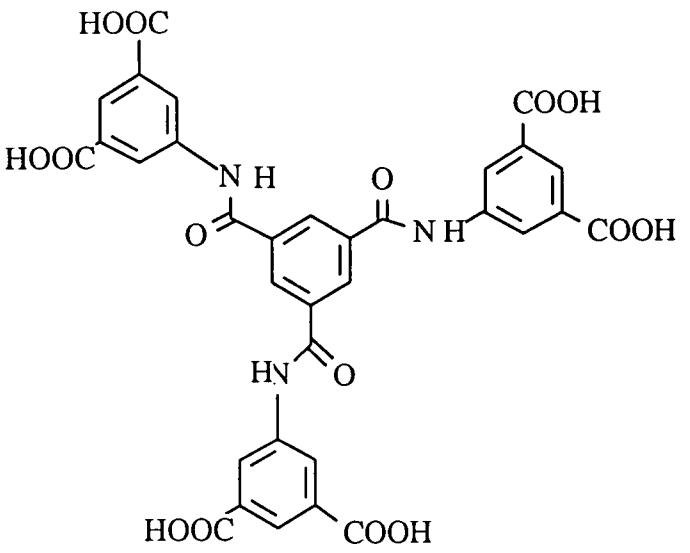


Figure 1.15 Hypothetical dendrimer core cell

The following chapters of this thesis will attempt to describe in more detail various approaches to realizing the above objectives.

CHAPTER TWO

AMIDE BOND FORMATION AND MODEL INITIATOR CORES

2.1 Introduction

There are many potentially useful reactions for the synthesis of amide bonds. This chapter details attempts to use some of these reactions to produce models of potential dendrimer core cells and, in doing so, assess their suitability for dendrimer growth. Some of the criteria used in the choice of particular systems are :

i) starting materials should be relatively inexpensive and easy to handle

ii) yields should be high

iii) products should be capable of purification by simple techniques

2.2 Amide bond formation

An important factor for consideration is the cost and availability of starting materials. Hence natural choices of reagents are easily available carboxylic acids and aromatic amines. However, carboxylic acids do not react with amines very readily [56], the process generally being endothermic in nature [57], and usually require activation if amide bond formation is to be effected [58]. Many coupling reagents, which activate the carbonyl group of free acids towards nucleophilic attack, have been studied [59]. However, one of the most popular and useful reagents for amide formation from free acids is dicyclohexylcarbodiimide which has been widely used in the field of peptide synthesis [58] (figure 2.1) .

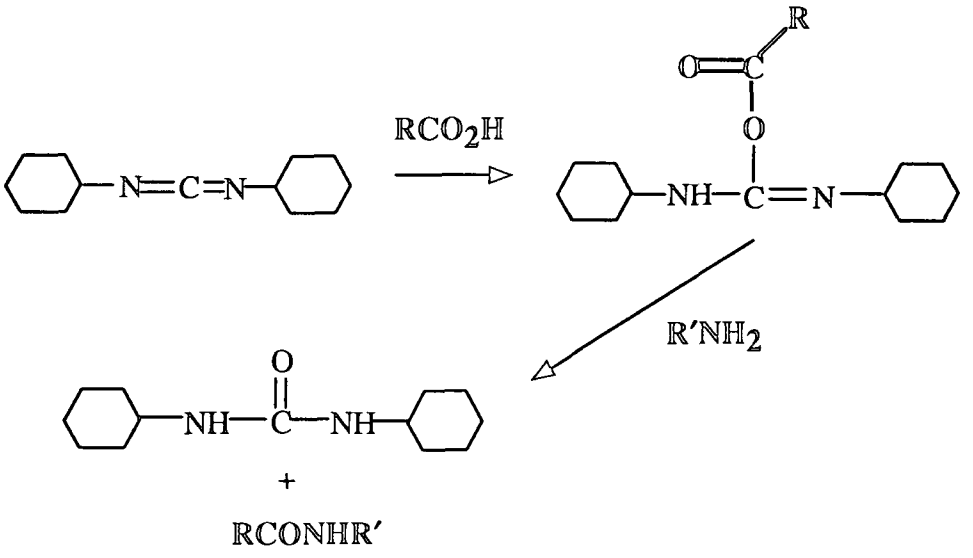


Figure 2.1 Use of carbodiimides as coupling agents

Probably the most frequently employed method of amide preparation is the acylation of amines with acid chlorides [58]. This method generally employs an excess of amine or a molar equivalent of amine plus an excess of a tertiary amine or an alkali metal hydroxide to absorb the hydrochloric acid formed during the reaction (figure 2.2).

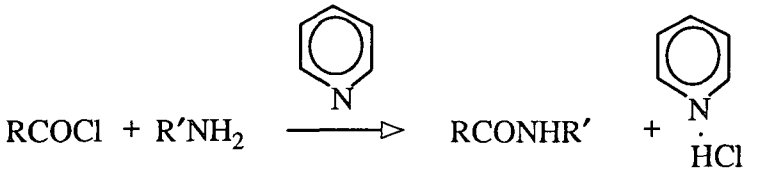


Figure 2.2 Amides via acid chlorides

The reaction of aromatic acid chlorides and aromatic amines is employed in the commercial production of aramids [50]. In some cases acylations can be accompanied by loss of a substituent other than hydrogen from the amino nitrogen. Thus, trialkylsilyl protected amines react with acid chlorides with the formation of trialkylsilylchloride as a by product [60-62]. This has also been successfully employed in the formation of aramids [63] (figure 2.3) .

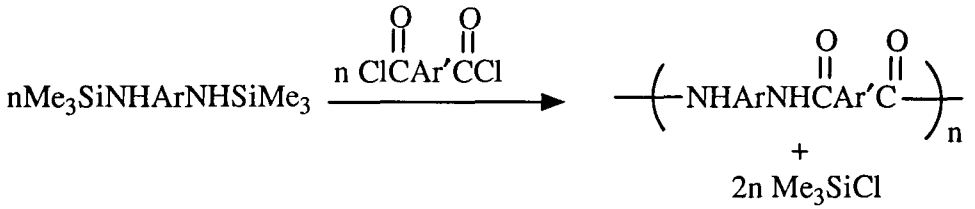


Figure 2.3 Aramids via silylamines

2.3 Synthesis of model dendrimer core cells

2.3a Use of carbodiimide coupling agents

The feasibility of using an aromatic trifunctional core and the utility of dicyclohexylcarbodiimide as a coupling reagent for these reactions was assessed in the reaction of 1,3,5-benzenetricarboxylic acid (trimesic acid) and aniline. The conditions for this reaction were those generally employed in the literature, as developed by Sheehan and Hess [64]. Reaction was carried out at room temperature, in diethyl ether, and the progress monitored by infra-red spectroscopy. The disappearance of the absorption at 2100cm^{-1}, due to the cumulated double bond system of the carbodiimide, signifying depletion of carbodiimide due to the formation of the intermediate shown above (figure 2.1). Although the reaction seemed to be successful, the by-product from the reaction, dicyclohexylurea, proved difficult to separate from the desired amide. Similar results were obtained with the reaction of p-toluic acid and aniline.

2.3b Synthesis from acid chlorides

To assess their utility as potential initiator cores, and to serve as models for the characterization of higher generations, a series of anilides was prepared from mono, di and tri functional aromatic acid chlorides. This necessitated the synthesis of trimesoyl chloride by the reaction of trimesic acid and thionyl chloride.

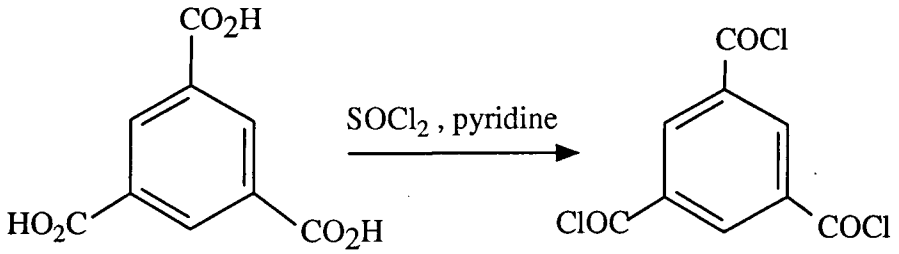
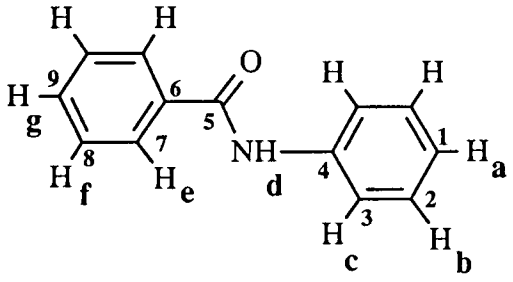


Figure 2.4 Synthesis of trimesoyl chloride

Trimesic acid was refluxed with an excess of thionyl chloride and a trace of pyridine to give trimesoyl chloride in good yield (87%). An infra-red spectrum of the product, $\left(3080cm^{-1}\ \upsilon C{-}H\ ,1765cm^{-1}\ \upsilon C{=}O,\ 1595cm^{-1}\ \upsilon C{=}H\right)$, showed the absence of any absorption attributable to carboxylic acid hydroxyl groups and a carbonyl absorption in the region typical of acid chlorides. A ^{1}H NMR spectrum (250.133 MHz, $CDCl_3$) showed a single peak at 9.1ppm.

Reaction of benzoyl, terephthaloyl, isophthaloyl and trimesoyl chlorides with aniline were carried out, in pyridine, at room temperature. A potential problem was encountered in the solubility of the higher acid chlorides in pyridine ; terephthaloyl and trimesoyl being only sparingly soluble. This was circumvented by the use of a vibromixer as a highly efficient method of mixing the reagents in this potentially heterogeneous reaction. Products were obtained in the form of brown oils which required washing with water , to remove pyridine hydrochloride, and recrystallizing from dimethylacetamide. Yields were high (80-99%) but some material loss was to be expected in the recrystallization process. The products were characterized by a combination of Fourier Transform Infra-Red Spectroscopy (FTIR), ^{13}C and ^{1}H Nuclear Magnetic Resonance Spectroscopy (NMR) and Mass Spectrometry (MS), summarized below:

Benzanilide (I)



Mass 197

The mass spectrum (CI) showed an M+1 peak at m/e 198. The parent ion (m/e 197) was discernable in the EI spectrum, with distinctive fragments at m/e 105 ($C_6H_5CO^+$) and 77 ($C_6H_5^+$) (Appendix 1.1).

An FTIR spectrum showed the following characteristic absorptions consistent with the assigned structure (Appendix 2.1):

3343cm^{-1}	υ N—H (amide)	3051cm^{-1}	υ C—H (aromatic)
1655cm^{-1}	υ C=O (amide I)	1599cm^{-1}	υ C···C
1535cm^{-1}	δ N—H (amide II)		

The ^{1}H NMR spectrum (399.952MHz, acetone-d6) is summarized below (Table 2.1 and Appendix 3.1):

shifts (ppm)	integration	multiplicity	assignment
7.11	1	t,t	a
7.35	2	m	b
7.50	2	m	f
7.57	1	t,t	g
7.86	2	m	c
8.00	2	m	e
9.55	1	s	d

Table 2.1 ^{1}H NMR data for benzanilide (I)

The amide proton (d) was apparent as a broad singlet, integrating as one proton, at a high value of δ (9.55) typical of secondary amides. The protons in the para positions (a) and (g) appeared as 'triplet of triplets', through coupling with not only the two adjacent meta protons but also with long range coupling to the two ortho protons of the phenyl ring. Comparisons with similar proton environments in the model compound (IV), described later in this section, allowed the signal at 7.11ppm to be assigned to proton (a) and hence that at 7.57ppm to proton (g). The aromatic proton with the highest chemical shift was expected to be proton (e) due to the 'ortho' effect of the carbonyl group which was consequently assigned to the signal at 8.00ppm. The remaining aromatic protons were assigned on the basis of a comparison with the chemical shifts of similar protons in the model compound (IV), described later.

The ^{13}C NMR spectrum (100.577MHz, acetone-d6) showed the expected 9 signals summarised below (Table 2.2 and Appendix 4.1).

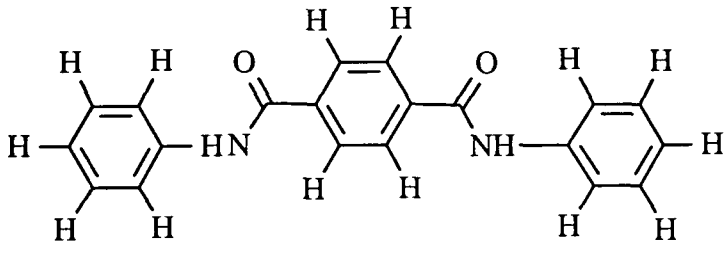
Chemical Shifts (ppm)	Assignments
120.95	3
124.48	1
128.24	2
129.19	8
129.42	7
132.24	9
136.27	6
140.28	4
166.28	5

Table 2.2 ^{13}C NMR data for benzanilide

The carbonyl carbon (5), the aromatic carbon next to nitrogen (4) and the aromatic carbon next to the carbonyl (6) all gave signals at typical chemical shifts for

these environments. The remaining aromatic protons were assigned on the basis of a comparison with the ^{13}C NMR spectrum of the tricarboxamide (IV), described later in this section.

N,N′-diphenyl-1,4-benzenedicarboxamide (II)



Mass 316

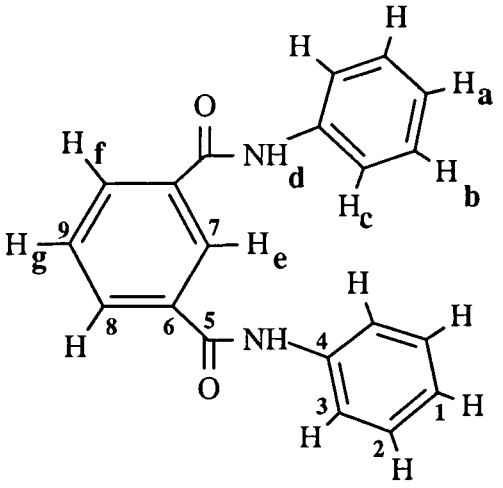
The mass spectrum (EI) showed the parent ion at m/e 316 and a base peak at m/e 224 (M-PhNH). The CI spectrum showed a M+1 peak at 317 (Appendix 1.2).

An FTIR spectrum showed the following characteristic absorptions (Appendix 2.2):

$3329cm^{-1}$	υ N—H (amide)	$3057cm^{-1}$	υ C—H (aromatic)
$1645cm^{-1}$	υ C=O (amide I)	$1599cm^{-1}$	υ C=C
$1530cm^{-1}$	δ N—H (amide II)		

No NMR data was available for this compound due to its insolubility in common deuterated solvents.

N,N′-diphenyl-1,3-benzenedicarboxamide (III)



Mass 316

The mass spectrum (EI) showed the parent ion at m/e 316 and a base peak at m/e 224 (M-PhNH) (Appendix 1.3).

The FTIR spectrum showed the following characteristic absorptions (Appendix 2.3):

$3257cm^{-1}$	υ N—H (amide)	$3060cm^{-1}$	υ C—H (aromatic)
$1639cm^{-1}$	υ C=O (amide I)	$1598cm^{-1}$	υ C···C
$1542cm^{-1}$	δN—H (amide II)		

The ^1H NMR spectrum (399.952 MHz, dmso-d6) is summarised below (Table 2.2 and Appendix 3.2):

The ^1H NMR data is consistent with the proposed structure and compares favourably with the data obtained for the model compounds (I) and (IV), also described in this chapter. The aromatic protons were assigned using a combination of their chemical shifts, integrals and multiplicities. Protons (a),(b) and (c) may be unambiguously assigned on the basis of their integrals combined with a comparison of similar proton environments in compounds (I) and (IV). Proton (b), as expected, shows coupling to both protons (a) and (c) (J=7.8Hz). Proton (a) not only exhibits the expected 3-bond coupling to protons (b) (J=7.8Hz) but also 4-bond coupling to

shifts (ppm)	integration	multiplicity	assignment
7.12	2	m	a
7.37	4	m	b
7.69	1	t	g
7.80	4	d,d	c
8.14	2	d,d	f
8.52	1	's'	e
10.42	2	s	d

Table 2.3 ^{1}H NMR data
N,N′-diphenyl-1,3-benzenedicarboxamide (III)

protons (c) (J=0.8Hz). Proton (g) is easily identified as a triplet, due to coupling with protons (f) (J=8.0Hz), integrating as one proton. Proton (f) appears as a 'doublet of doublets'. The expected coupling to proton (g) is seen as well as further splitting due to long range coupling to proton (e) (J=1.6Hz). Proton (e), on first inspection, appears to be a singlet but further examination reveals the presence of long range coupling to proton (f) (J=1.6Hz).

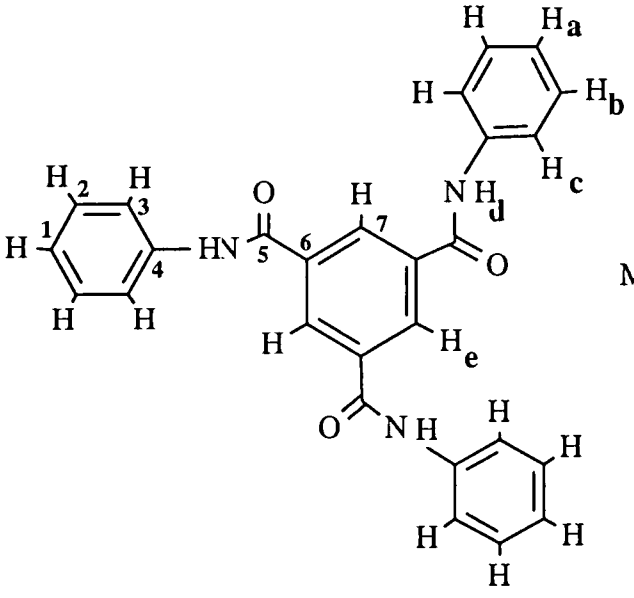
The ^{13}C NMR (100.577 MHz, dmso-d6) is summarised below (Table 2.4 and Appendix 4.2):

Chemical Shifts (ppm)	Assignments
120.86	3
124.32	1
127.48	2
129.11	9
129.16	7
131.13	8
135.68	6
139.53	4
165.55	5

Table 2.4 ^{13}C NMR data
N,N′-diphenyl-1,3-benzenedicarboxamide (III)

The ^{13}C NMR spectrum shows the expected 9 peaks. Carbons (1), (2) and (3) were assigned on the basis of a comparison with similar carbon environments in the model compounds (I) and (IV). Carbons (4), (5) and (6) appeared at chemical shifts typical for aromatic carbon next to nitrogen, carbonyl carbons and aromatic carbon adjacent to a carbonyl group respectively. Carbons (7), (8) and (9) were assigned with the aid of tables of incremental shifts for substituted benzenes [75].

N,N′,N″-triphenyl-1,3,5-benzenetricarboxamide (IV)



Mass 435

The mass spectrum (EI) showed the parent ion at m/e 435 and a base peak at m/e 343 (M-PhNH). The CI spectrum showed an M+1 peak at m/e 436 (Appendix 1.4).

The FTIR spectrum showed the following characteristic absorptions (Appendix 2.4):

$3288cm^{-1}$	υ N—H (amide)	$3061cm^{-1}$	υ C—H (aromatic)
$1647cm^{-1}$	υ C=O (amide I)	$1600cm^{-1}$	υ C=C
$1546cm^{-1}$	δ N—H (amide II)		

The ^{1}H NMR spectrum (399.952 MHz, DMSO-d6) is summarised below (Table 2.5 and Appendix 3.3):

shifts (ppm)	integration	multiplicity	assignment
7.13	3	t	a
7.38	6	t	b
7.86	6	d	c
8.75	3	s	e
10.70	3	s	d

Table 2.5 ^{1}H NMR data

N,N′,N″- triphenyl-1,3,5-benzenetricarboxamide

The amide protons (d) were immediately obvious at very high values of δ (10.70). The ortho protons (e) were apparent as a singlet, integrating as 3 protons, at a high value of δ (8.75) due to the deshielding effect of the nearby carbonyl groups. The remaining aromatic protons were assigned on the basis of their multiplicities and integrals. The signals in this particular spectrum are somewhat broader than expected, judging by the results for the analogous compounds (I) and (III), described above. Hence, the expected four bond coupling between the aromatic protons is not resolved, in this case. Proton (a), for example, appeared as a triplet through coupling with two equivalent protons (b) (J=7.6Hz), rather than as a 'triplet of triplets' as was noted for benzanilide, described previously. Similarly, proton (c) appeared as a doublet due to coupling with proton (b) (J=7.6Hz). Proton (b) appeared as a multiplet coupled to both proton (a) and (c).

The ^{13}C NMR spectrum (100.577 MHz, DMSO-d6) consisted of the expected 7 peaks and is summarised below (Appendix 4.3 and Table 2.6)

Chemical Shifts (ppm)	Assignment
120.54	3
124.11	1
128.82	2
129.96	7
135.47	6
139.05	4
164.63	5

Table 2.6

^{13}C Data for N,N′,N″ -triphenyl-1,3,5-benzenetricarboxamide (IV)

The carbonyl carbons (5) were apparent, at 164.63 ppm, in the region of the spectrum typical of carbonyl carbons. Carbon (4) was assigned to the signal at 139.05 ppm, a typical value for aromatic carbons next to nitrogen. Similarly carbon (6) was seen at 135.47ppm, in the region typical of aromatic carbons adjacent to carbonyl groups. The remaining aromatic carbons were assigned on the basis of their expected chemical shifts, as calculated from tables of incremental shifts of substituted benzenes [75].

The NMR data agrees well with that obtained by Miller and Neenan [44], although these authors curiously quote 9 carbon signals in their ^{13}C NMR data.

2.3c Synthesis from silylamines

A modification to the acid chloride systems detailed above (2.3b) is the use of silylamines. Trimethylsilylaniline can be prepared by the addition of trimethylchlorosilane to aniline either in the absence of solvent or in a solvent such as toluene or benzene [64].

$$(CH_3)_3SiCl + C_6H_5NH_2 \longrightarrow (CH_3)_3SiNHC_6H_5 + C_6H_5NH_3Cl$$

The reaction is reversible and hence requires an excess of trimethylsilyl

chloride. Some of the aniline is also lost in the form of aniline hydrochloride. An alternative is the addition of a tertiary amine to trap the hydrogen chloride formed during the reaction [66]. A disadvantage of this system is the susceptibility of N-substituted silylamines to hydrolysis, exposure to air usually being sufficient to affect hydrolysis [60].

A sample of trimethylsilylaniline was prepared in 20% yield by addition of trimethylsilyl chloride to aniline, in the absence of any solvent. Analysis of this material by Gas-liquid Chromatography / Mass Spectrometry (10% SE30, 150 ^{0}C, nitrogen carrier) showed it to be a mixture of 98% (by peak area) the expected product (parent ion m/e 165, M-CH_3 m/e 150) and 2% aniline (Appendix 1.5).

Reaction of this material with benzoyl chloride, in dry toluene gave a white precipitate recovered by filtration (97% yield). An i.r. spectrum of this material was identical to that obtained from the product of the reaction of benzoyl chloride and aniline (I) above. Similarly, reaction of trimesoyl chloride with trimethylsilylaniline gave a product identical to (IV) above.

2.4 Experimental details

2.4a General procedure for the dicyclohexylcarbodiimide catalysed reaction of an aromatic carboxylic acid and aniline

Reagents : p-toluic acid, Aldrich 98%

trimesic acid, Fluka >97%

dicyclohexylcarbodiimide, Aldrich 99%

aniline, Aldrich 99%, distilled under a nitrogen atmosphere

Apparatus : 250 ml, 3-necked , round bottomed flask

Leibig condenser fitted with a $CaCl_2$ drying tube

pressure equalising dropping funnel

overhead stirrer

Procedure

Trimesic acid (3.10g, 14.8 mmol) and dicyclohexylcarbodiimide (9.08g, 44.1 mmol) were dissolved in diethylether ($100cm^3$) and a solution of aniline (4.12g, 44.3 mmol) in diethylether ($50cm^3$) added dropwise, to the stirred reaction mixture. Stirring was continued , at room temperature, for 5hrs. during which period a white precipitate was formed. The white precipitate of dicyclohexylurea was removed by filtration and the solution reduced in volume by rotary evaporation. Petroleum ether (40-60) was added to precipitate out a white solid (6.7g) which was recovered by filtration.

2.4b Synthesis of trimesoyl trichloride

Reagents : trimesic acid, Fluka >97%

thionyl chloride, Fluka >99%

Apparatus : 250 ml flange flask

reflux condenser fitted with a $CaCl_2$ drying tube

gas scrubbing tower (see figure 2.5)

Procedure

The procedure is based upon that used by Sandler and Karo [67].

Trimesic acid (4.20g, 20.0 mmol) and an excess of thionyl chloride (29.20g, 245.3 mmol) were placed in a 250ml flange flask, fitted with a reflux condenser and connected to a gas scrubbing tower. Pyridine (0.12mls) was added and the mixture refluxed for 18 hrs. This resulted in a yellow solution. Excess thionyl chloride was removed under vacuum (10^{-3}mm Hg) to leave a slightly viscous yellow liquid. A kugelrohr distillation (130-150 ^{0}C, 0.7mm Hg) yielded a white solid (4.60g, 87% yield).

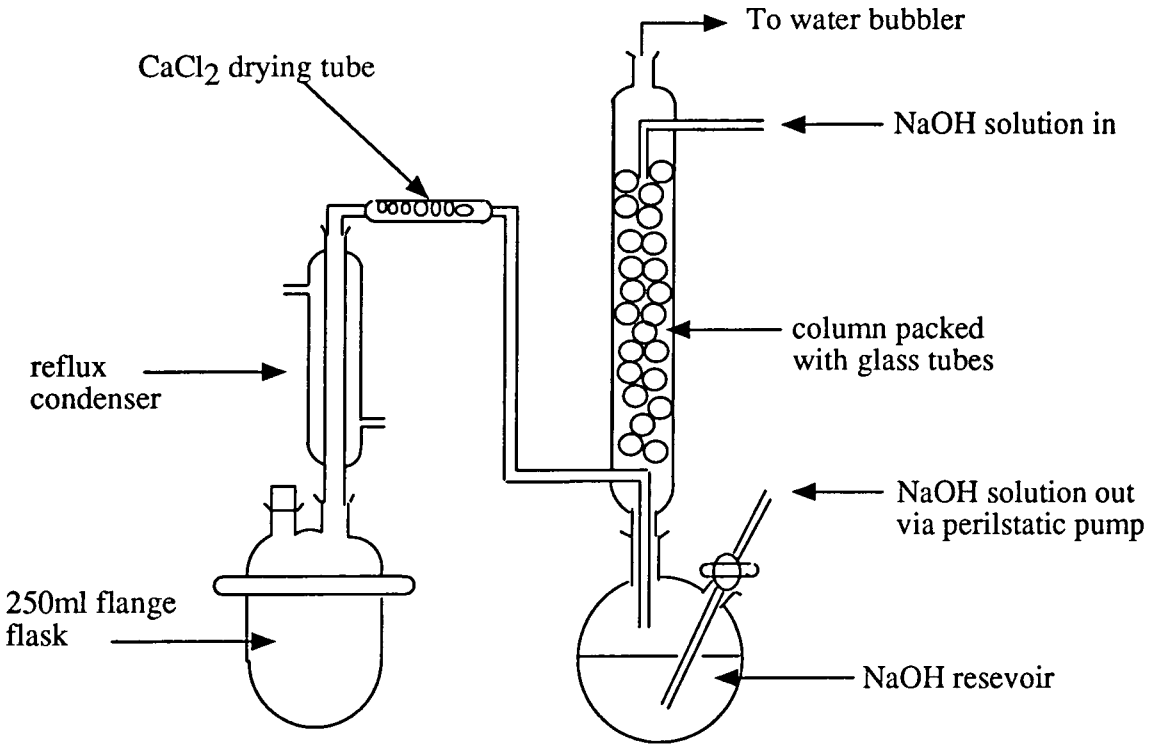


Figure 2.5 Apparatus for synthesis of acid chlorides

2.4c General procedure for reaction of acid chlorides with aniline

Reagents ; benzoyl chloride, Aldrich 99%

isophthaloyl dichloride, Aldrich 98%

terephthaloyl dichloride, Aldrich 99%

trimesoyl trichloride, as prepared above (2.3b)

aniline, Aldrich 99%, distilled under a nitrogen atmosphere

Apparatus ; 250ml flange flask

Leibig condenser fitted with a $CaCl_2$ guard tube

pressure equalizing dropping funnel

vibro mixer

gas absorption trap

Procedure

Trimesoyl trichloride (8.93g, 33.6mmol) was added to pyridine (100mls) in a 250ml

flange flask. The mixture was cooled to 0^0C and agitated using a vibromixer. A solution of aniline (9.80g, 105.4mmmol) in pyridine (100mls) was added dropwise. Mixing was continued for 2hrs. at 0^0C and 17hrs. at room temperature. The pyridine was removed by rotary evaporation to give a red brown oil which was washed with distilled water and the resulting solid recovered by filtration and dried in a vacuum desiccator. This resulted in an off white powder (11.75g, 80% yield) which was recrystallised from a dimethylacetamide / water mixture.

2.4d Synthesis of trimethylsilylaniline

Reagents : aniline, Aldrich 99%, distilled under a nitrogen atmosphere
chlorotrimethylsilane, Aldrich 98%
pyridine, Lancaster Synthesis

Apparatus : 250ml, 3-necked flask
Leibig condenser
overhead stirrer
nitrogen inlet
sinter stick

Procedure

A 250ml, 3-necked flask fitted with a condenser, overhead stirrer and nitrogen inlet was filled with chlorotrimethylsilane (34.5g, 317.7mmmol). The liquid was cooled to 0^0C with an ice-bath before the addition of aniline (26mls, 284.8mmols), dropwise by syringe. A white precipitate formed immediately and coagulated into a viscous mass within a few minutes. The mixture was left at room temperature for 1hr. before removal of the precipitate, by filtration under a nitrogen atmosphere, to leave a yellow liquid. Unreacted aniline was removed by distillation, under reduced pressure (126^0C, 28mmm Hg) with a nitrogen bleed. The remaining liquid was vacuum transferred to leave a clear liquid (9.7g, 20% yield).

2.4e Reaction of trimethyl silylaniline and benzoyl chloride

Reagents : Benzoyl chloride, Aldrich 99%

trimethylsilylaniline, as prepared (2.4d)

toluene, dried over sodium wire

Apparatus : 250ml flange flask

Leibig condenser

nitrogen inlet

vibromixer

Procedure

A 250ml flange flask was filled with benzoyl chloride (1.0g, 7.12mmol) and dry toluene (100mls), under a nitrogen atmosphere. The solution was stirred at 0^0C, with a vibromixer, and trimethylsilylaniline (2.0g, 12.12mmol) added dropwise by syringe. The solution was stirred at room temperature for 30 minutes before recovery of the resulting white precipitate by filtration. The precipitate was dried under vacuum to give 1.36g of a white powder (97% yield).

2.5 Discussion

The reactions detailed above demonstrate the relative efficacy of the various amide forming reactions for dendrimer growth. The carbodiimide method is a simple, easy technique using readily available and inexpensive starting materials. However, the similarity of the by-product, dicyclohexylurea, to the resulting amides makes purification difficult. Similar problems have been circumvented in peptide chemistry by the employment of water soluble carbodiimides [68], although they tend to be somewhat expensive. Nevertheless, carbodiimides may be useful in the growth of the higher generation dendrimers where differences in solubility may be reasonably

expected.

The use of silylamines offers the advantage of a good, clean, high yield reaction under neutral conditions. However, the difficulties in monomer preparation and its subsequent handling make the method of limited utility.

The employment of acid chlorides offers the advantage of easily prepared starting materials, high yields and relatively easy purification techniques and was therefore the method of choice for the subsequent amide syntheses, detailed in the next two chapters.

CHAPTER THREE

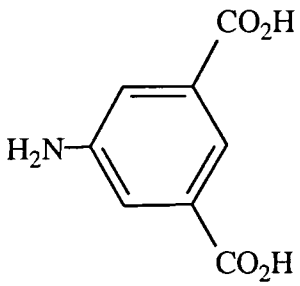
DENDRITIC POLYAMIDES

VIA

A DIVERGENT SYNTHESIS

3.1 A proposed divergent synthesis

Dendritic growth requires monomers of XRYn type, where n>1. Hence, for the synthesis of dendritic polyamides, monomers of the general type $H_2NR(CO_2H)_2$ or $HO_2CR(NH_2)_2$ are required. As already indicated (1.7 above), monomers of the former type would parallel the branch points employed by Aharoni [51,52] for network formation. Hence the monomer chosen for the proposed divergent synthesis was a derivative of 5-aminoisophthalic acid :



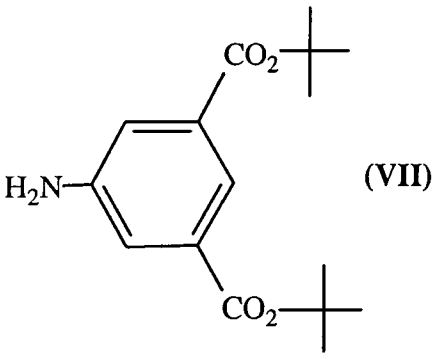
5-aminoisophthalic acid

3.1a Protecting groups

It was envisaged that the target of a truly monodisperse, non branch defective dendrimer would require a synthesis involving protective group strategies if **controlled** dendritic growth was to be achieved. The monomer type chosen above requires outward growth from carboxylic acid functions which are normally protected in the form of carboxylic acid esters [70]. The particular ester chosen was a *tert*-butyl ester due to the reported ease of conversion to the free acid (and isobutene) simply by heating to 200^0C [70]. In addition, *tert*-butyl esters are easily prepared from acid chlorides and *tert*-butanol.

3.1b A Basic Building Block

The protected monomer chosen to comply with the above criteria was di-t-butyl-5-aminoisophthalate (VII) .



(VII)

Di-t-butyl-5-aminoisophthalate

However, in order to prepare the *tert*-butyl ester, from an acid chloride, the amine function had to be protected to avoid concomitant amide formation. The amine function was, therefore, masked in the form of a nitro group. Conversion of the nitro group to an amine thus required a selective reduction that would leave both the aromatic ring and the ester function intact. Sodium borohydride in the presence of

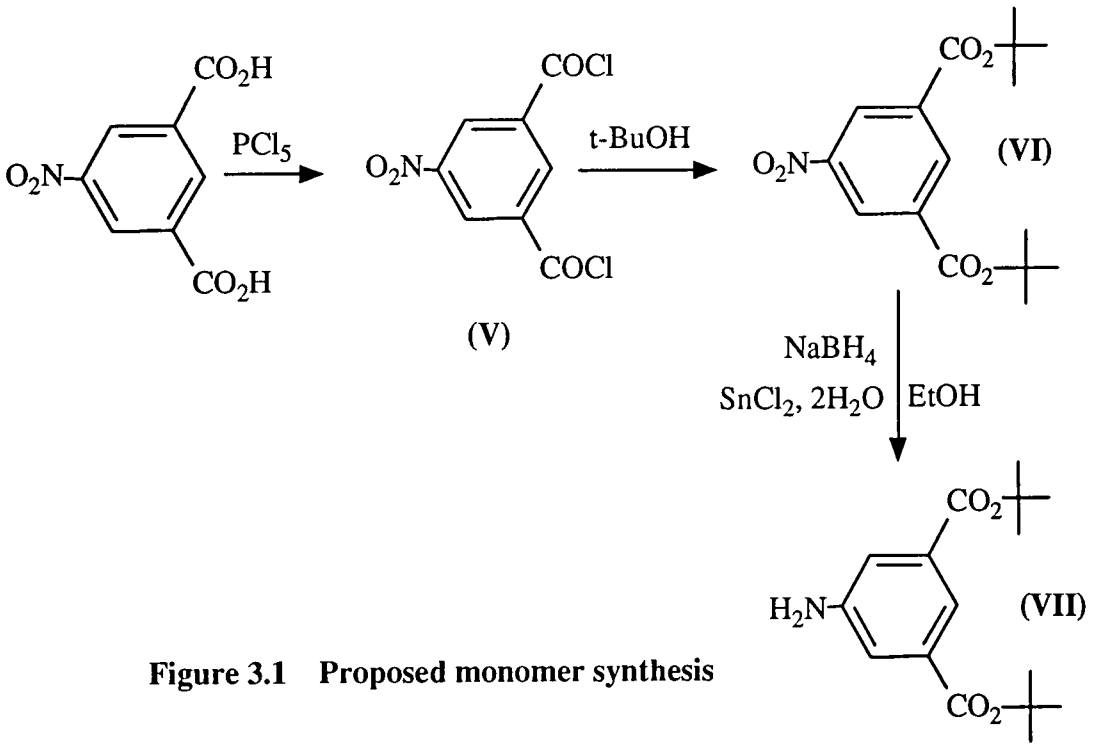


Figure 3.1 Proposed monomer synthesis

transition metal salts is reported to reduce nitro groups selectively [71-74]. In

particular, a sodium borohydride / stannous chloride system is reported to reduce aromatic nitro groups selectively, in the presence of carboxylic ester groups, in good yields (98%) [71]. The complete monomer synthesis, utilizing the reactions discussed above, is summarised in the scheme shown below (figure 3.1);

3.1c A proposed synthetic route to dendritic polyamides

The proposed route for the incorporation of the above monomer units into a dendritic structure is shown below (figure 3.2).In this scheme the monomer (VII) is reacted with a suitable acid chloride initiator core, such as trimesoyl trichloride, to give a first generation dendrimer. The ester functionalities of the dendrimer are converted to carboxylic acid groups, by pyrolysis, and then to acid chlorides by reaction with thionyl chloride. The resulting dendritic acid chloride can then be reacted with more of monomer (VII) to give a second generation dendrimer. It was envisaged that this sequence could be repeated a number of times to build up higher generation dendrimers.

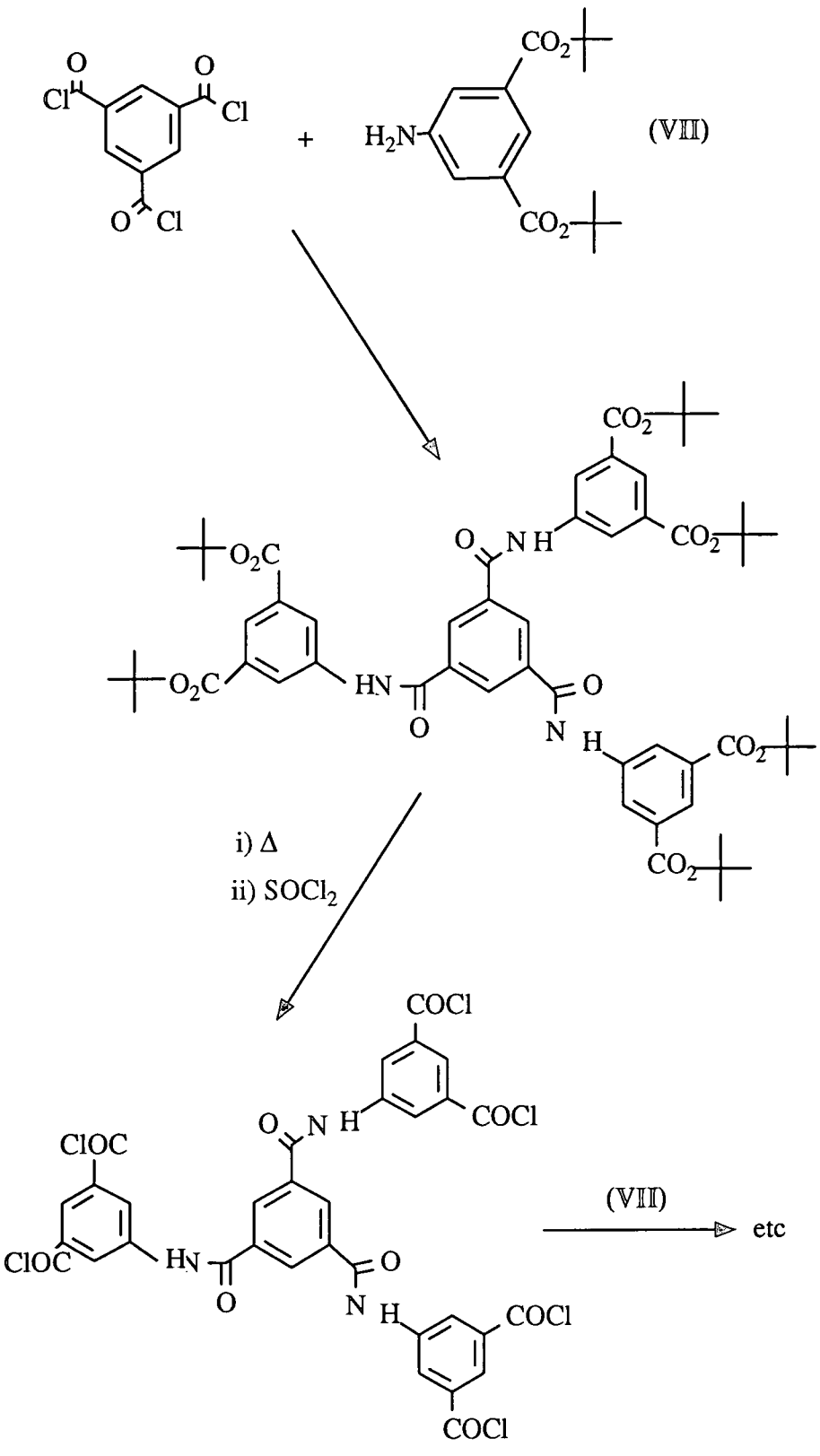
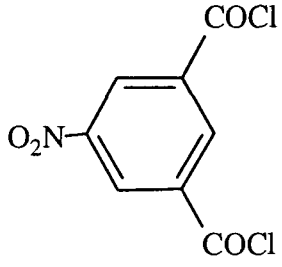


Figure 3.2 Divergent polyamide dendrimer synthesis

3.2 Attempted divergent synthesis

3.2a Monomer synthesis

The preparation of 5-nitroisophthaloyl chloride (V) was carried out, in good yield (95%), by heating 5-nitroisophthalic acid with phosphorous pentachloride and removing the resulting phosphorous oxychloride by-product under reduced pressure.



(V)

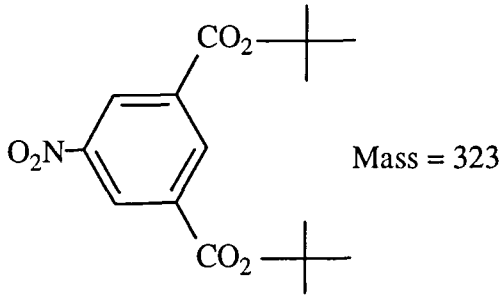
5-nitroisophthaloyl chloride

The mass spectrum failed to show a parent ion, nevertheless, the most prominent group of fragment ions (m/e 212 and 214) showed a single chlorine pattern corresponding to the loss of a chlorine atom from the parent molecule (Appendix 1.6).

Analysis by infra-red spectroscopy revealed the following characteristic absorptions (Appendix 2.5);

$3095cm^{-1}$	υ C—H (aromatic)	$1760cm^{-1}$	υ C= O (acid chloride)
$1620cm^{-1}$	υ C=C	$1545cm^{-1}$	υ N—O (asymmetric)
$1350cm^{-1}$	υ N—O (symmetric)	$845cm^{-1}$	υ C—N

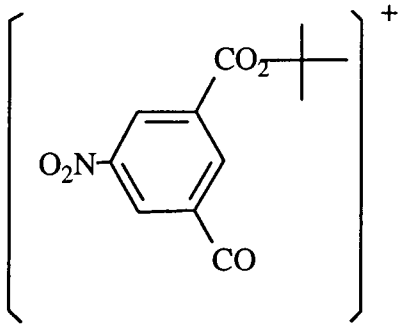
This material (V) was esterified by mixing with tert-butanol and recrystallising from ethanol to give a 74% yield of the diester (VI).

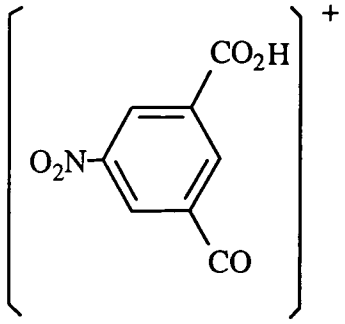


Mass = 323

Di-t-butyl-5-nitroisophthalate (VI)

A mass spectrum (CI) gave a highest mass of m/e 341 (M+18). No molecular ion was discernable in the EI spectrum but the following distinctive fragments were observed (Appendix 1.7):

m/e 250 

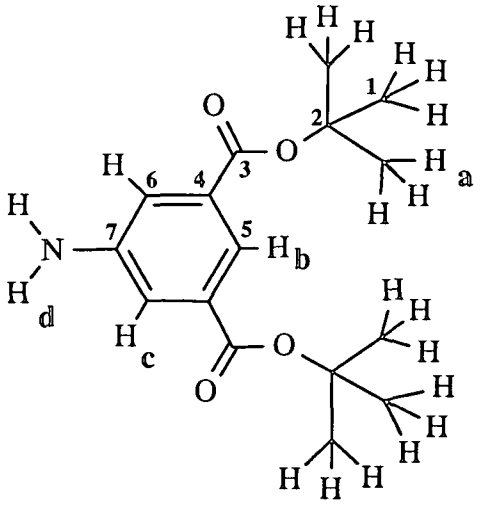
m/e 194 

m/e 57 $(CH_3)_3C^+$ (base peak)

An infra-red spectrum of the diester (VI) showed the following characteristic absorptions (Appendix 2.6).

3100cm^{-1} υ C—H (aromatic)	2990cm^{-1} υ C—H (aliphatic)
1730cm^{-1} υ C=O (ester)	1620cm^{-1} υ C=C
1540cm^{-1} υ N—O (asymmetric)	1355cm^{-1} υ N—O (symmetric)
840cm^{-1} υ C—N	

Reduction of the diester (VI) by heating with $SnCl_2.2H_2O$ / $NaBH_4$ in ethanol gave a reasonable yield (67%) of di-t-butyl-5-aminoisophthalate (VII). This was characterised by a combination of FTIR, MS, ^1H and ^{13}C NMR spectroscopy, summarized below:



Mass 293

Di-t-butyl-5-aminoisophthalate (VII)

The mass spectrum (EI) showed the parent ion at m/e 293, the base peak at m/e 181 $[H_2NC_6H_3(CO_2H)_2]^+$ and a characteristic fragment ion at m/e 57 $[(CH)_3C]^+$ (Appendix 1.8).

The FTIR spectrum showed the following characteristic absorptions (Appendix 2.7):

$3459cm^{-1}$ / $3373cm^{-1}$	υ N—H (primary amine)	$3230cm^{-1}$	υ C—H (aromatic)
$2970cm^{-1}$	υ C—H (aliphatic)	$1694cm^{-1}$	υ C=O (ester)

The ^1H NMR spectrum (399.952MHz, dmso-d6) is summarized below (Table 3.1 and Appendix 3.4).

Chemical Shifts	Integral	multiplicity	Assignment
1.50	18	s	a
5.63	2	s	d
7.30	2	d	c
7.55	1	t	b

Table 3.1

^1H NMR data for di-t-butyl-5-aminoisophthalate

The methyl protons (a) were immediately obvious as singlet, integrating as 18 protons, at 1.5ppm. The amine protons were assigned to the broad singlet at 5.63ppm. The remaining aromatic protons were assigned on the basis of their integrals. The aromatic protons showed coupling typical of meta aromatic protons (J=1.6Hz), the signal at 7.30ppm appearing as a doublet and that at 7.55ppm as a triplet.

The ^{13}C NMR spectrum (100.577MHz, dmso-d6) consisted of the expected 7 peaks and is summarised below (Table 3.2 and Appendix 4.4):

Chemical Shifts (ppm)	Assignments
27.72	1
80.58	2
116.78	5
117 .75	6
132.15	4
145.21	7
164.79	3

Table 3.2

^{13}C NMR data for di-t-butyl-5-aminoisophthalate

Tables of incremental shifts have been compiled for substituted benzenes [75] which allow the calculation of expected chemical shifts for aromatic carbon atoms. Carbons (4), (5), (6) and (7) were assigned on this basis. The remaining carbons were seen in the regions expected for aliphatic carbon (1), carbon adjacent to oxygen (2) and carbonyls (3).

3.2b Divergent growth

The suitability of the monomer (VII) and the feasibility of the suggested reiterative reaction sequence (figure 3.2) were assessed in the preparation of a model dendrimer branch utilizing a benzoyl chloride core (figure 3.3).

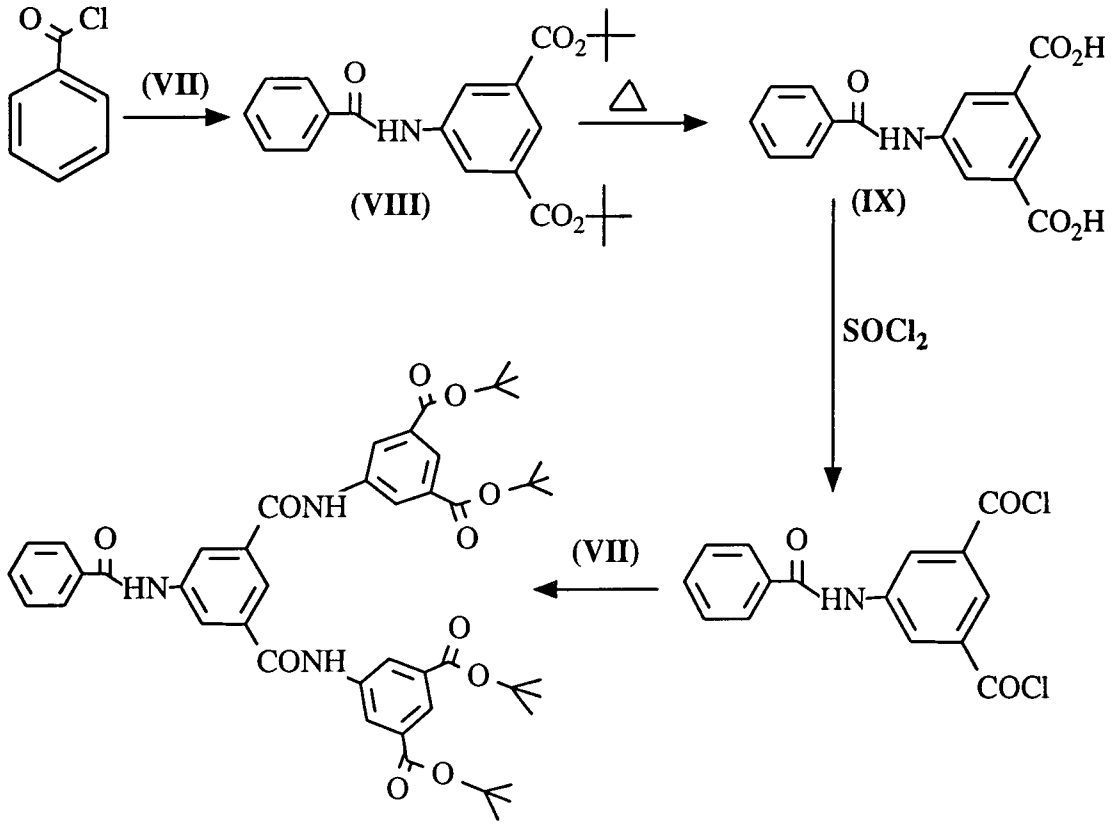
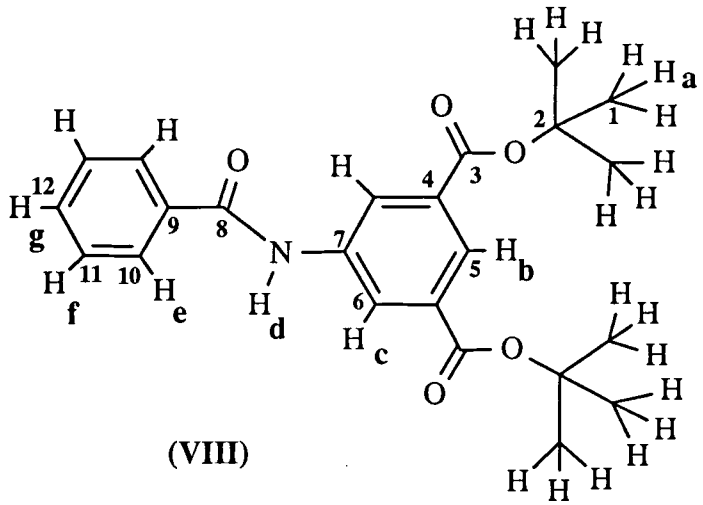


Figure 3.3 Dendritic growth from benzoyl chloride

The purpose of this exercise was to demonstrate a complete growth cycle, converting the end groups from ester functionalities, to carboxylic acid groups, then to acid chlorides followed by coupling to an amine to give an amide.

Di-t-butyl-5-aminoisophthalate (VII) was reacted with benzoyl chloride, using the conditions established in chapter 2, to give the amide (VIII) in excellent yield (99%).



(VIII)

Mass 397

The mass spectrum (EI) showed parent ion at m/e 397. The CI spectrum showed a M+18 peak at m/e 415 and the following distinctive fragments (Appendix 1.9):

359 303 105 ($PhCO^+$)

The FTIR spectrum showed the following characteristic absorptions (Appendix 2.8);

3317cm^{-1} υ N—H (amide)	3067cm^{-1} υ C—H (aromatic)
2977cm^{-1} υ C—H (aliphatic)	1718cm^{-1} υ C=O (ester)
1654cm^{-1} υ C=O (amide I)	1602cm^{-1} υ C=C
1544cm^{-1} δ N—H (amide II)	

The ^{1}H NMR spectrum (399.952 MHz, acetone-d6) is summarised below (Table 3.3 and Appendix 3.5).

Chemical shifts	integral	multiplicity	assignment
1.62	20	s	a
7.54	2	m	f
7.59	1	m	g
8.06	2	m	e
8.29	1	m	b
8.70	2	m	c
9.90	1	s	d

Table 3.3 ^{1}H NMR data for compound (VIII)

The ^{1}H NMR spectrum is consistent with the proposed structure. However, there is a small amount of impurity apparent at 1.57ppm which, combined with a slight error in the phasing, may account for the somewhat high integration valuefor the t-butyl groups (20 as opposed to 18). Protons (e), (f) and (g) were assigned on the basis of a comparison with the spectrum of benzanilide (I), whilst the remaining aromatic protons were assigned on the basis of their integrals.

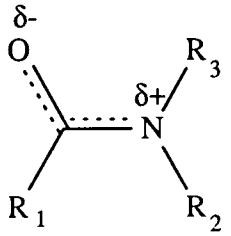
The ^{13}C NMR spectrum (100.577MHz, acetone-d6) is summarised below (Table 3.4 and Appendix 4.5).

Chemical shifts ppm	Assignment
28.23	1
81.98	2
125.29	6
125.38	
125.84	5
128.42	11
129.32	10
132.64	12
133.64	4
135.67	9
135.70	
140.63	7
140.72	
165.15	3
166.58	8
166.65	

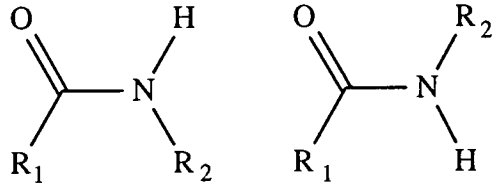
Table 3.4 ^{13}C NMR data for compound (VIII)

The carbon assignments were made by comparison with the ^{13}C NMR spectra of compounds (VII), (XI) and (XIII), described later. Some of the carbon nuclei seem to exist in two slightly different environments, an extra peak appearing 0.03 - 0.09ppm lower than the main signals for carbons (6), (7), (8) and (9). The intensity of these peaks is consistently less (about half) than that for the main signals for these

carbons, perhaps suggestive of the presence of a minor isomer. The particular carbons showing this effect all appear to be in the vicinity of the amide bond. N-monosubstituted amides are known to exist in two different conformations, resulting from restricted rotation about the C-N bond [78]. The atoms of the amide group are usually assumed to be coplanar, allowing maximum conjugation of the π electrons in the carbonyl bond and the non-bonding pair of the nitrogen atom.



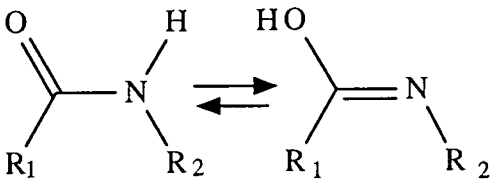
As a result of this partial double bond character, rotation about the C-N bond is slow, the energy barrier being in the order of 20 Kcal/mole. Both cis and trans conformers have been observed and are resolvable on the NMR time-scale.



cis *trans*

In general, the preferred conformation of N-substituted amides is the trans isomer except when steric constraints favour the cis isomer.

Further isomers are possible through amide-iminol tautomerism, although effects of this nature, if observable, would perhaps be manifest in the proton NMR spectrum.



In the particular case of compound (VIII), above, cis-trans isomerism alone is an unlikely explanation of the observed NMR phenomena. The cis isomer is inherently unlikely, due to steric constraints, unless accompanied by concomitant

rotations about the bonds connecting the phenyl rings to the amide group. Whilst this may reduce steric effects interaction of the π-systems of the phenyl rings with the amide group would be removed.

A thermogravimetric analysis of compound (VIII) showed a 28% weight loss, at 220^{0}C, corresponding to the loss of two tertiary butyl groups (as isobutene) from the molecule (figure 3.4).

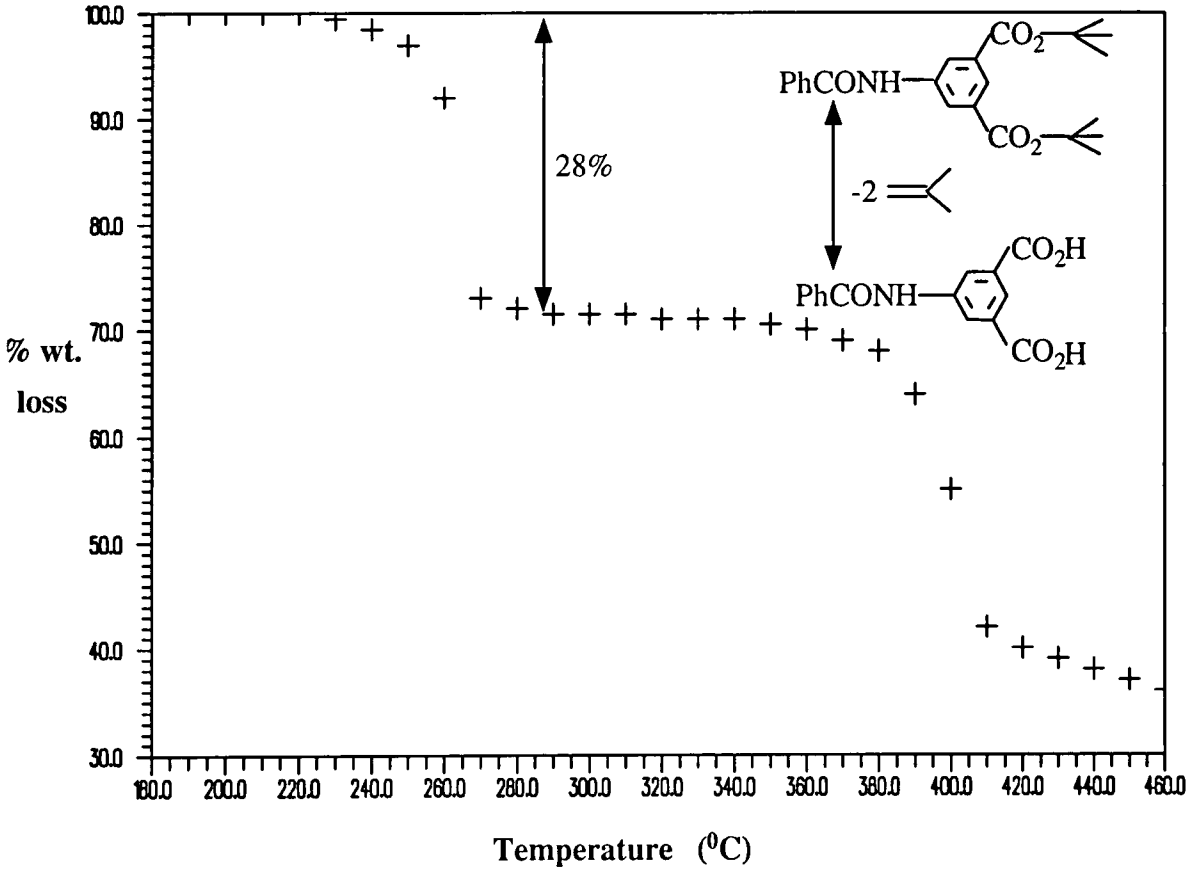


Figure 3.4 Thermogravimetric analysis of compound (VIII)

A sample of the carboxylic acid (IX) was prepared by heating the diester (VIII) to 200^{0}C.

The mass spectrum (EI) showed the parent ion at m/e 285 and characteristic fragments at m/e 268 (M-OH), 105 ($PhCO^+$) and 77 ($C_6H_5^+$). The CI spectrum

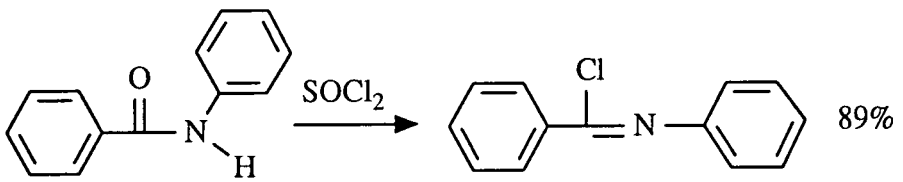
showed a M+18 peak at m/e 303 , a M+1 peak (m/e 286) and a characteristic fragment ion at m/e 105 ($PhCO^+$) (Appendix 1.10).

An infra-red spectrum showed the following characteristic absorptions (Appendix 2.9):

2000-3500cm^{-1}	υ O–H (carboxylic acid)	1720cm^{-1}	υ C=O (carboxylic acid)
1655cm^{-1}	υ C=O (amide I)	1605cm^{-1}	υ C=C
1550cm^{-1}	δ N–H (amide II)		

Elemental analysis, calculated for $C_{15}H_{11}NO_5$: C, 63.18; H, 3.86; N, 4.91%. Found : C, 63.25; H, 3.82; N, 4.74%.

Treatment of the carboxylic acid (IX) with either thionyl chloride or phosphorous pentachloride produced a red powder. Analysis by thin-layer chromatography showed it to be a complex mixture of coloured components. Separation and characterization of these components was not carried out. It is postulated that the problems encountered in the above reaction are due to reaction of the amide moiety with thionyl chloride. Secondary amides are known to react with a range of chlorinating agents including thionyl chloride, phosphorous pentachloride and phosphorous oxychloride (the Von Braun reaction) [76]. Benzamide, for instance, is known to react with thionyl chloride to give a chloroimine in good yield [77].



3.3 Experimental details

3.3a Synthesis of 5-nitroisophthaloyl dichloride (V)

Reagents : 5-nitroisophthalic acid, Aldrich 99%

phosphorous pentachloride, Aldrich 98%

Apparatus: 2dm^3 flange flask

Leibig condenser, fitted with $CaCl_2$ drying tube

gas scrubbing tower

Procedure

A $2dm^3$ flange flask was charged with 5-nitroisophthalic acid (113.0g, 535.5mmol) and phosphorous pentachloride (226g, 1084.5mmol). The mixture was heated on a water bath (approx. 70^0C) with occasional shaking. The flasks contents began to liquify, with vigorous evolution of gas, after approximately 30 mins. The resulting liquid was refluxed for 4hrs and phosphorous oxychloride removed under reduced pressure to give a white solid. This was recrystallised from petroleum ether (40-60), yield 126.16g, (95%).

3.3b Esterification of 5-nitroisophthaloyl dichloride (V)

Reagents : *tert*-butanol, Koch and Light

pyridine, Lancaster Synthesis, distilled from KOH

Apparatus: 500ml flange flask

Leibig condenser

nitrogen inlet

gas absorption tower

Procedure

A mixture of 5-nitroisophthaloyl dichloride (23.46g, 94.6mmol) and pyridine (200mls) was cooled to 0^0C, under a nitrogen atmosphere, and mixed using a vibromixer. Tert-butanol (50.58g, 683.5mmol) was added resulting in a very exothermic reaction, the solvent beginning to reflux after approx. 10 mins. The reaction was kept under control by continual cooling with an ice bath and mixing continued for 2.5 hrs. The mixture was left to stand overnight ,at room temperature, before removal of solvents by rotary evaporation. The remaining material was washed

with distilled water and recrystallised from ethanol to give a white solid (22.48g 74% yield).

3.3c Reduction of di-t-butyl-5-nitroisophthalate (VI)

Reagents : sodium borohydride, Aldrich >98%

stannous dichloride dihydrate, BDH >98%

Apparatus : 500ml 2-necked flask

100ml pressure equalising dropping funnel

Leibig condenser

nitrogen inlet

Procedure

A mixture of di-t-butyl-5-nitroisophthalate (VI) (10.0g, 30.96mmol), stannous dichloride dihydrate (31.77g, 140.77mmol) and ethanol (200mls) was placed in a 500ml 2-necked flask and the apparatus flushed with nitrogen. The mixture was heated to 65^0C and sodium borohydride solution (0.60g in 100mls ethanol) added dropwise over a period of 40 mins. The solution was maintained at 65-70^0C for 2.25hrs before allowing to cool to room temperature. The solution was poured into distilled water ($1dm^3$) and the resulting white precipitate removed by filtration and recrystallised from a mixture of dimethylacetamide and water. (6.12g, 67% yield).

3.3d Benzoylation of di-t-butyl-5-aminoisophthalate (VII)

Reagents : benzoyl chloride, Aldrich 99 %

pyridine, Lancaster Synthesis

dimethylacetamide, Lancaster Synthesis

Apparatus : 250ml flange flask

nitrogen inlet

vibromixer

gas absorption trap

Procedure

Di-t-butyl-5-aminoisophthalate (1.01g, 3.45mmol) was dissolved in a 50:50 mixture of dimethylacetamide and pyridine (100mls) and mixed, at 0^0C , using a vibromixer. Benzoyl chloride (0.50g, 3.56mmol) was added by syringe and mixing continued at room temperature for one hour. The solvents were reduced in volume, to about 10mls, by rotary evaporation and distilled water (200mls) added. The resulting white precipitate was removed by filtration and recrystallised from aqueous methanol. (yield 1.36g, 99%)

3.3e Deprotection of t-butyl esters

Apparatus : 50ml 2-necked flask

Leibig condenser

nitrogen inlet

Procedure

A sample of the protected ester (VIII) (0.36g) was heated to 200^0C, under a nitrogen atmosphere, using a silicone oil bath, for a period of 2 hrs. The solid was observed to melt in the region of 160^0C (oil bath temperature), followed by the evolution of gas and solidification at 200^0C. This gave 0.27g. of an off-white solid which was recrystallised from a methanol / water mixture (0.1g. recovered, 39% yield).

3.4 Discussion

The above reactions have demonstrated the usefulness of the monomer (VII), and in particular the utility of the tertiary butyl ester protecting group, in the repetitive chemistry needed for dendritic growth. Unfortunately dendrimer growth from acid chlorides is not a viable method due to the possible reaction of the amide bond with chlorinating agents. However, a first generation carboxylic acid or ester terminated dendrimer can be synthesized using the above method. Continued outward dendritic

growth from the terminal acid groups to higher generations could, perhaps, be achieved by the employment of suitable coupling agents. One such potentially useful coupling agent is triphenylphosphite which has been successfully employed (by Aharoni *et al*) to incorporate aromatic amides such as tris(p-carboxyphenyl)-1,3,5-benzene tricarboxamide (figure 1.14, chapter 1) into networks [51, 52].

CHAPTER FOUR

DENDRITIC POLYAMIDES

VIA

A CONVERGENT SYNTHESIS

4.1 Synthetic scheme

Due to the disappointing results obtained with the divergent approach, described in chapter three, the method was adapted to use essentially the same reagents and reactions but in a convergent scheme. The modified approach uses 5-nitroisophthaloyl dichloride as the basic building block. Reaction of this with an aromatic amine such as aniline or di-t-butyl-5-aminoisophthalate produces a nitro terminated 'wedge' or dendron. The nitro function is then reduced to an amine, as in the previous monomer synthesis. The new amine terminated dendron can then be reacted with a core molecule or with more nitroisophthaloyl chloride to produce a larger nitro terminated dendron as shown below (figure 4.1)

Since this work was started a very similar synthesis has appeared in the literature [44]. However, this differs in the use of a platinum catalysed hydrogenation of the nitro group in the reduction step. Yields are not reported.

4.2 Convergent synthesis

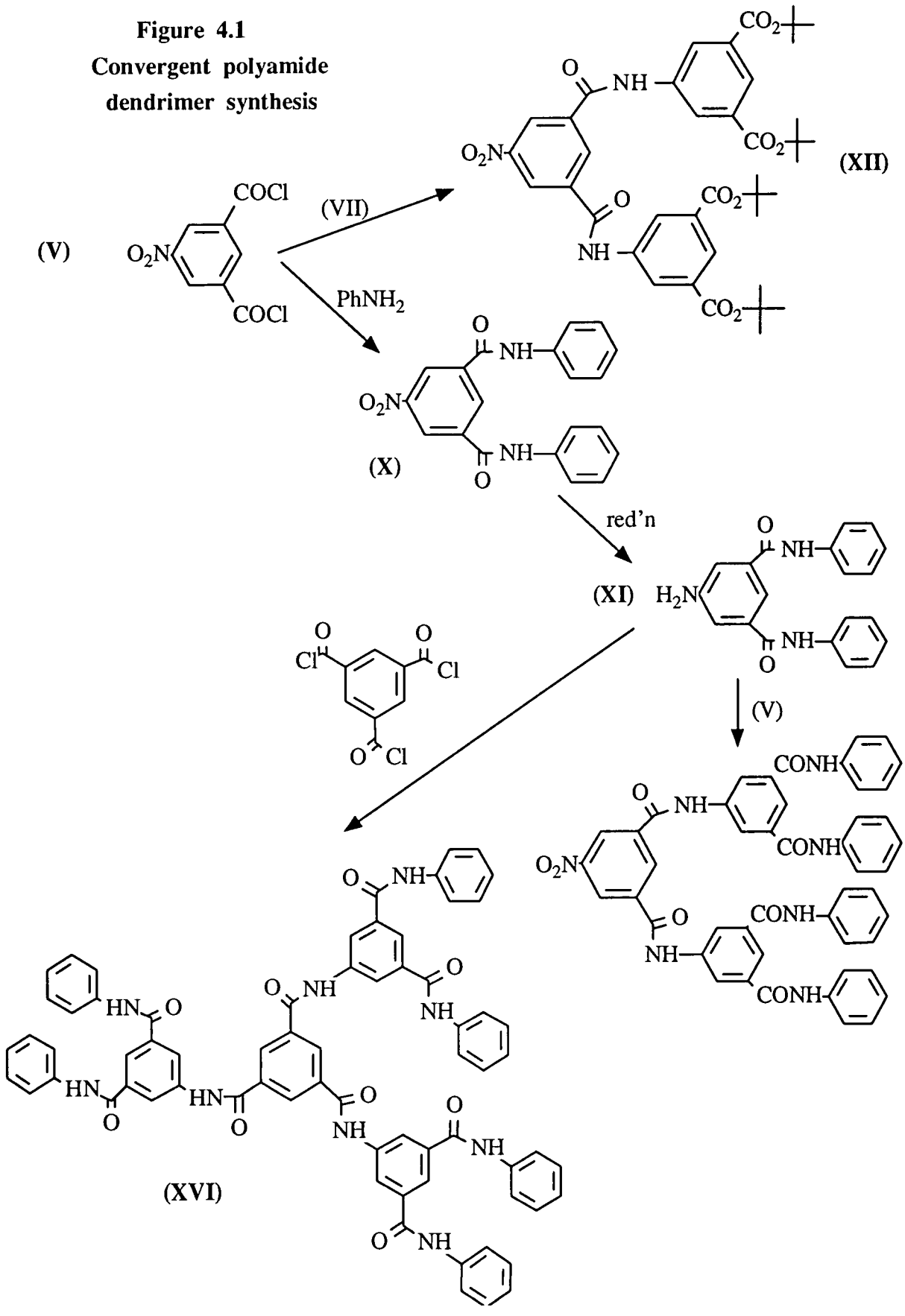
4.2a Synthesis of dendron 'wedges'

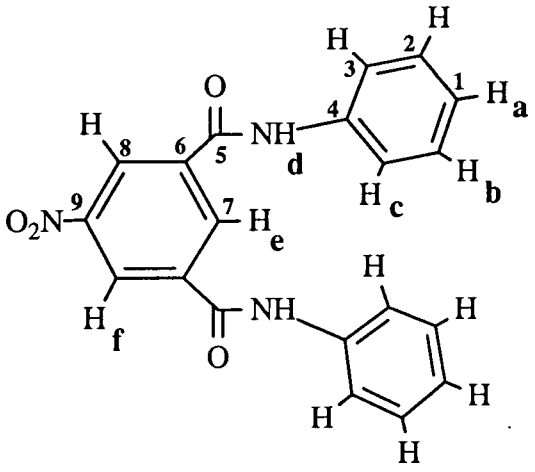
The starting material for the preparation of dendron 'wedges' was 5-nitroisophthaloyl chloride (V), prepared as for the divergent synthesis, described in chapter 3.

4.2a(i) N,N′-diphenyl-5-nitro-1,3-benzenedicarboxamide (X)

5-Nitroisophthaloyl chloride (V) was reacted with aniline, in the usual manner, to give the nitro terminated dendron N,N′-diphenyl-5-nitro-1,3-benzene-dicarboxamide (X) in good yield (84%).

Figure 4.1
Convergent polyamide dendrimer synthesis





Mass = 361

N,N′-diphenyl-5-nitro-1,3-benzenedicarboxamide (X)

The mass spectrum (EI) showed the parent ion at m/e 361 whilst the CI spectrum showed a M+1 peak at m/e 362 (Appendix 1.11).

Analysis by FTIR spectroscopy showed the following characteristic absorptions (Appendix 2.10):

$3273cm^{-1}$ υ N—H (amide)	$3081cm^{-1}$ υ C—H (aromatic)
$1657cm^{-1}$ υC=O (amide I)	$1599cm^{-1}$ υ C=C
$1531cm^{-1}$ δN—H (amide II)	$1500cm^{-1}$ υ N:-:O (asymmetric)
$1323cm^{-1}$ υN:-:O (symmetric)	

The ^{1}H NMR spectrum (400MHz, acetone-d6) is summarised below (Table 4.1 and Appendix 3.6):

Protons (a), (b) and (c) were assigned on the basis of their integrals and a comparison with the ^{1}H NMR spectrum of benzanilide (I), described in chapter 2. Protons (e) and (f) were distinguished with the aid of a ^{1}H / ^{13}C heteronuclear correlation spectrum (HETCOR), described below (Table 4.3 and Appendix 5.1). The splitting patterns familiar from the model compounds described in the previous chapters are seen for protons (a), (b) and (c). Three bond coupling between the adjacent protons (a) and (b) (J=7.6Hz) as well as protons (b) and (c) (J=8.4Hz) can be

Chemical Shifts (ppm)	Integral	Multiplicity	Assignment
7.17	2	m	a
7.40	4	m	b
7.86	4	m	c
8.96 8.97	3	m	f e
10.09	2	s	d

Table 4.1 ^{1}H NMR data
N,N′-diphenyl-5-nitro-1,3-benzenedicarboxamide (X)

seen. Four bond coupling is observed between protons (a) and (c) (J=1.2Hz). Although protons (e) and (f) are obviously split, through four bond coupling with each other, the signals overlap to give a complex multiplet.

The ^{13}C NMR spectrum (400MHz, acetone-d6) is summarized below (Table 4.2 and Appendix 4.6).

Chemical shifts ppm	Assignment
121.16 121.25	3
125.24	1
125.72	8
129.67	2
133.19	7
138.14	6
139.68 139.76	4
149.40	9
163.62 163.63	5

Table 4.2

^{13}C NMR data
N,N′-diphenyl-5-nitro-1,3-benzenedicarboxamide (X)

Carbons (1), (2) and (3) were assigned with the aid of a ^{1}H / ^{13}C HETCOR

spectrum (Table 4.3 and Appendix 5.1). Carbons (7) and (8) were distinguished by a combination of HETCOR and tables of chemical shifts [75]. The remaining carbons were assigned on the basis of their chemical shifts. Carbons (3), (4) and (5) each appeared as two signals. This is probably the same phenomenon as was observed for compound (VIII), described in chapter 3, and may be due to conformational effects of the amide bond.

Proton	*correlates with*	**Carbon**
a (7.17ppm)	.....	**1** (125.24ppm)
b (7.40ppm)	.....	**2** (129.67ppm)
c (7.86ppm)	.....	**3** (121.25ppm)
f (8.96ppm)	.....	**8** (125.72ppm)
e (8.97ppm)	.....	**7** (133.19ppm)

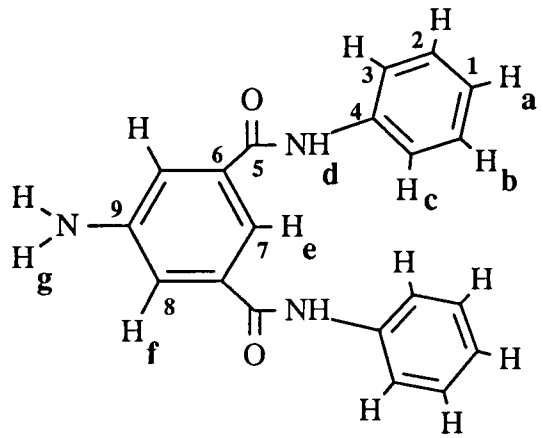
Table 4.3

Heteronuclear correlation data for compound (X)

Heteronuclear shift correlation (HETCOR) is one of a number of 2-D NMR methods that employ the technique of cross-polarization [79]. In the particular case of the proton / carbon-13 correlation experiment the observed carbon-13 signal is restricted to magnetization components transferred from protons. A signal in the spectrum therefore corresponds to a ^{13}C chemical shift on the F2 axis and a corresponding ^{1}H chemical shift on the F1 axis. This is particularly useful for the lower series dendritic systems described in this thesis as, having assigned the proton spectrum, very similar carbon environments can be distinguished with the aid of a HETCOR spectrum. As the observed signal is reliant upon the transfer of magnetization components from protons, quaternary carbons are, of course, not seen.

4.2a(ii) N,N′-diphenyl-5-amino-1,3-dicarboxamide (XI)

The nitro terminated dendron (X) was reduced using the sodium borohydride / stannous chloride system, described in chapter 3, to give the amine terminated dendron, N,N′-diphenyl-5-amino-1,3-dicarboxamide (XI), in reasonable yield (67%).



Mass = 331

N,N′-diphenyl-5-amino-1,3-dicarboxamide (XI)

The mass spectrum (EI) showed the parent ion at m/e 331, whilst the CI spectrum showed M + 18 and M + 1 peaks at m/e 349 and 332 respectively (Appendix 1.12).

Analysis by FTIR showed the following characteristic absorptions (Appendix 2.11):

$3422cm^{-1}$ / $3333cm^{-1}$	υ N–H (primary amine)	$3228cm^{-1}$	υ N–H (amide)
$3038cm^{-1}$	υ C–H (aromatic)	$1631cm^{-1}$	υ C=O (amide I)
$1594cm^{-1}$	υ C=C	$1534cm^{-1}$	δ N–H (amide II)

The ^1H spectrum (400MHz, dmso-d6) is summarised below (Table 4.4 and Appendix 3.7):

The amide protons (d) and the amine protons (g) were easily identified as the broad singlets at 10.25 and 5.60ppm respectively. The aromatic protons (a), (b) and (c) were assigned by comparison with the ^1H NMR spectrum of benzanilide (I),

Chemical Shifts (ppm)	Integral	Multiplicity	Assignment
5.60	1	s	g
7.09	2	m	a
7.29	2	m	f
7.35	4	m	b
7.64	1	m	e
7.78	4	m	c
10.25	2	s	d

Table 4.4

^{1}H NMR data for N,N′-diphenyl-5-amino-1,3-dicarboxamide (XI)

described in chapter 2. Protons (e) and (f) were assigned by a combination of their integrals and a comparison with the ^{1}H NMR spectrum of the aromatic amine (VII), described in chapter 3.

The ^{13}C spectrum (400MHz, dmso-d6) showed the expected 9 peaks and is summarised below (Table 4.5 and Appendix 4.7).

Chemical Shifts (ppm)	Assignment
114.06	7
115.83	8
120.39	3
123.75	1
128.74	2
136.25	6
139.29	4
149.02	9
166.08	5

Table 4.5

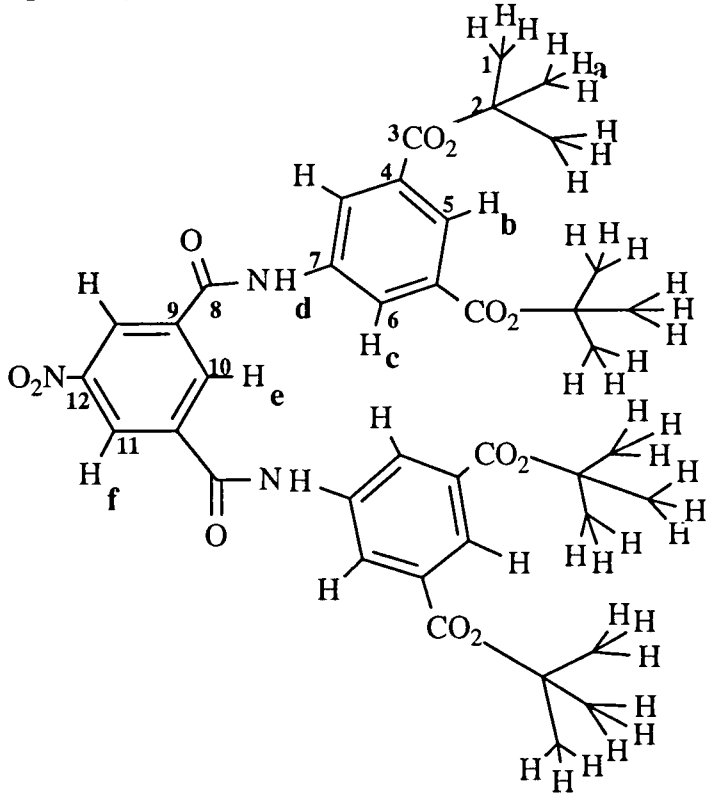
^{13}C NMR data for N,N′-diphenyl-5-amino-1,3-dicarboxamide (XI)

Carbons (1), (2), (3) and (5) were assigned by comparison with similar carbon

environments in compound (X), see above. Carbons (4) and (6) were assigned by comparison with the ^{13}C spectrum of compound (IV), described in chapter 2. Similarly, carbons (7), (8) and (9) were assigned on the basis of a comparison with similar carbons in compound (VII), described in chapter 3.

4.2a(iii) Adduct of 5-nitroisophthaloyl chloride (V) and di-t-butyl-5-aminoisophthalate (VII)

Ester functionalised dendrons were also prepared by the reaction of 5-nitroisophthaloyl chloride (V) with di-t-butyl-5-aminoisophthalate (VII).



(XII)

Mass spectroscopy failed to show a mass peak using EI, CI or DCI, the base peak in the EI spectrum being simply due to the $(CH_3)_3C^+$ fragment.

An analysis by FTIR showed the following characteristic peaks (Appendix 2.12):

3316cm^{-1} υ N—H (amide) 3091cm^{-1} υ C—H (aromatic)

2978cm^{-1} υ C—H (aliphatic) 1721cm^{-1} υ C=O (ester)

1693cm^{-1} υ C=O (amide I) 1607cm^{-1} υ C=C

1575cm^{-1} δ N—H (amide II) 1539cm^{-1} υ N=O (asymmetric)

1344cm^{-1} υ N=O (symmetric)

The ^{1}H NMR spectrum (400Hz, acetone d6) is summarised below (Table 4.6 and Appendix 3.8):

Chemical shifts (ppm)	Integral	Multiplicity	Assignment
1.62	38	s	a
8.30	2	t	b
8.67	4	d	c
9.02	2	d	f
9.12	1	t	e
10.46	1	s	d

Table 4.6 ^{1}H NMR for compound (XII)

The tertiary butyl and amide protons were immediately obvious at 1.62 and 10.46ppm respectively, although the integration is slightly high for the butyl groups (38 instead of 36) and slightly low for the amide protons (1 as opposed to 2), probably for similar reasons to those discussed for compound (VIII) earlier. Protons (b) and (c) were apparent at similar chemical shifts to the equivalent protons in compound (VIII), described in chapter 3. Protons (e) and (f) were distinguished on the basis of their integrals. The expected splitting patterns are seen due to four bond coupling between the aromatic protons (b) and (c) (J=1.6Hz) as well as (e) and (f) (J=1.6Hz). Proton (e) is expected to be seen as a triplet but is not quite resolved in this spectrum.

The ^{13}C NMR spectrum (400MHz, acetone d6) is summarised below (Table 4.7 and Appendix 4.8)

Chemical shift ppm	Assignment
28.25	1
82.12	2
125.50 125.59	6
126.12	11
126.45	5
133.43	4
133.74	10
137.45 137.48	9
139.95 140.04	7
149.36	12
163.78 163.85	8
164.97	3

Table 4.7

^{13}C NMR data for compound (XII)

The carbons of the tertiary butyl groups (1 and 2) were immediately apparent at 28.25 and 82.12ppm. The aromatic carbons (5), (6), (10) and (11) were assigned with the aid of a ^{1}H / ^{13}C HETCOR spectrum (Table 4.8 and Appendix 5.2). Carbons (7), (9) and (12) were assigned by comparison with the chemical shifts of similar carbon environments in compound (X), described earlier. The carbonyl carbons of the ester (3) and amide (8) moieties were distinguished by comparison with the chemical shifts of the carbonyl carbons in compounds (X) and (VII) respectively. As was commented upon earlier, for compounds (VIII) and (X) the carbons in the vicinity of the amide function (6), (7), (8) and (9) give rise to two signals each in the carbon-13 spectrum.

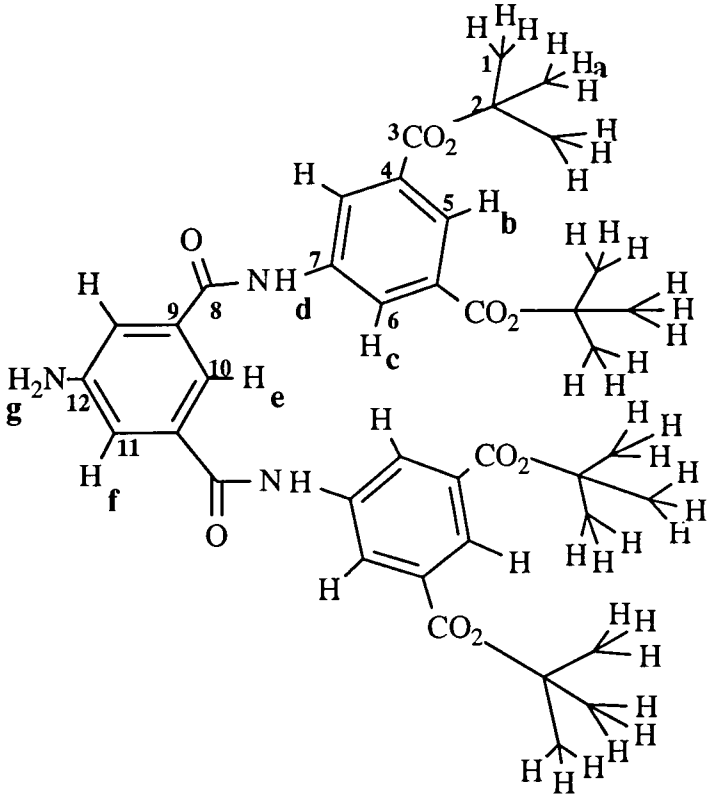
The signals at 125.50 and 125.59ppm are not distinguished by HETCOR which is supportive of the view that they are both due to the same carbon (6), but in different conformers, and so couple to the same proton (c).

Proton	*correlates with*	Carbon
a (1.62ppm)	.....	**1** (28.25ppm)
b (8.30ppm)	.....	**5** (126.45ppm)
c (8.67ppm)	.....	**6** (125.50ppm) / (125.59ppm)
f (9.02ppm)	.....	**11** (126.12ppm)
e (9.12ppm)	.....	**10** (133.74ppm)

Table 4.8
Heteronuclear correlation data for compound (XII)

4.2a(iv) Product from the reduction of compound (XII)

The nitro terminated 'wedge' (XII), described above, was reduced using the usual sodium borohydride / stannous dichloride system, described earlier, to give the corresponding amine (XIII) in reasonable yield (52%).



(XIII)

The mass spectrum failed to show a parent ion using either EI or CI.

The FTIR spectrum showed the following characteristic absorptions (Appendix 2.13):

$3463cm^{-1}$, $3378cm^{-1}$ } υ N–H (primary amine)

$3307cm^{-1}$ υ N—H (amide)

$3077cm^{-1}$ υ C–H (aromatic)

$2979cm^{-1}$ υ C—H (aliphatic)

$1718cm^{-1}$ υ C=O (ester)

$1660cm^{-1}$ υ C=O (amide I)

$1605cm^{-1}$ υ C=C

$1560cm^{-1}$ δ N—H (amide II)

The ^{1}H NMR spectrum is summarised below (Table 4.9 and Appendix 3.9):

Chemical shift ppm	Integral	Multiplicity	Assignment
1.56	36	s	a
5.68	2	s	g
7.32	2	d	f
7.70	1	t	e
8.12	2	t	b
8.63	4	d	c
10.65	2	s	d

Table 4.9

^{1}H NMR data for compound (XIII)

The protons of the tertiary butyl groups (a) were readily apparent as a singlet, integrating as 36 protons, at 1.56ppm. The broad singlets, each integrating as 2 protons, at 5.68 and 10.65ppm were attributable to the amine and amide protons respectively. The aromatic protons were assigned using a combination of their multiplicities and integrals. Protons (b) and (e) were both seen as triplets due to 4-bond coupling with protons (c) and (f) respectively (both seen as doublets, J = 1.6Hz).

The ^{13}C NMR spectrum is summarised below (Table 4.10 and Appendix 4.9)

Chemical shifts ppm	Assignment
27.72	1
81.40	2
114.03	10
116.01	11
124.01	5 + 6 ?
132.07	4
135.56	9
139.96	7
149.09	12
164.07	3
166.24	8

Table 4.10

^{13}C data for compound (XIII)

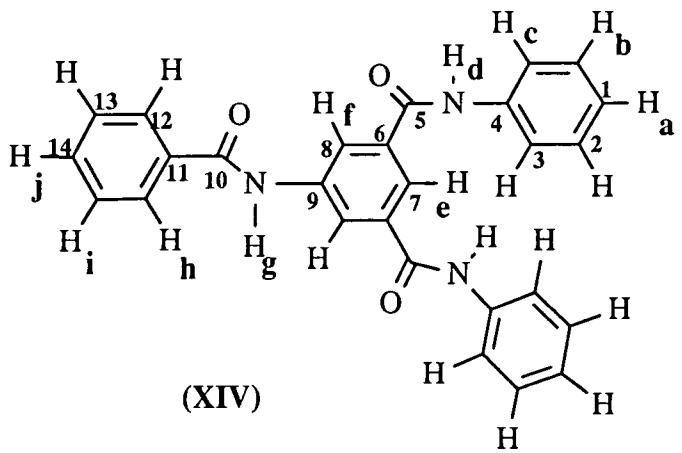
The carbonyl carbons (3) and (8) were tentatively assigned on the basis of their intensities, by comparison with related systems the 4 ester carbonyl carbons were expected to give rise to a more intense signal than the 2 amide carbonyl carbons. The assignments for carbons (1), (2), (4), (7) and (9) were made by comparison with similar carbon environments in compound (VIII), described in chapter 3. Similarly carbons (10), (11) and (12) were assigned on the basis of a comparison with compound (XI), described earlier. A curious feature of this spectrum is that only one signal is seen between 120 and 130ppm, the region in which carbons (5) and (6) were expected to appear. This may be due to both carbons fortuitously appearing with the same chemical shift and indeed the signal at 124.01ppm does appear to be more intense than would be expected for just 4 carbons.

4.2b coupling to initiator cores

The amine terminated dendron N,N′-diphenyl-5-amino-1,3-dicarboxamide (XI) was coupled to benzoyl, isophthaloyl and trimesoyl chlorides to create the model dendritic systems (XIV), (XV) and (XVI). The products were characterized by a

combination of MS, FTIR and ^{1}H ^{13}C NMR spectroscopy described below:

4.2b(i) Product of N,N′-diphenyl-5-amino-1,3-dicarboxamide (XI) plus benzoyl chloride



(XIV)

Mass = 435

The mass spectrum (CI) showed a M + 1 peak at m/e 436. The EI spectrum showed the parent ion at m/e 435 and characteristic fragmentations at m/e 343 (M - PhNH) and m/e 105 ($PhCO^{+}$) (Appendix 1.13).

A FTIR spectrum showed the following characteristic absorptions (Appendix 2.14):

3285cm^{-1}	υ N—H (amide)	3057cm^{-1}	υ C—H (aromatic)
1654cm^{-1}	υ C=O (amide I)	1594cm^{-1}	υ C=C
1539cm^{-1}	δ N—H (amide II)		

The ^{1}H NMR spectrum (400MHz, dmso d6) is summarised below (Table 4.11 and Appendix 3.10):

The ^{1}H NMR data agrees well with that obtained for benzanilide (I), described in chapter 2, protons (a), (b), (c), (h), (i) and (j) being assigned on the basis of their chemical shifts, compared to similar protons in compound (I), and their integrals. The remaining aromatic protons (e and f) and the amide protons (d and g) were

Chemical shifts (ppm)	Integral	Multiplicity	Assignment
7.12	2	t	a
7.38	4	t	b
7.55	3	t	i
7.62		t	j
7.81	4	d	c
8.04	2	d	h
8.28	1	s	e
8.56	2	s	f
10.48	2	s	d
10.67	1	s	g

Table 4.11 ^{1}H NMR data for compound (XIV)

distinguished on the basis of their integrals. The signals in this spectrum are somewhat broader than usual and hence the expected four bond coupling is not seen, for example, both protons (e) and (f) are seen as singlets rather than the expected triplet and doublet. The pattern of ordinary three bond coupling is, however, consistent for the proposed structure. Proton (a) is seen as a triplet through coupling with the two adjacent protons (b) (J=7.2Hz). Proton (b) is coupled to both proton (a) and proton (c), seen as a doublet (J=8.0Hz). A similar pattern of splitting is seen for protons (h) and (i) (J=8.4Hz) and protons (i) and (j) (J=7.2Hz).

The ^{13}C NMR spectrum (400MHz, dmso-d6) showed the expected 14 peaks and is summarised below (Table 4.12 and Appendix 4.10):

Carbons (1), (2), (3), (8) and (12) were assigned with the aid of a ^{1}H / ^{13}C HETCOR spectrum (Table 4.13 and Appendix 5.3). The signal at 128.52ppm was assigned to carbon (13), a value typical of meta aromatic carbons. Carbons (4), (6), (9) and (11) were assigned on the basis of comparisons with the ^{13}C NMR spectra of compounds (I) and (IV).

Chemical shifts (ppm)	Assignment
120.37	3
121.73	7
122.61	8
123.87	1
127.76	12
128.52	13
128.73	2
131.94	14
134.39	11
135.87	6
139.06	4
139.59	9
165.19	5
165.84	10

Table 4.12

^{13}C NMR data for compound (XIV)

Proton	*correlates with*	Carbon
a (7.12ppm)	.....	**1** (123.87ppm)
b (7.38ppm)	.....	**2** (128.73ppm)
i (7.55ppm)	.....	**13** (128.52ppm)
j (7.62ppm)	.....	not seen (14?)
c (7.81ppm)	.....	**3** (120.37ppm)
h (8.04ppm)	.....	**12** (127.76ppm)
e (8.28ppm)	.....	not seen (7?)
f (8.56ppm)	.....	**8** (122.61ppm)

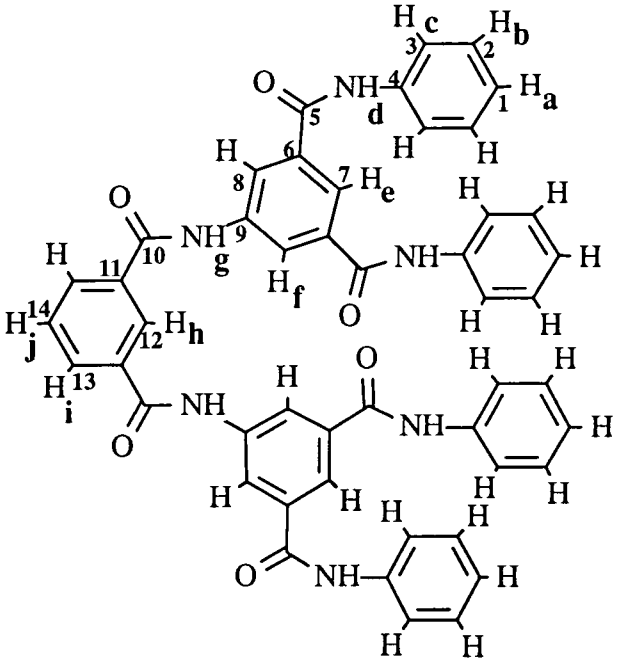
Table 4.13

Heteronuclear correlation data for compound (XIV)

The intensity of a signal in the HETCOR spectrum is dependant upon both the relative abundance of a particular carbon environment and the degree of polarization transfer from the attached protons. Hence carbons (7) and (14) in compound (XIV)

are expected to give rise to low intensity signals in the HETCOR spectrum as they correspond to only one carbon each. The data from a two-dimensional experiment may be presented as a stacked plot or, more usually (as in this case), by taking a section through the plot, as a contour map. Low intensity signals, such as those for carbons (7) and (14) above, may be 'missed' depending upon the threshold level at which the section is taken through the spectrum.

4.2b(ii) Product of N,N′-diphenyl-5-amino-1,3-dicarboxamide (XI) plus isophthaloyl chloride



(XV)

No parent ion was detectable in the mass spectrum using either EI, CI or DCI.

FTIR showed the following characteristic absorptions (Appendix 2.15):

$3287cm^{-1}$ υ N—H (amide)	$3061cm^{-1}$ υ C—H (aromatic)
$1655cm^{-1}$ υ C=O (amide I)	$1596cm^{-1}$ υ C–C
$1542cm^{-1}$ δ N—H (amide II)	

The ^{1}H NMR spectrum (400MHz, dmso-d6) is summarized below (Table 4.14

and Appendix 3.11):

Chemical shifts (ppm)	Multiplicity	Integral	Assignment
7.13	m	4	a
7.39	m	8	b
7.79	t	1	j
7.83	m	8	c
8.29	d , d	2	i
8.33	m	2	e
8.62	d	4	f
8.74	m	1	h
10.51	s	4	d
10.89	s	2	g

Table 4.14

^{1}H NMR data for compound (XV)

The above data is consistent with the proposed structure and is in good agreement with the model compounds (III) and (XIV), described earlier. The protons can be unambiguously assigned by reference to their chemical shifts (compared to compounds (III) and (XIV)) in combination with their integrals and multiplicities. The usual pattern of multiplets is seen for protons (a), (b) and (c). Proton (a) is seen as a multiplet (probably in actual fact a 'triplet of triplets' which is not quite fully resolved) through coupling to the two adjacent meta protons (b) (J=7.6Hz) plus 4 bond coupling to the two ortho protons (c) (J=1.2Hz). Similarly proton (c) approximates to a 'doublet of doublets' through coupling with the adjacent proton (b) (J=7.6Hz) and further long range coupling with proton (a) (J=1.2Hz). Proton (j), as expected, is seen as a triplet (J=8.0Hz) due to coupling with the two adjacent protons (i), whereas proton (i) is also split by 4 bond coupling to proton (h) (J=1.6Hz) to give a 'doublet of doublets'. Protons (e), (f) and (h) are only split by long range coupling to protons (f) (J=1.2Hz), (e) (J=1.2Hz) and (i) (J=1.6Hz), respectively.

The ^{13}C NMR spectrum (400MHz, dmso-d6) is summarised below (Table 4.15 and Appendix 4.11):

Chemical shifts ppm	Assignment
120.42	3
121.92	7
122.68	8
123.94	1
127.33	12
128.77	2
128.94	14
131.11	13
134.80	11
135.97	6
139.07	4
139.53	9
165.19	5
165.34	10

Table 4.15

^{13}C data for compound (XV)

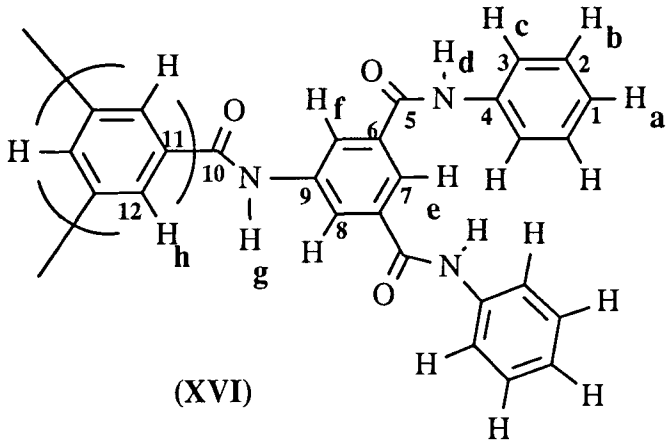
The aromatic carbons (1), (2), (3), (7), (8), (12), (13) and (14) were assigned with the aid of a ^{1}H / ^{13}C HETCOR spectrum (Table 4.16 and Appendix 5.4). The carbonyl carbons were distinguished on the basis of their intensities, the signal due to the four outermost carbonyl carbons (5) being expected to give rise to a signal about twice the intensity of that for the two inner carbonyl carbons (10). The remaining quaternary carbons were assigned on the basis of a comparison with similar carbon environments in compounds (III) and (XIV). These assignments were to some extent confirmed by the relative intensities of the signals, the signals for carbons (4) and (6) being expected to be approximately twice as intense as those for carbons (9) and (11) respectively.

Proton	*correlates with*	Carbon
a (7.13ppm)	.....	**1** (123.94ppm)
b (7.39ppm)	.....	**2** (128.77ppm)
j (7.79ppm)	.....	**14** (128.94ppm)
c (7.83ppm)	.....	**3** (120.42ppm)
i (8.29ppm)	.....	**13** (131.11ppm)
e (8.33ppm)	.....	**7** (121.92ppm)
f (8.62ppm)	.....	**8** (122.68ppm)
h (8.74ppm)	.....	**12** (127.33ppm)

Table 4.16

Heteronuclear correlation data for compound (XV)

4.2b(iii) Product of N,N′-diphenyl-5-amino-1,3-dicarboxamide (XI) plus trimesoyl chloride



(XVI)

No parent ion was apparent in the mass spectrum (EI or CI)

The FTIR spectrum showed the following characteristic absorptions (Appendix 2.16):

3300cm^{-1} υ N—H (amide)	3064cm^{-1} υ C—H (aromatic)
1659cm^{-1} υ C=O (amide I)	1597cm^{-1} υ C=C
1538cm^{-1} δ N—H (amide II)	

The ^{1}H NMR spectrum (400MHz, dmso-d6) is summarised below (Table 4.17 and Appendix 3.12):

Chemical shifts (ppm)	Multiplicity	Integral	Assignment
7.12	t	6	a
7.38	m	12	b
7.80	d	12	c
8.31	s	3	e
8.57	s	6	f
8.82	s	3	h
10.50	s	6	d
11.04	s	3	g

Table 4.17

^{1}H NMR data for compound (XVI)

The ^{1}H NMR spectrum agrees well with the proposed structure and is in good agreement with the model compounds (IV) and (XIV). Protons (a), (b) and (c) were assigned by comparison with similar proton environments in compound (IV), whilst protons (e), (f) and (h) were assigned by comparison with compound (XIV). A small amount of impurity was seen giving rise to signals in the region 8.3 to 9.0ppm. The pattern of splittings is consistent with the proposed structure, although fine splitting due to four bond coupling is not resolved in this spectrum. Hence, proton (a) is seen as a triplet coupled to the two adjacent protons (b) (J=8.0Hz), whilst proton (c) is seen as a doublet through coupling with proton (b) (J=8.0Hz).

The ^{13}C NMR spectrum (400MHz, dmso-d6) is summarised below (Table 4.18 and Appendix 4.12)

Carbons (1), (2), (3) and (8) were assigned with the aid of a ^{1}H / ^{13}C HETCOR spectrum (Table 4.19 and Appendix 5.5). The remaining non-quaternary carbon atoms (7 and 8) were assigned by comparison with the chemical shifts of similar carbon

Chemical shifts (ppm)	Assignment
120.53	3
122.19	7
122.86	8
124.09	1
128.89	2
131.63	12
135.33	11
136.01	6
139.08	4
139.41	9
164.60	5
165.23	10

Table 4.18

^{13}C NMR data for compound (XVI)

environments in the model compounds (IV) and (XIV). The quaternary carbons were tentatively assigned on the basis of a comparison with the model compounds (IV) and (XIV) but distinguishing between similar carbon environments on the grounds of their intensities.

Proton	*correlates with*	Carbon
a (7.16ppm)	.....	**1** (124.13ppm)
b (7.41ppm)	.....	**2** (128.90ppm)
c (7.83ppm)	.....	**3** (120.57ppm)
e (8.35ppm)	.....	not seen (7?)
f (8.61ppm)	.....	**8** (122.91ppm)
h (8.86ppm)	.....	not seen (12?)

Table 4.19

Heteronuclear correlation data for compound (XVI)

The low intensity signals assigned to carbons (7) and (12), arising from three carbons each, are not seen in the HETCOR spectrum, probably for the same reasons as discussed for compound (XIV) earlier.

4.3 Experimental details

4.3a Synthesis of N,N′-diphenyl-5-nitro-1,3-benzenedicarboxamide (X)

Reagents : aniline, Aldrich 99%, distilled under a nitrogen atmosphere

pyridine, Lancaster Synthesis

Apparatus : $2dm^3$ flange flask

Leibig condenser

nitrogen inlet

vibromixer

gas scrubbing tower

Procedure

5-Nitroisophthaloyl dichloride (166.0g, 669.4mmol) and pyridine (750mls) were placed in a $2dm^3$ flange flask fitted with a condenser, nitrogen inlet vibromixer and gas outlet attached to an aqueuos alkaline filled scrubbing tower for removal of HCl. The mixture was cooled to 0^0C and aniline (125mls, 1357.5mmols) added by syringe. Mixing was continued, at 0^0C, for 1hr and a further 17.5 hrs at room temperature. The solvent was removed by rotary evaporation and the resulting brown oil washed with water and hot methanol, to give a white solid. The white solid was recrystallised from a mixture of acetone and petroleum ether (40-60) to give N,N′-diphenyl-5-nitro-1,3--benzenedicarboxamide (X)(202.43g, 84% yield).

4.3(b) Reduction of N,N′-diphenyl-5-nitro-1,3-benzenedicarboxamide

Reagents : sodium borohydride, Aldrich >98%

$SnCl_2.2H_2O$, BDH .97%

Apparatus : 50ml flange flask

Leibig condenser

nitrogen inlet

vibromixer

Procedure

N,N′-Diphenyl-5-nitro-1,3-benzenedicarboxamide (1.0g, 2.77mmol) and ethanol were placed in a 50ml flange flask. Mixing was effected by means of a vibromixer and the mixture heated to 70^0C. Stannous dichloride dihydrate (3.16g, 3.16mmol) was added and heating continued for 10 minutes before the addition of sodium borohydride (0.05g, 1.32mmol in 10 ml ethanol) dropwise over a period of 6 mins. Heating / mixing was continued for 5.5 hrs. The solution was allowed to cool and poured into distilled water and the resulting white precipitate recovered by centrifugation (0.98g). Recrystallization from aqueous methanol gave N,N′-diphenyl-5-amino-1,3-benzene-dicarboxamide as a white solid (0.62g, 67% yield).

4.3(c) General procedure for the coupling of amines to initiator cores

Reagents : pyridine, Lancaster Synthesis

dimethylacetamide, Lancaster Synthesis

benzoyl chloride, Aldrich 99%

isophthaloyl dichloride, Aldrich 98%

terephthaloyl dichloride, Aldrich 99%

trimesoyl trichloride, as prepared (2.4b above)

Apparatus : 250 ml flange flask

Leibig condenser

nitrogen inlet

vibromixer

Procedure

In a typical experiment a mixture of benzoyl chloride (0.50g, 3.56mmol), pyridine (50mls) and dimethylacetamide (50mls) was cooled to 0^0C, under a nitrogen

atmosphere. A solution of N,N′-diphenyl-5-amino-1,3-benzenedicarboxamide (1.00g, 3.02mmol) in dimethylacetamide (10mls) was added dropwise by syringe. Mixing was continued at 0^0C for 1.5hrs then at room temperature for 16hrs. Removal of the solvents produced a brown oil which was washed with water and recrystallized from ethanol to give compound (XIV) as a white solid (0.55g, 43% yield).

4.4 Discussion

The work outlined in this chapter has demonstrated the general utility of the convergent approach to dendrimer synthesis. Two types of dendron 'wedges' have been synthesized (compounds XI and XIII), which allows aryl, ester or acid (through pyrolysis of the ester) terminated dendrimers to be created. Coupling of these 'wedges' to a core molecule has been successfully demonstrated, with compound (XI), to give uni, di and tri-directional second generation dendrimers (compounds (XIV), (XV) and (XVI)). A drawback with this method, at present, appears to be the reduction of nitro terminated 'wedges' to the corresponding amines. Although it is thought that this step is a high yield process, the recovery of the product from the resulting solution of tin salts is problematical. Further work may circumvent these problems, however, other workers, as mentioned earlier, have opted for a platinum catalysed hydrogenation [44]. Another possibility is the employment of a protected amine, as is often encountered in peptide synthesis. Amino groups have been successfully masked in the form of pthalimido groups during peptide synthesis [80]. Deprotection of the phthalimido group can be carried out by reaction with hydrazine [81], hydrazine hydrate [80] or phenylhydrazine [82]. The amine function of 5-aminoisophthalic acid is known to react with phthalic anhydride [83] to give a protected amine which has been used in the synthesis of aromatic polyamides. Similar techniques could be employed in the synthesis of dendron 'wedges' as shown below (figure 4.2).

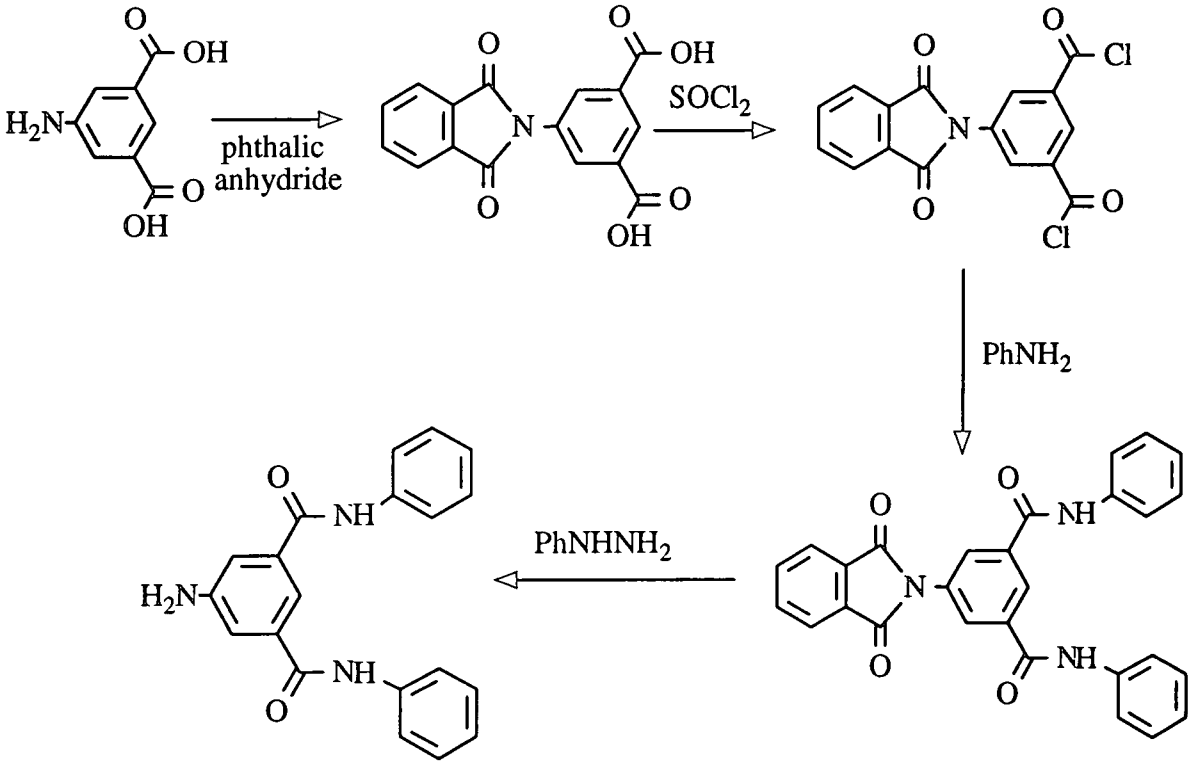


Figure 4.2 Use of amine protecting groups in dendron 'wedge' synthesis

CHAPTER FIVE

SUMMARY

AND

SUGGESTIONS FOR FURTHER WORK

5.1 Conclusions

The work presented here has explored the viability of some approaches to the synthesis of dendritic polymers. The utility of the coupling reaction between aromatic acid chlorides and aromatic amines was demonstrated, in chapter two, in the synthesis of some useful model compounds, which were subsequently used to aid characterization of higher dendritic systems. The work detailed in chapter three not only highlighted some of the problems encountered in the use of acid chlorides within a divergent methodology but also demonstrated the efficacy of the t-butyl ester moiety as a protecting group. These problems were circumvented by the adoption of the convergent approach, described in chapter four, which was used in the successful synthesis of uni, di and tri-directional, second generation, dendrimers (compounds (XIV), (XV) and (XVI)). That these compounds can, in fact, be regarded as dendrimers is readily apparent if they are decribed using the dendrimer terminology discussed in chapter one. For instance, compound (XVI) is described, using this terminology, below (figure5.1):

Indeed in this context the model compounds (I), (III) and (IV), described in chapter 2, can be seen as the first generation members of the corresponding series of uni, di and tri-directional dendrimers.

5.2 Suggestions for further work

Using the reactions described, in this thesis, together with a convergent methodology it should be possible to build up a series of dendritic polyamides based on mono, di and trifunctional cores. However, if the targets of reasonable quantities of material and higher generation dendrimers are to be realized, most of the reactions described above will require optimization. Nevertheless, the work presented here

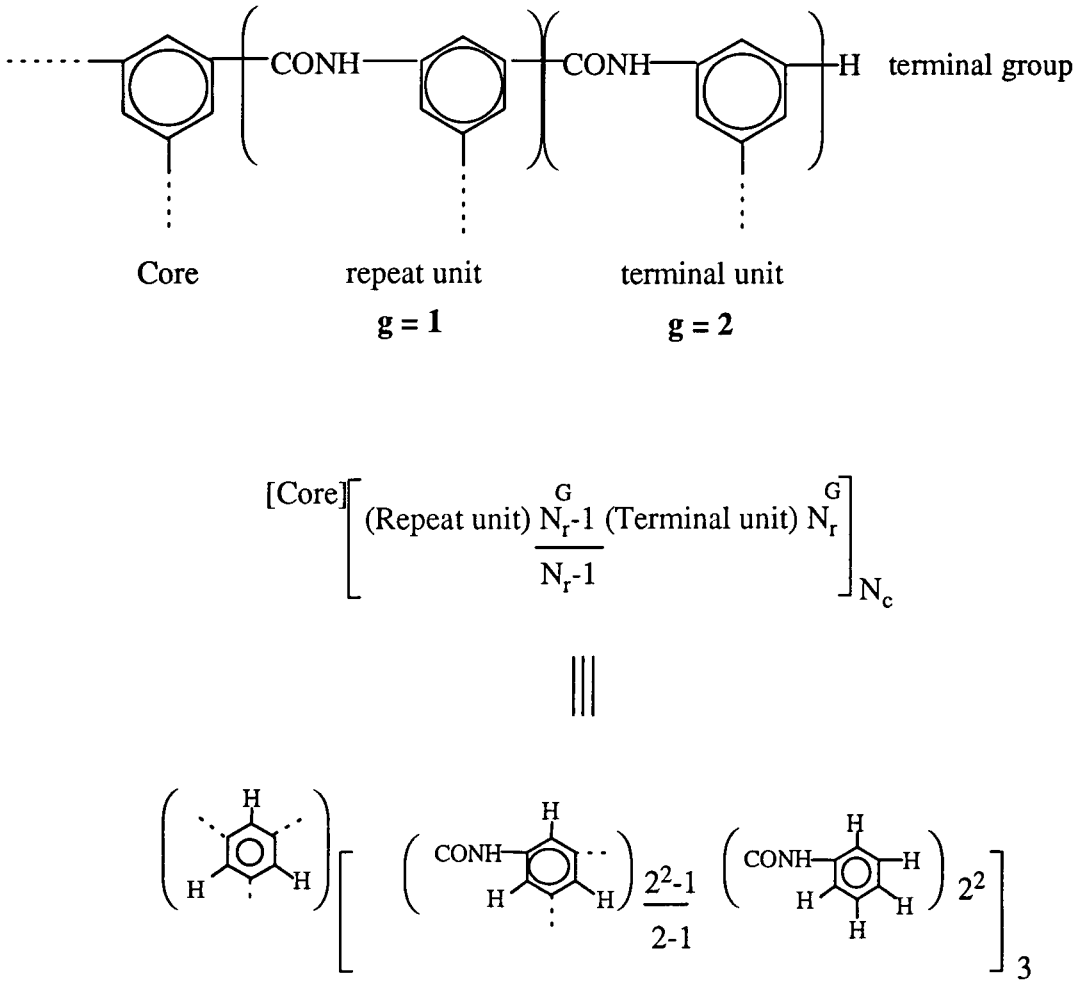


Figure 5.1 Dendrimer terminology of compound (XVI)

provides a basis for the synthesis of at least nine different series of dendritic polyamides, utilizing three different core molecules and the three potential terminal units (figure 5.2).

The employment of a variety of different anilines, as the terminal unit, could increase the variety of potential dendrimers still further. One such alternative is the incorporation of fluoroaniline into the outer layer of the dendrimer, which presents the possibility of synthesizing dendrimers with essentially fluorinated surfaces (figure 5.3).

The range of possible architectures, accessible from the present system, could

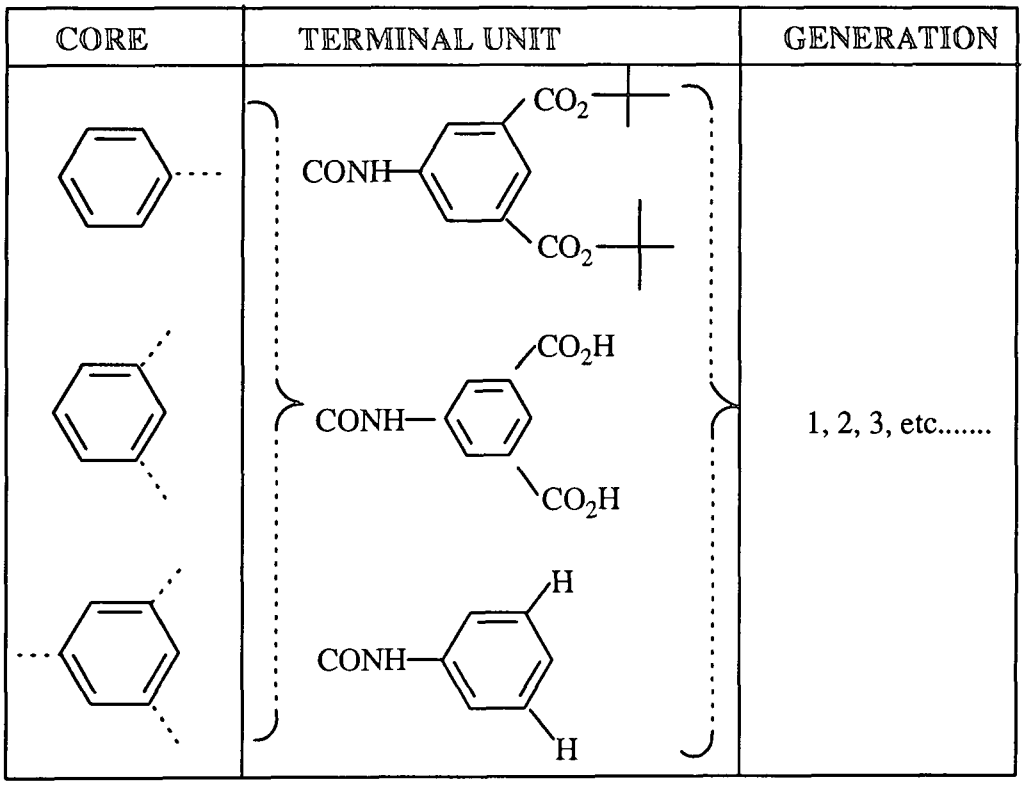


Figure 5.2 Variation in structural components of dendritic polyamides

probably be increased still further by using the present dendritic molecules as 'hypercores' for further outward growth, either directly from surface functionalities already present or by the attachment of extender groups.

The properties of the materials described in this thesis have not, as yet, been investigated. However, with the production of significant amounts of both the compounds discussed and their higher generation analogues, the investigation of properties will be possible.

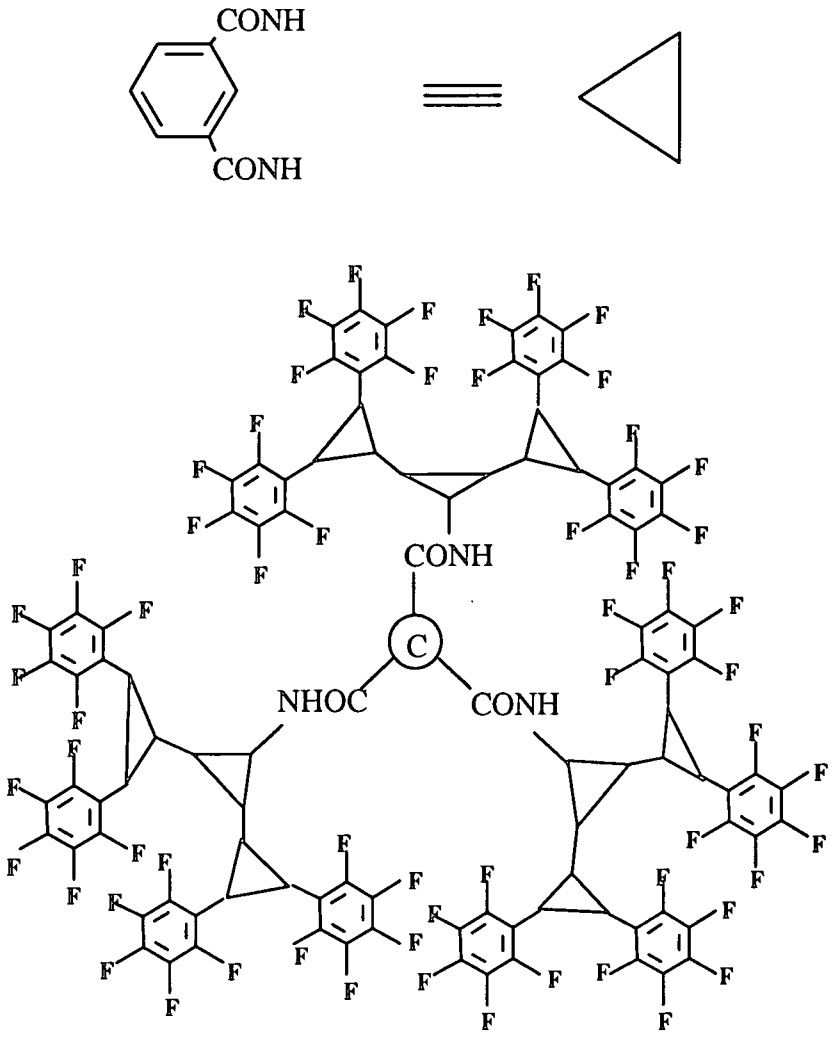
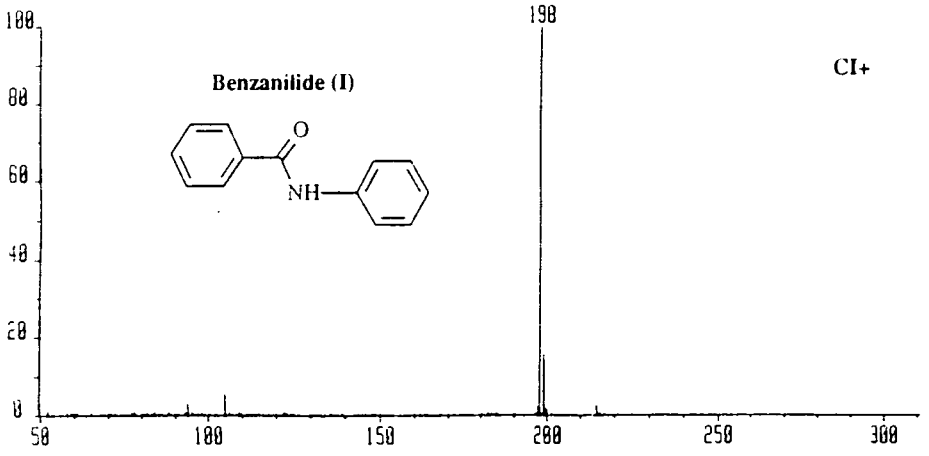


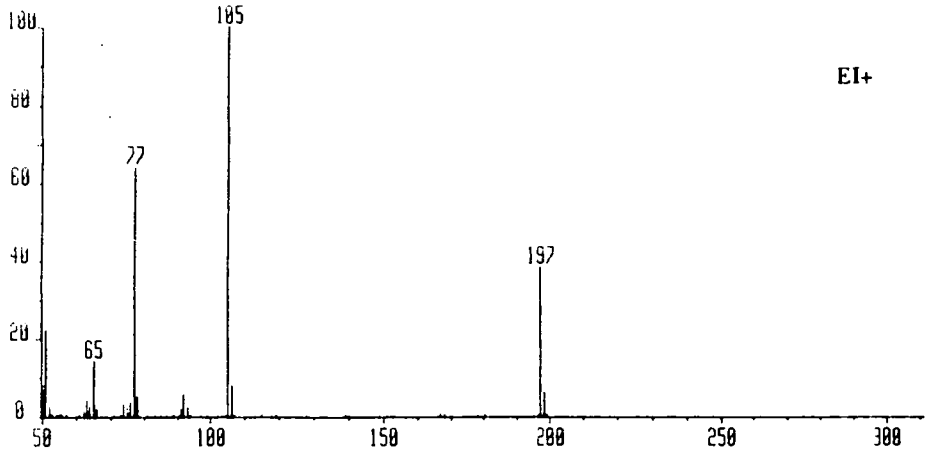
Figure 5.3 dendrimer with a fluorinated 'surface'

APPENDICES 1.1 to 1.13

MASS SPECTRA

APPENDIX 1.1





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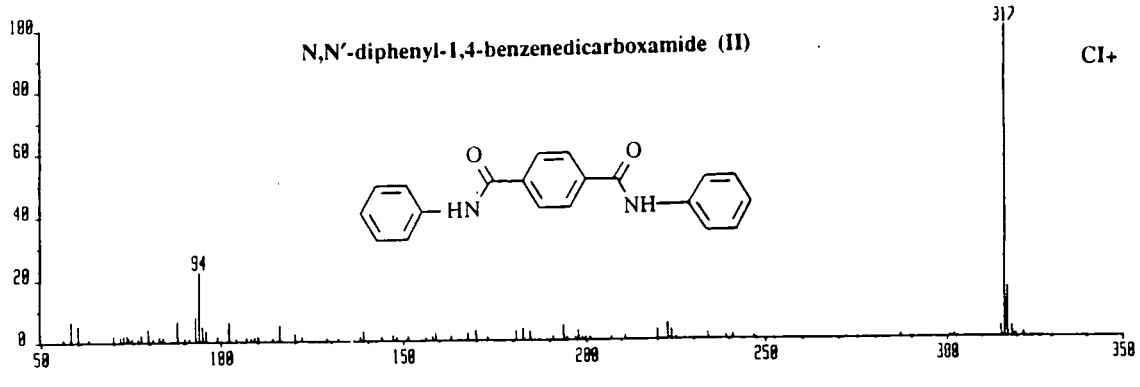

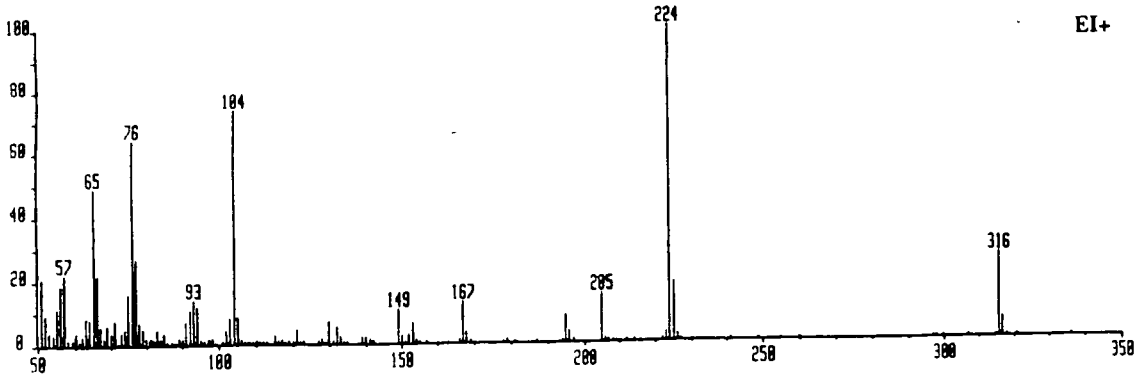

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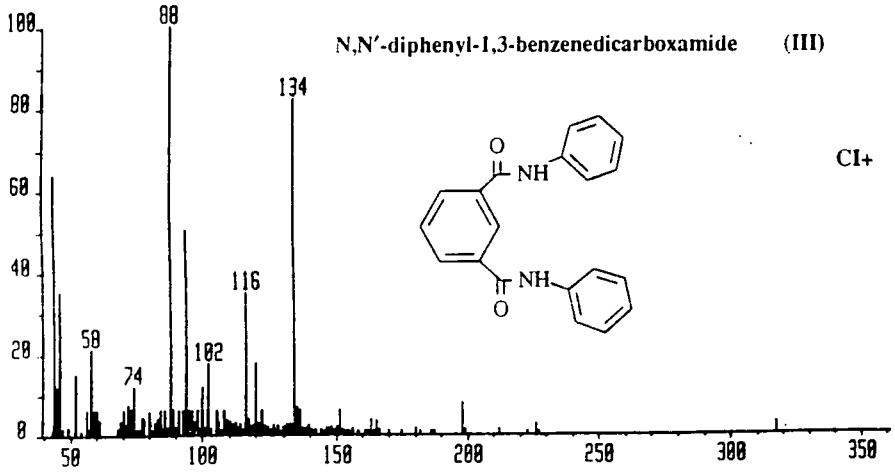

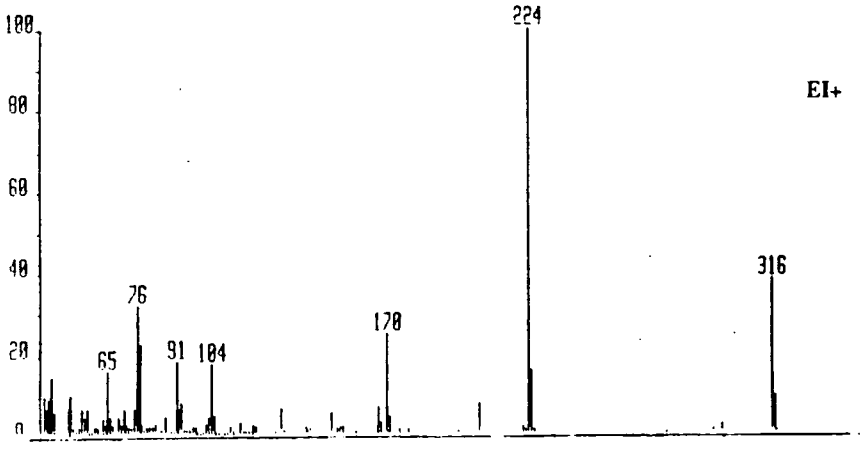

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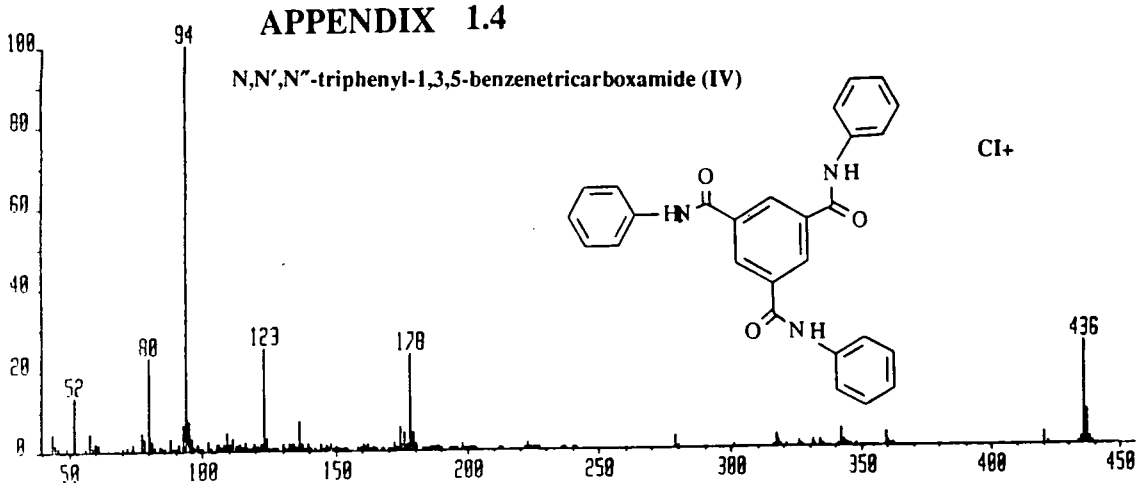

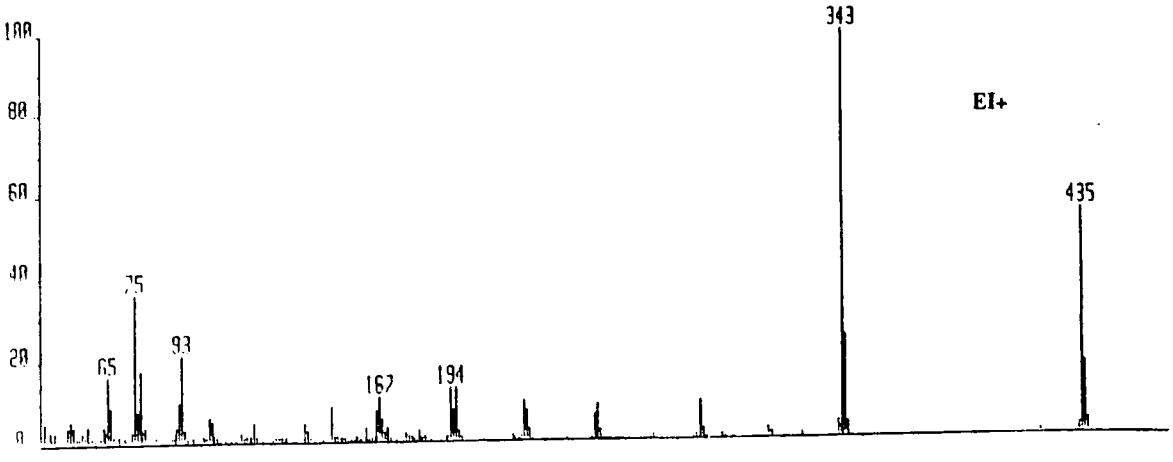

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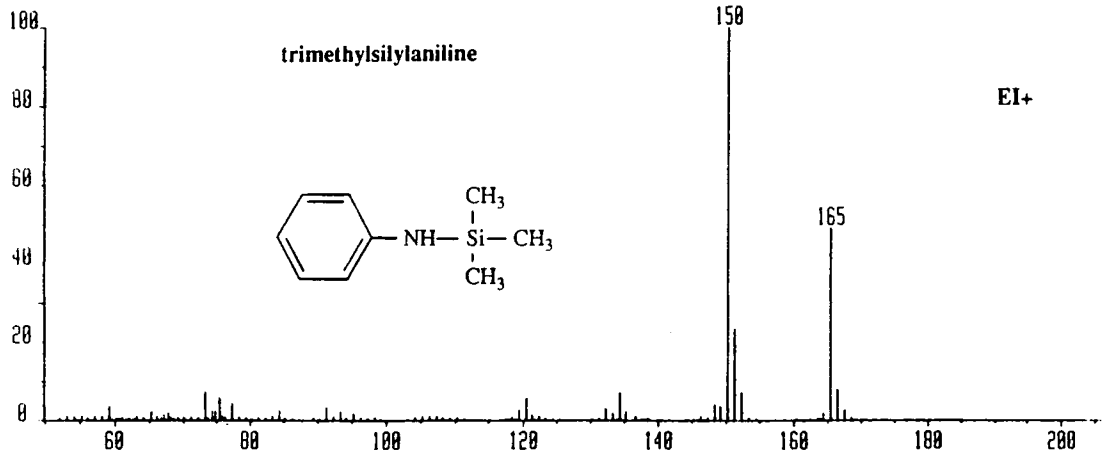

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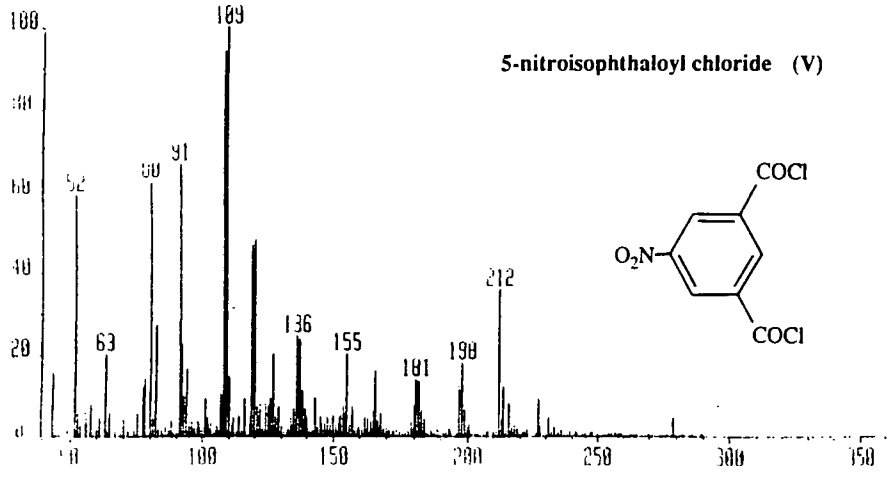

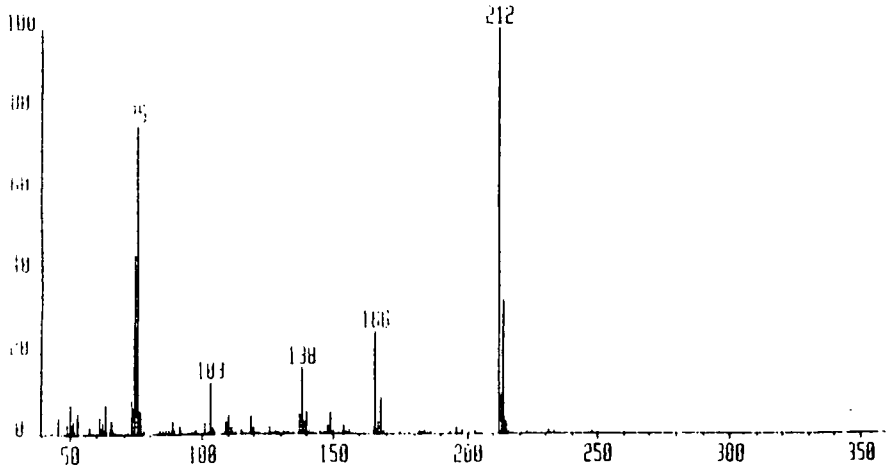

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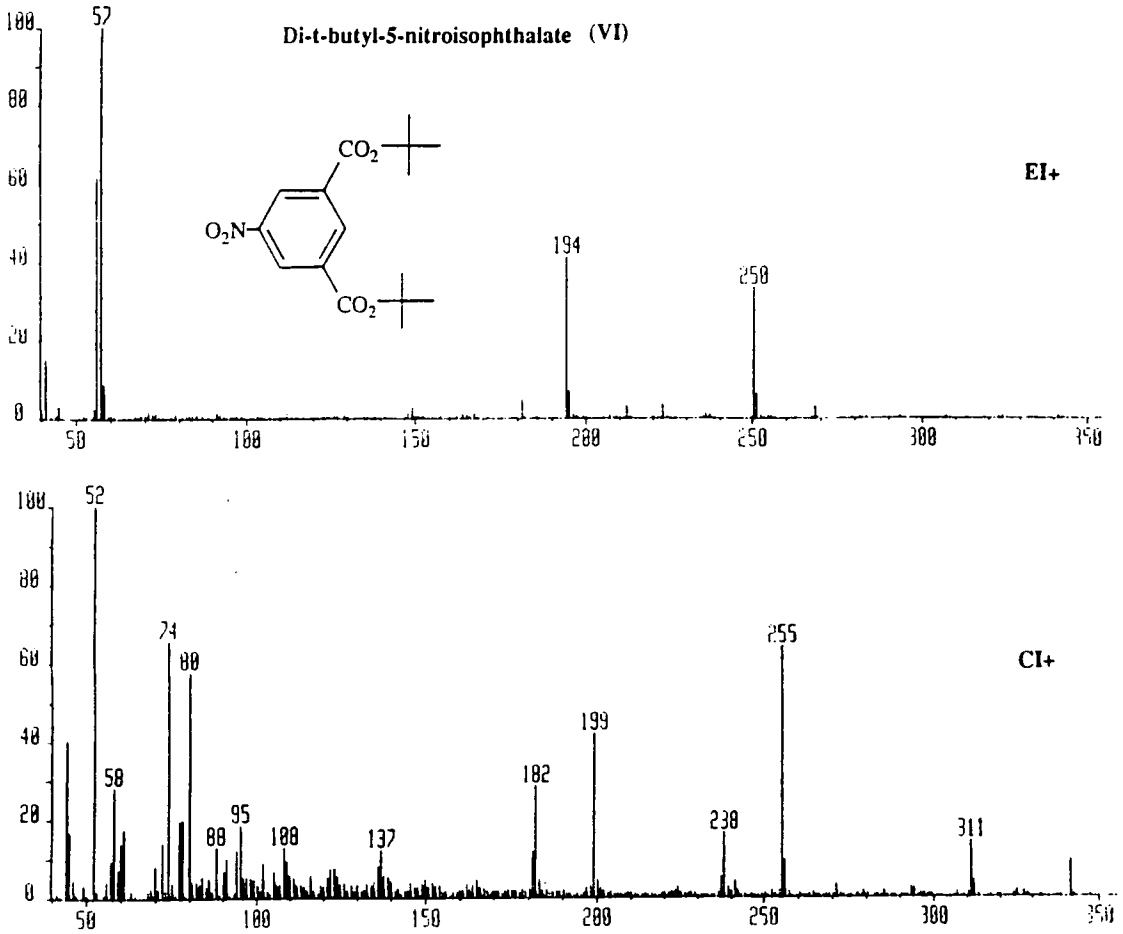

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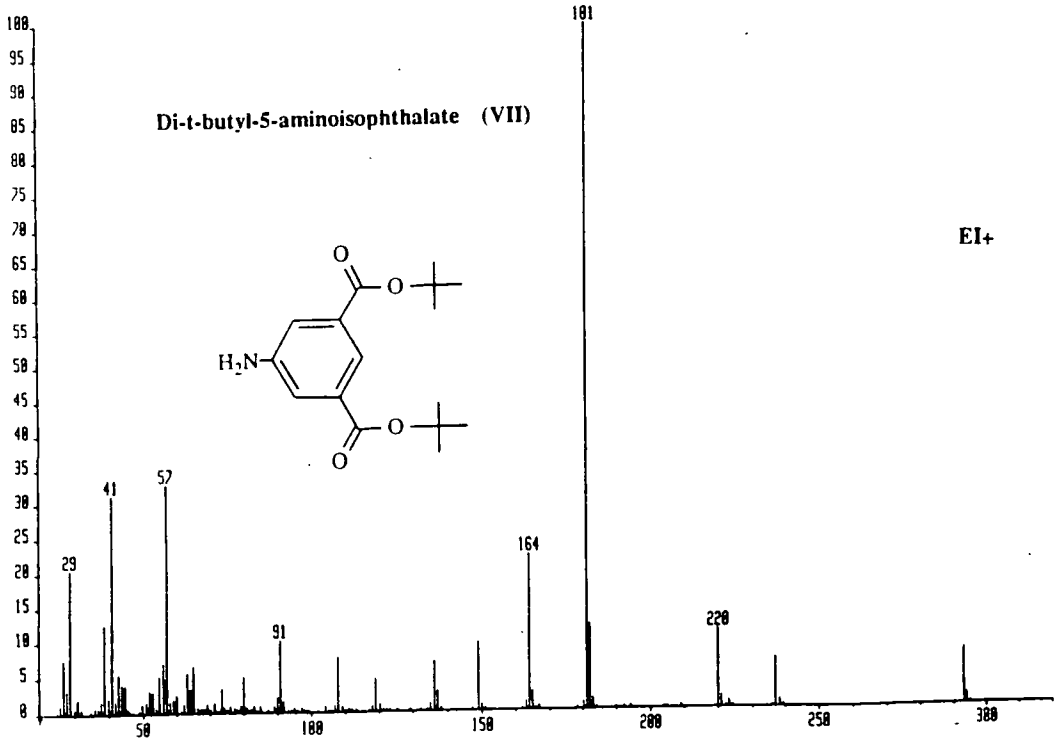

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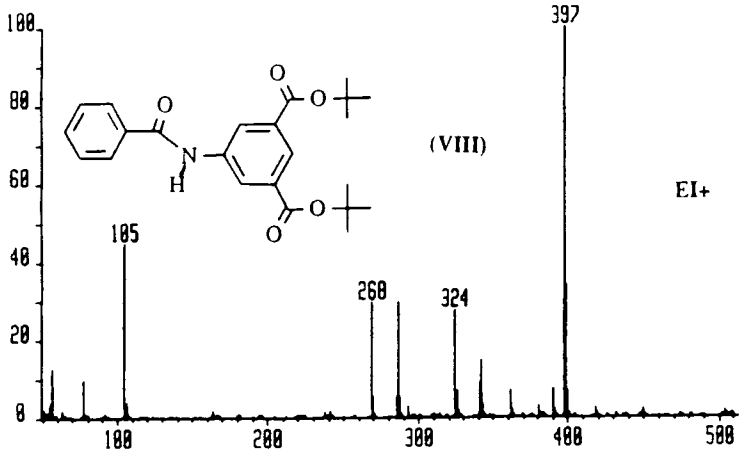

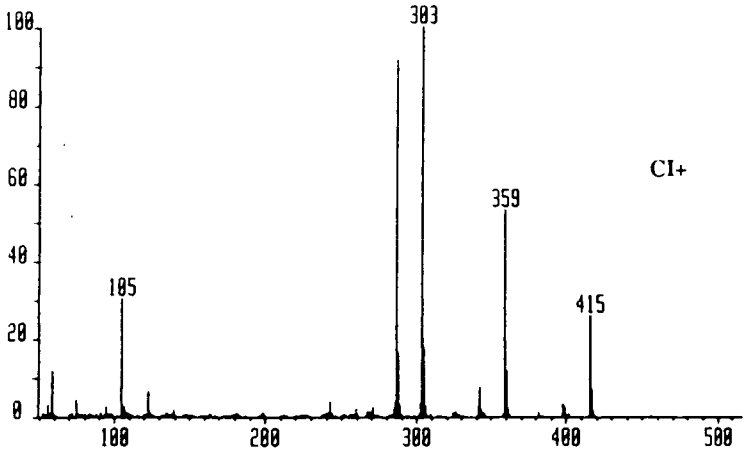

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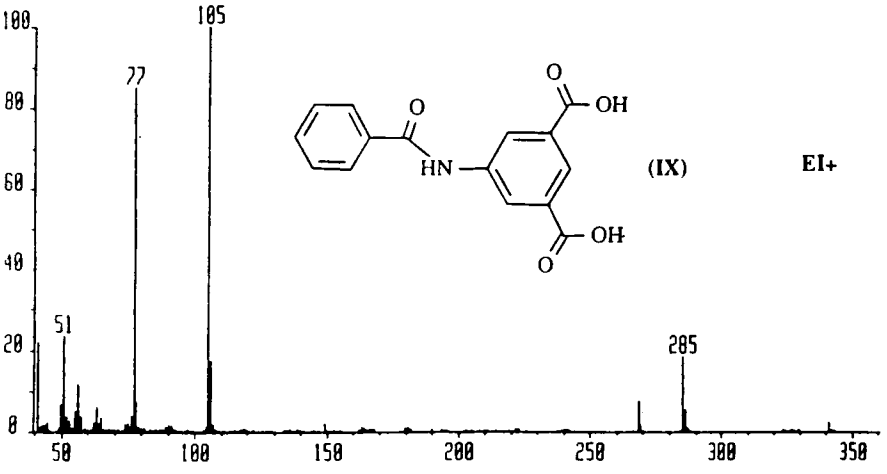

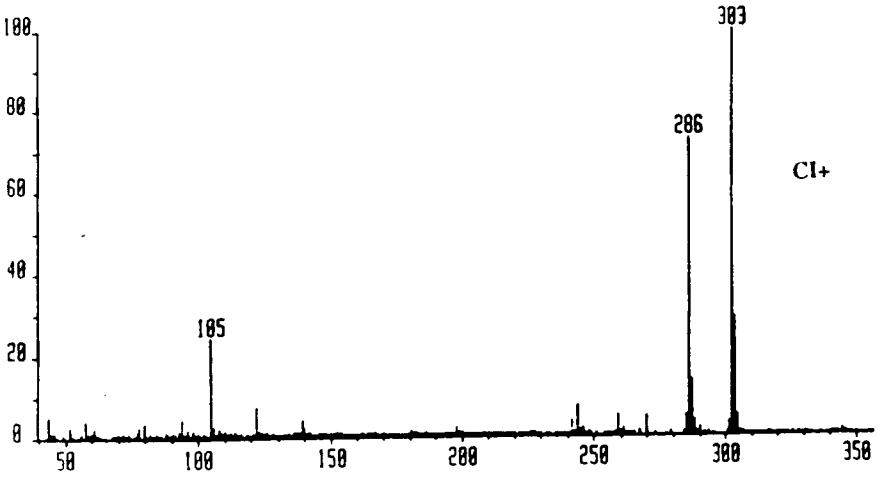

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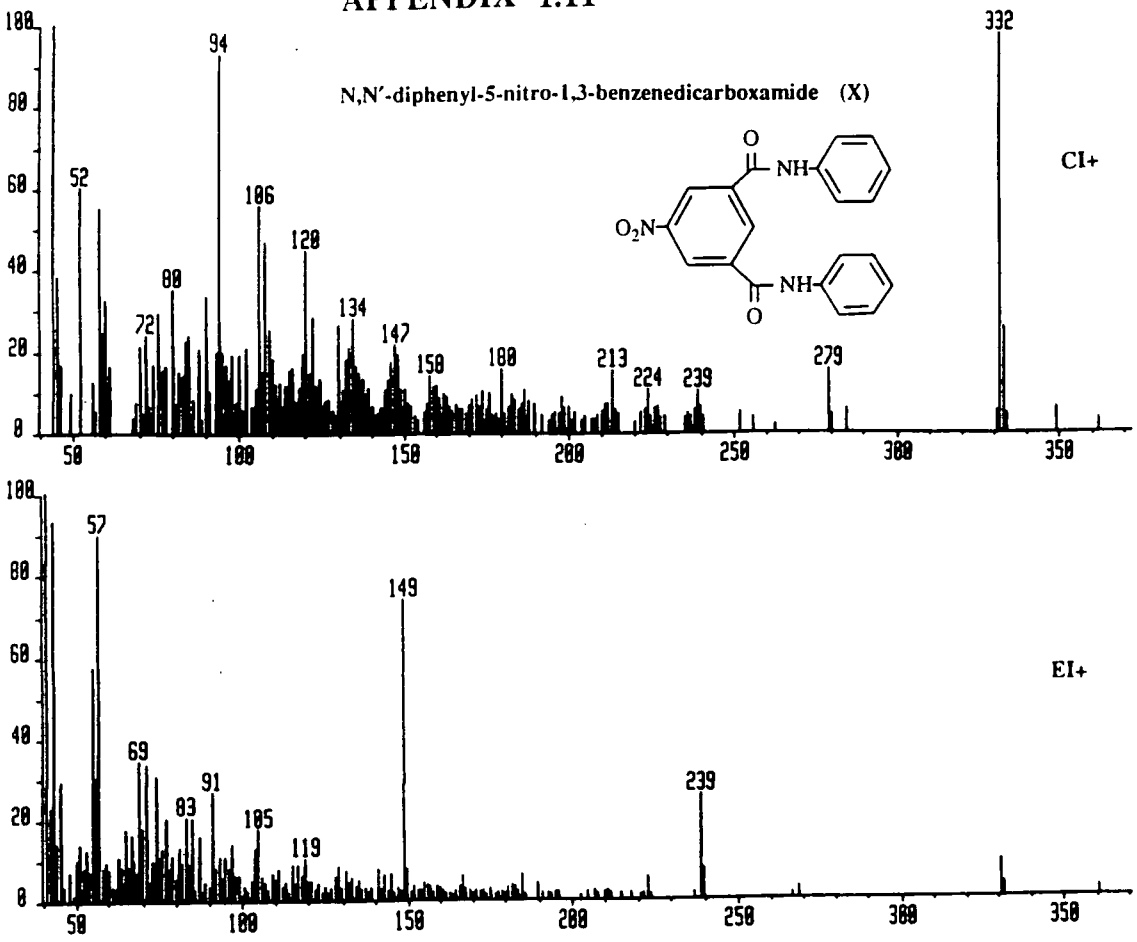

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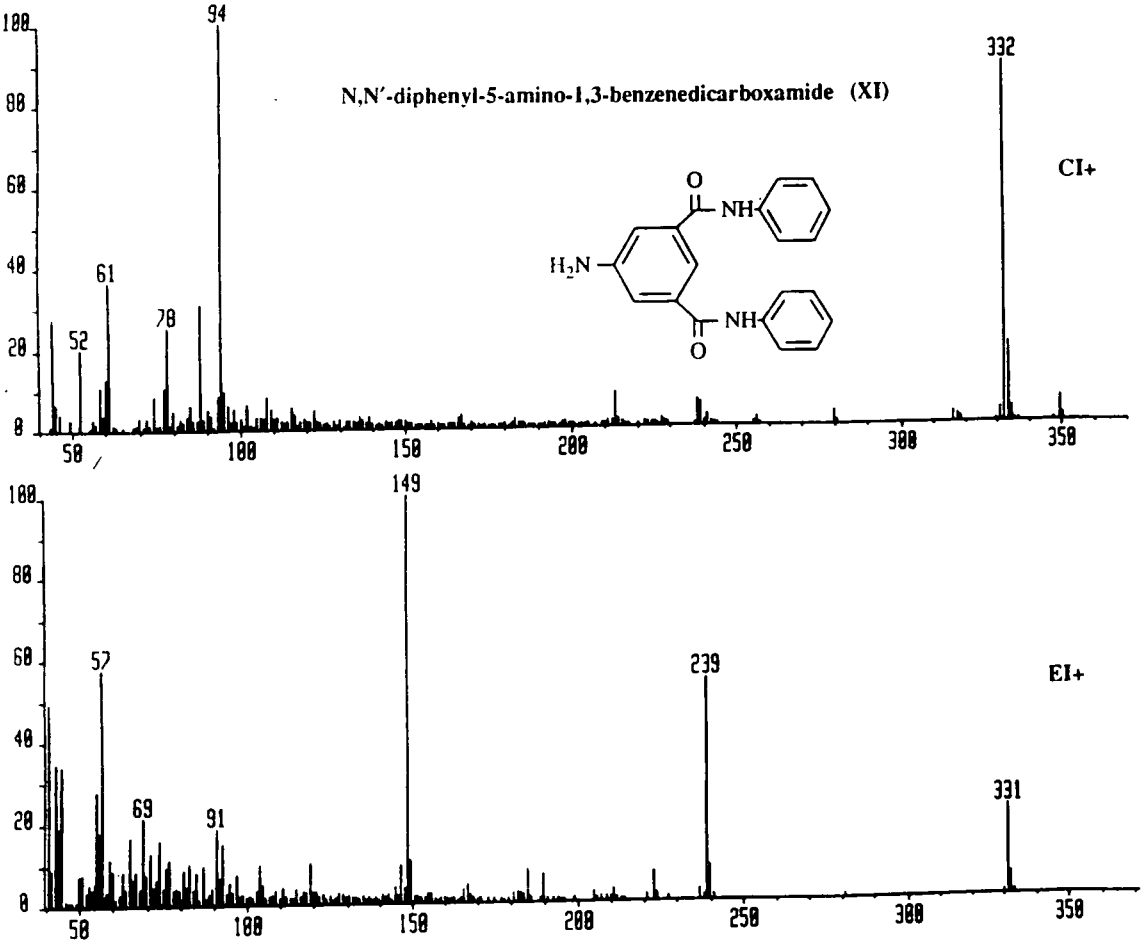

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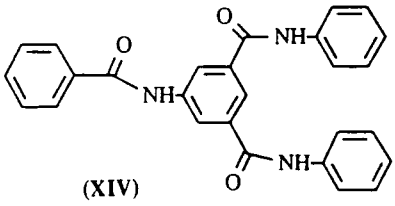
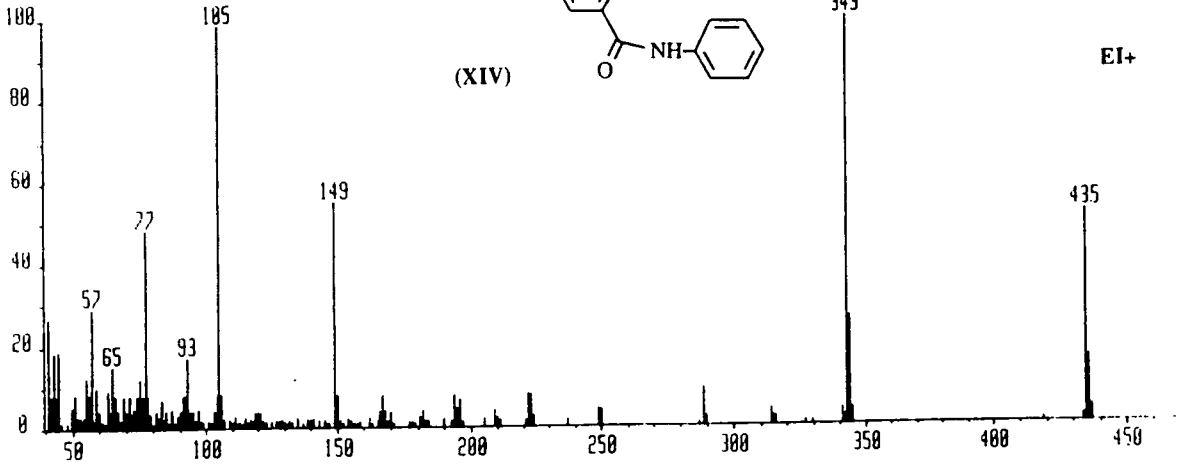
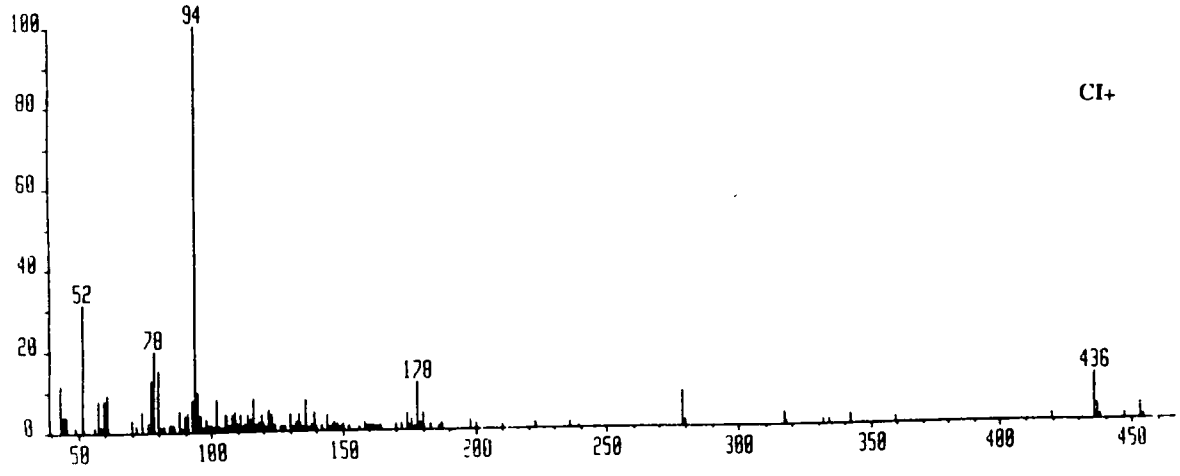


(XIV)

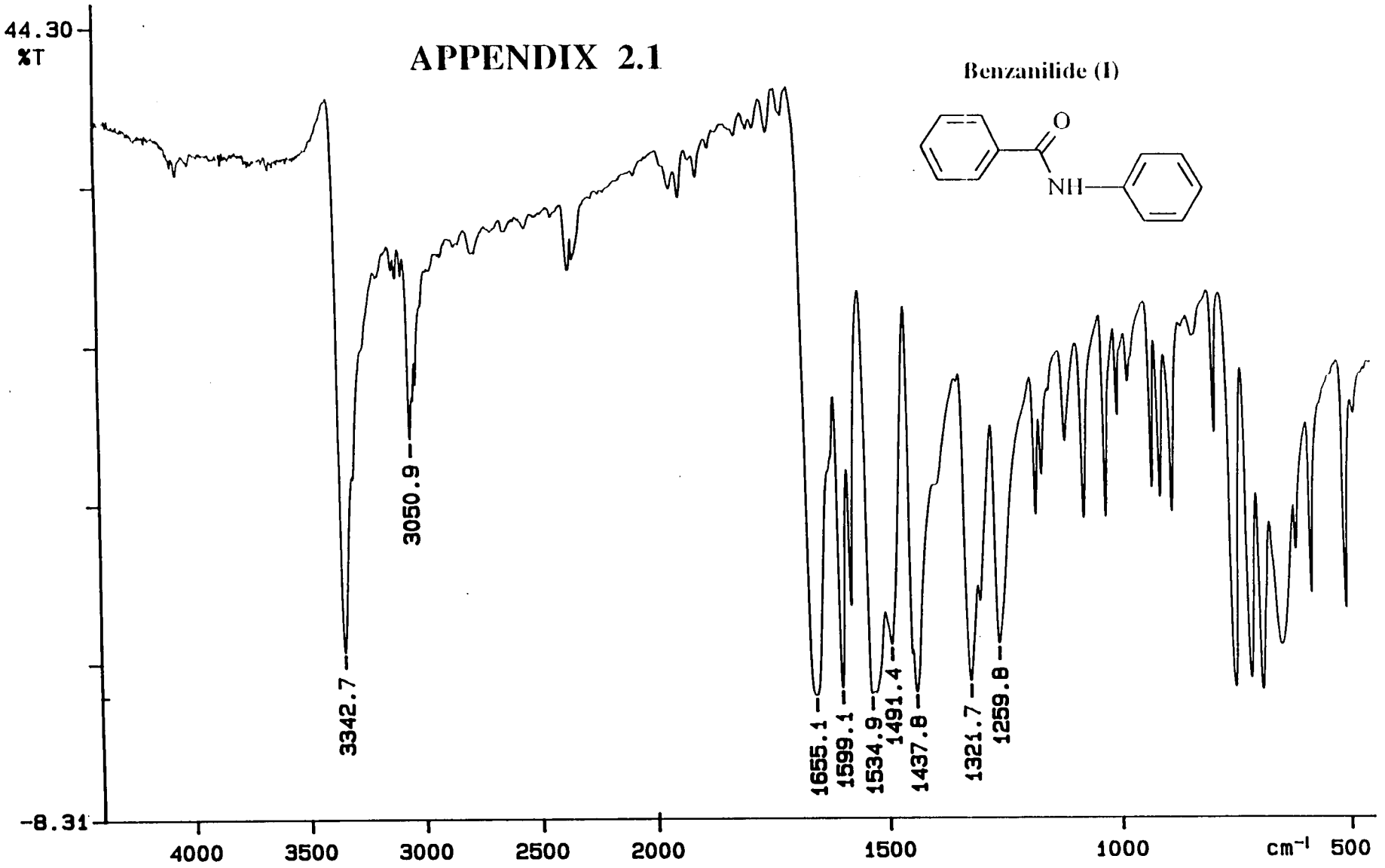




APPENDICES 2.1 to 2.16

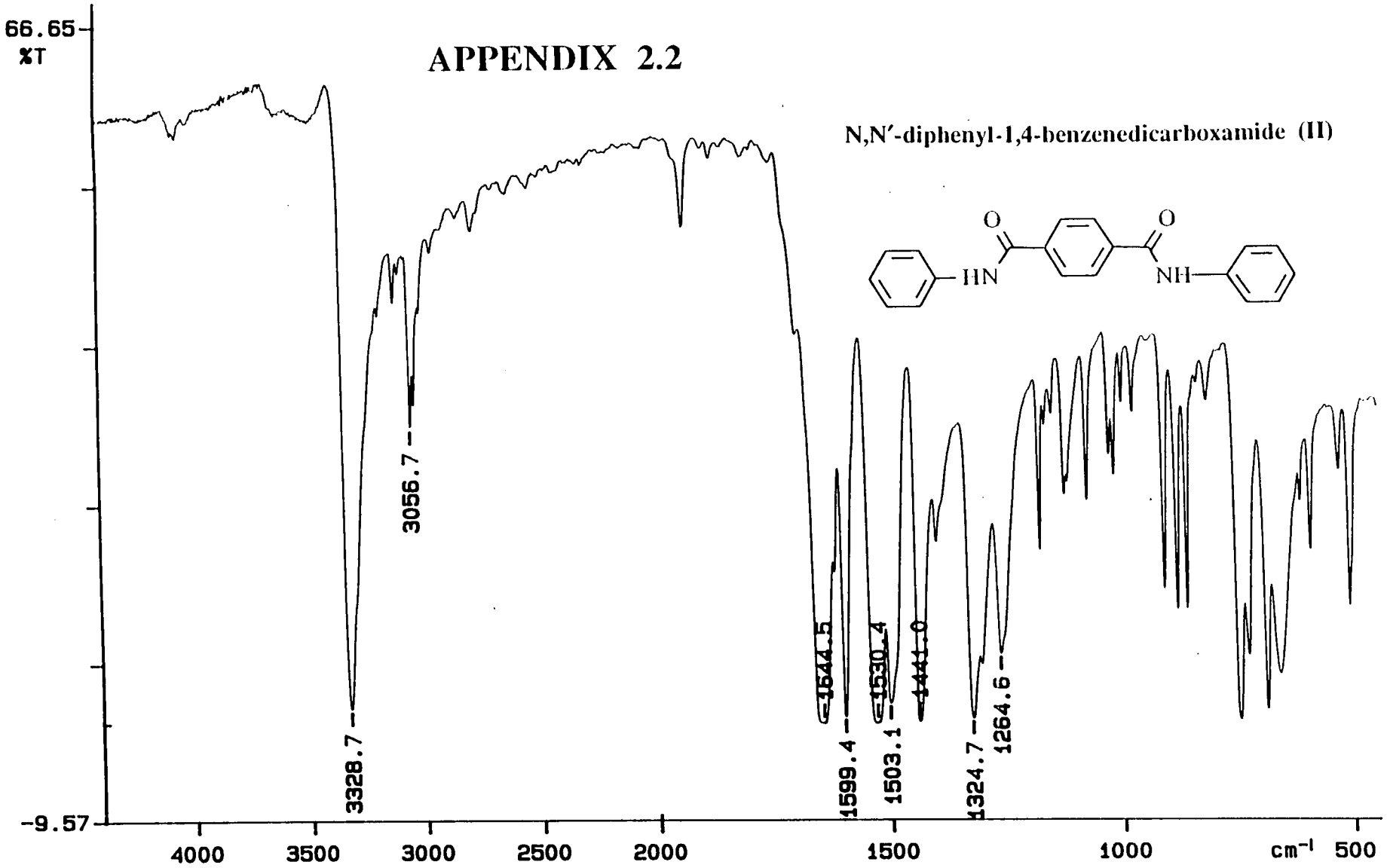
FTIR SPECTRA

APPENDIX 2.1



Benzanilide (I)

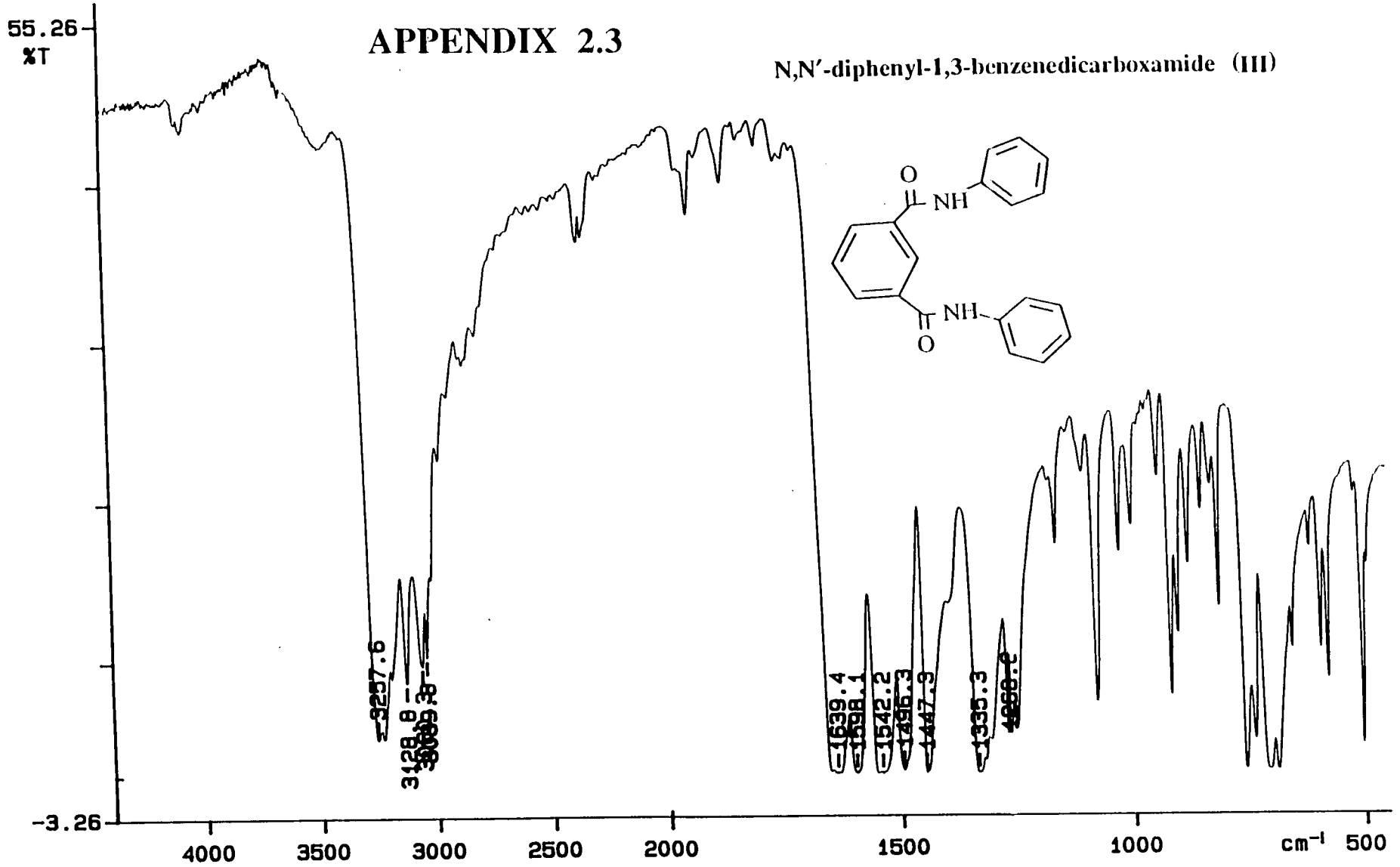
APPENDIX 2.2



N,N′-diphenyl-1,4-benzenedicarboxamide (II)

APPENDIX 2.3

N,N′-diphenyl-1,3-benzenedicarboxamide (III)



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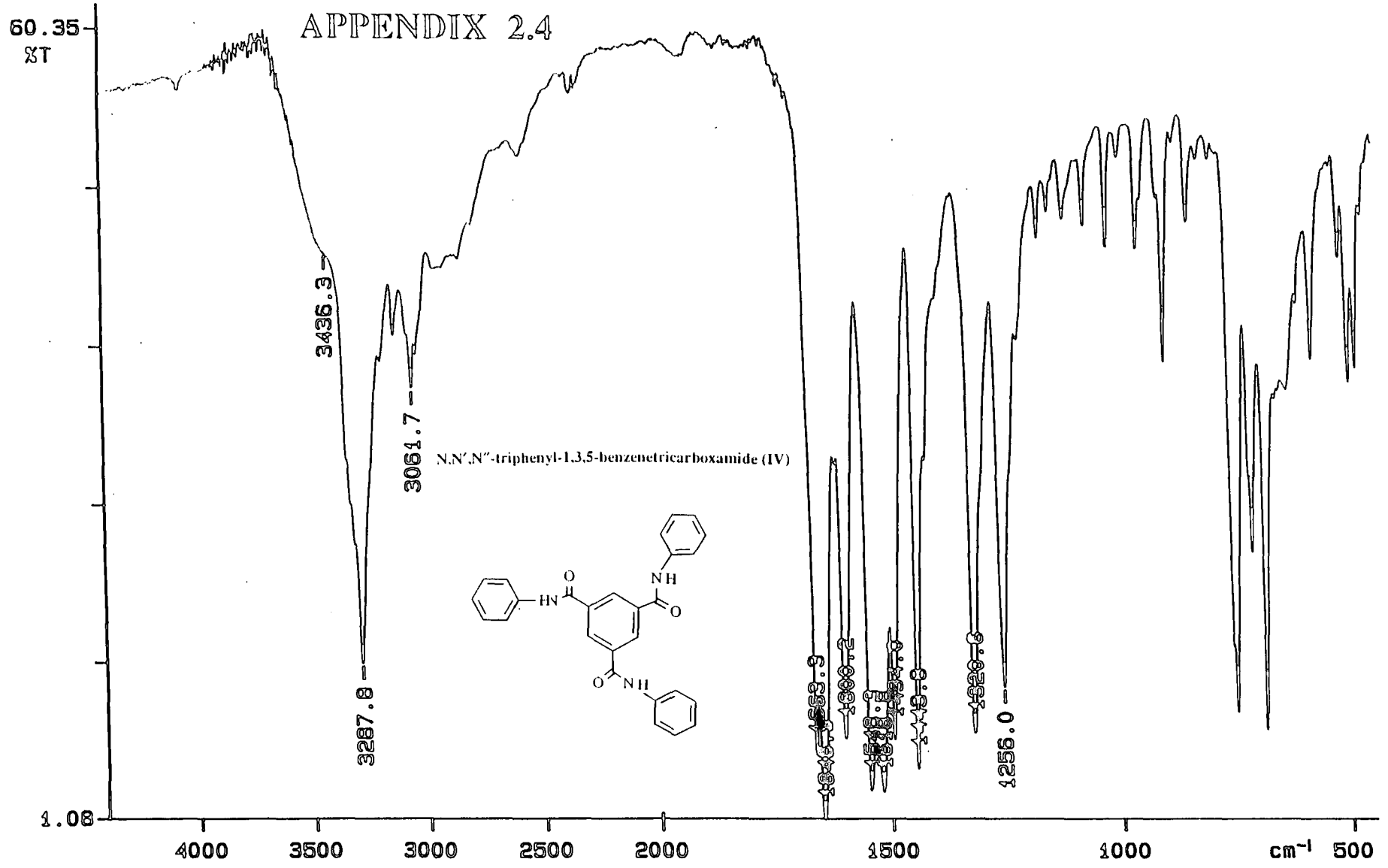
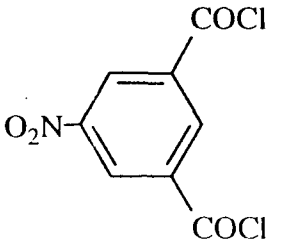

60.35
%T
3436.3
3061.7
3287.8
1256.0
1.08
4000
3500
3000
2500
2000
1500
1000
cm-1
500
N,N',N''-triphenyl-1,3,5-benzenetricarboxamide (IV)
HN
O
NH
O
O
NH

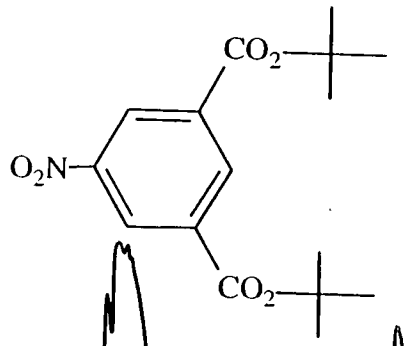
APPENDIX 2.5

5-nitroisophthaloyl chloride (V)



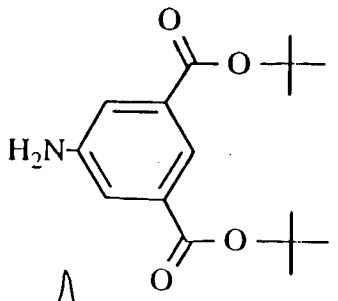
APPENDIX 2.6

Di-t-butyl-5-nitroisophthalate (VI)



APPENDIX 2.7

Di-t-butyl-5-aminoisophthalate (VII)



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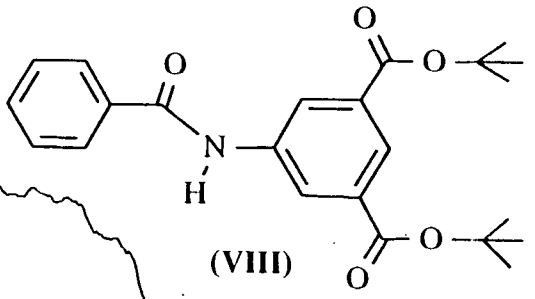
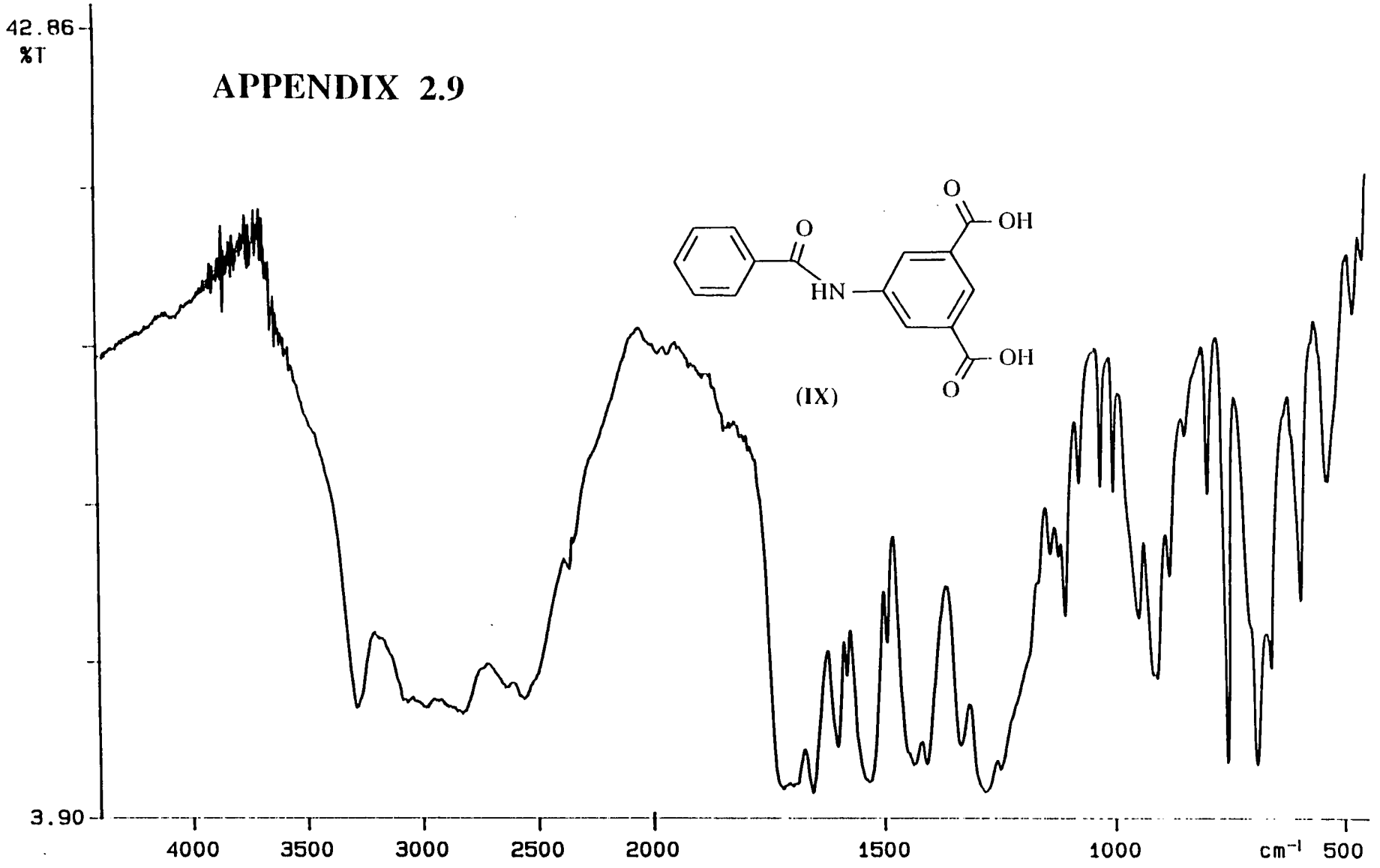


(VIII)

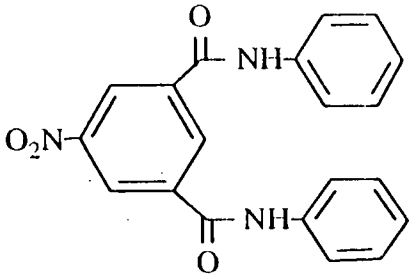
APPENDIX 2.9



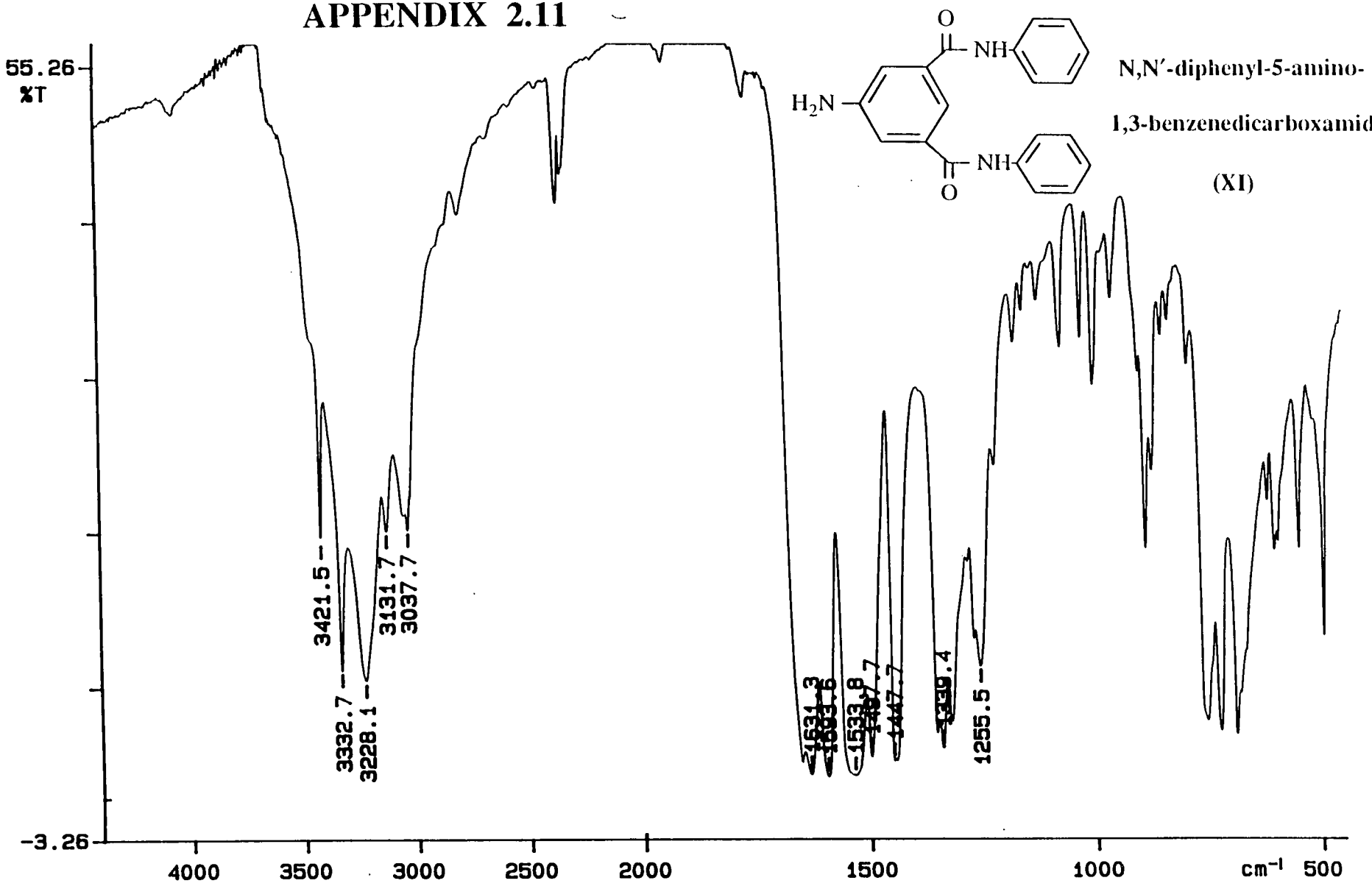
(IX)

APPENDIX 2.10

N,N′-diphenyl-5-nitro-1,3-benzenedicarboxamide (X)



APPENDIX 2.11

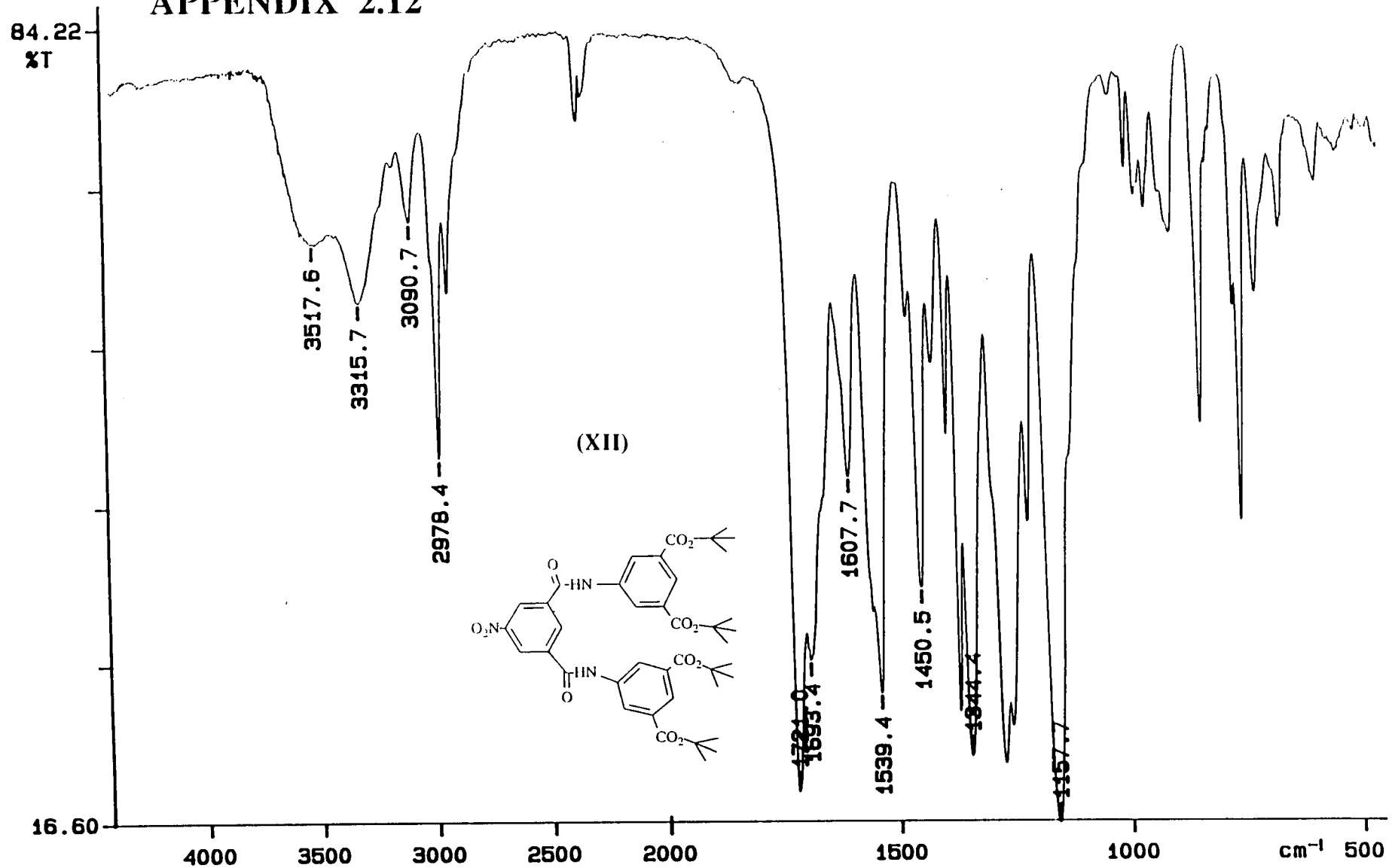


N,N′-diphenyl-5-amino-

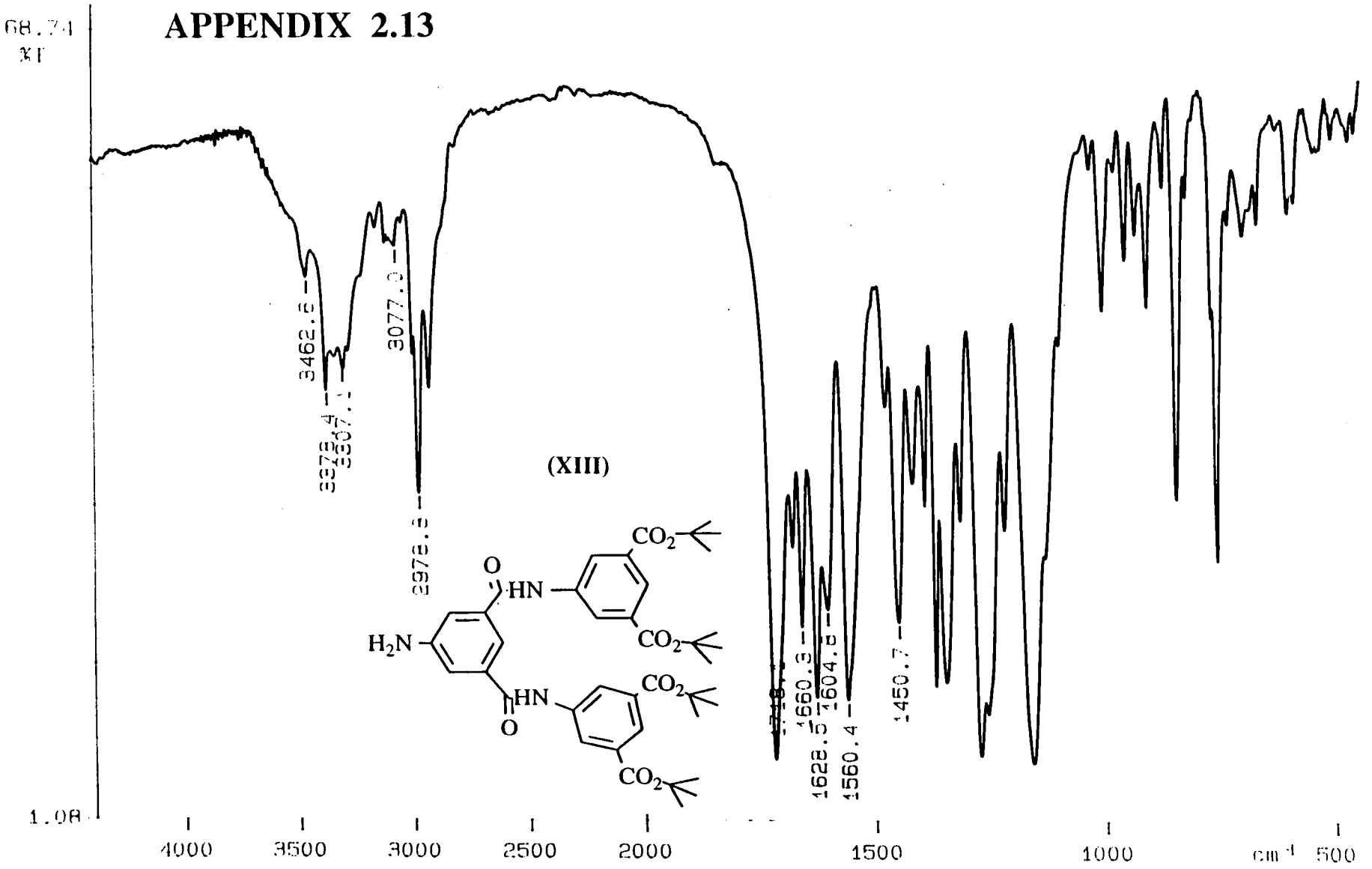
1,3-benzenedicarboxamide

(XI)

APPENDIX 2.12

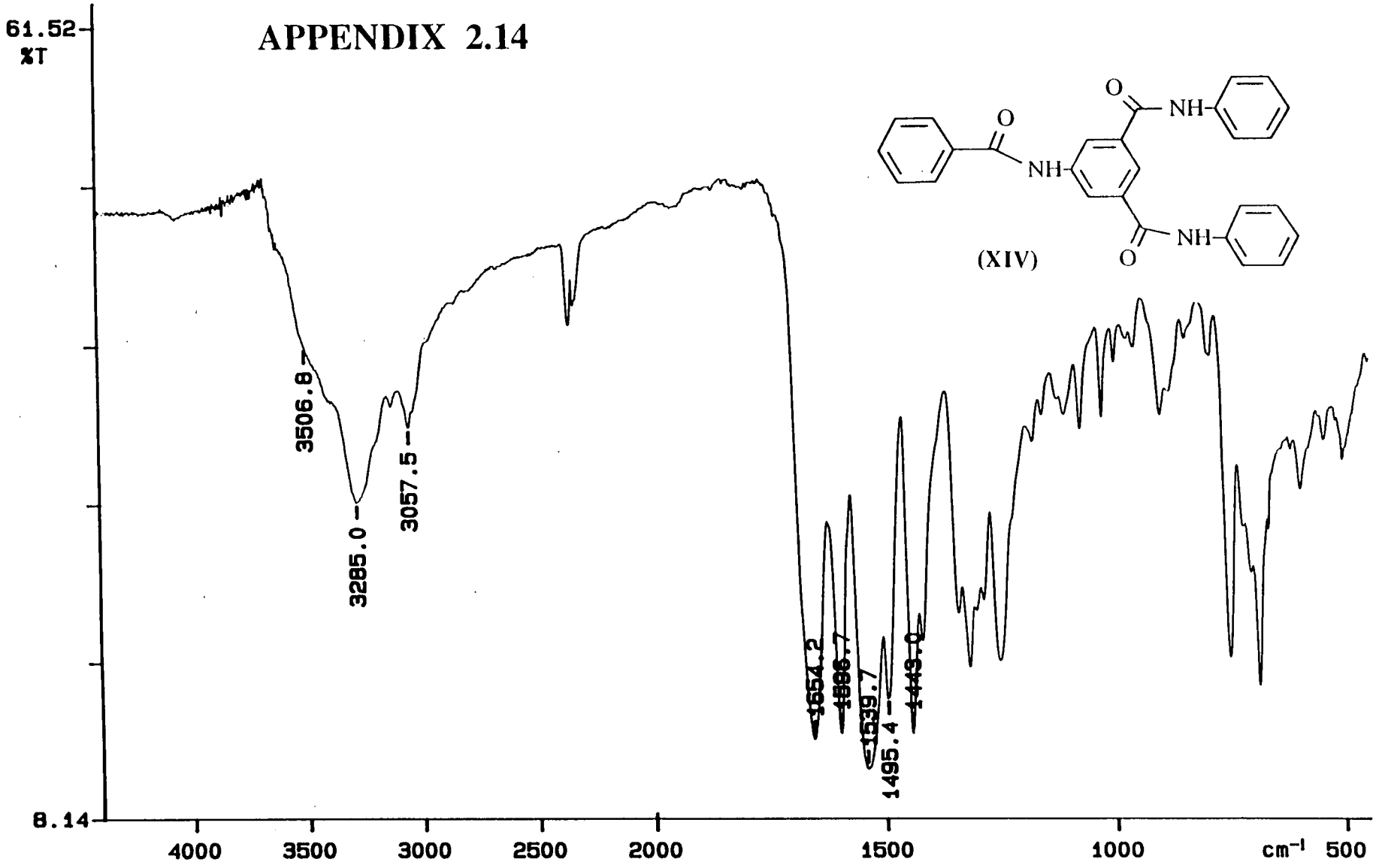


APPENDIX 2.13



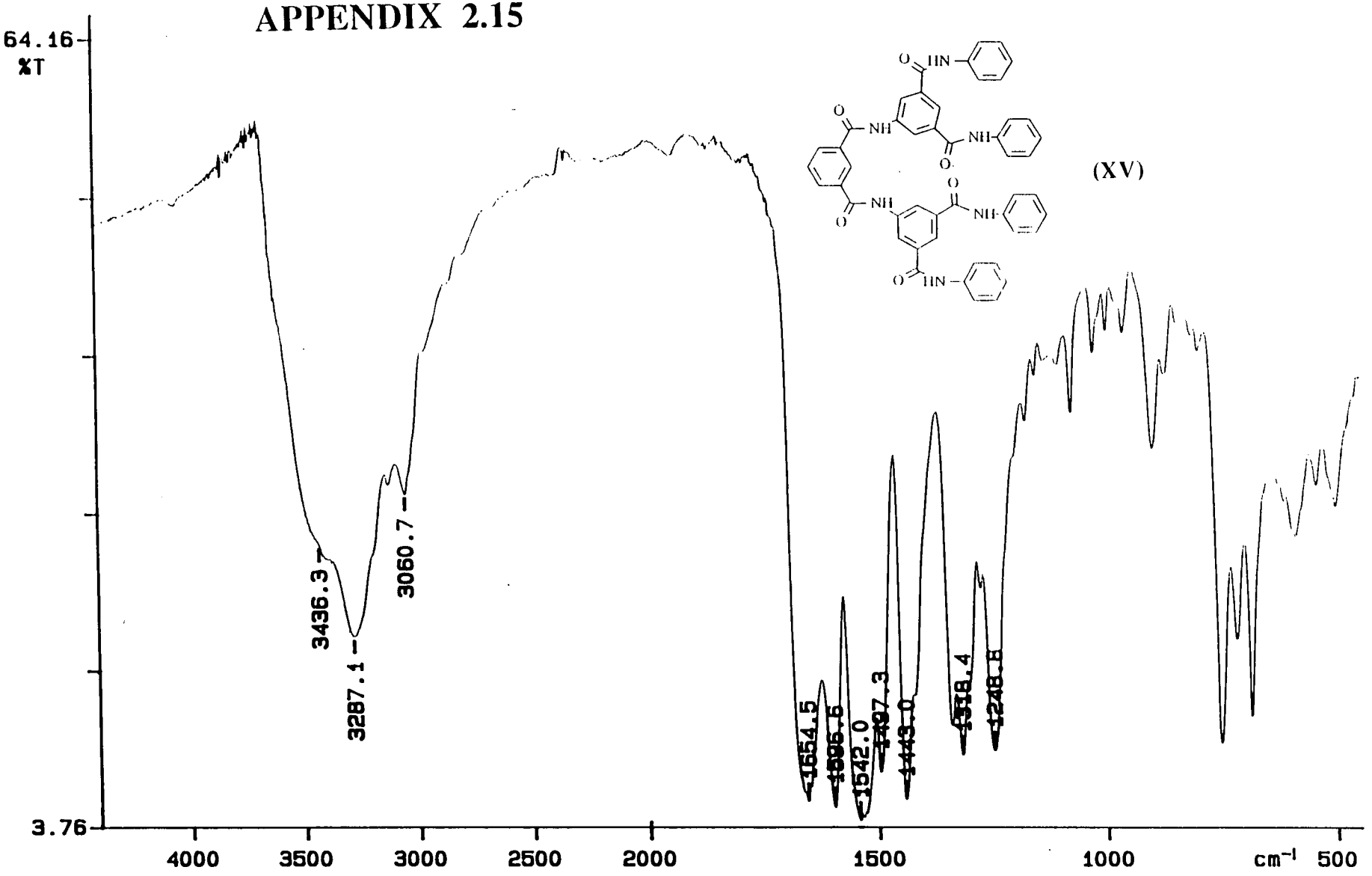
(XIII)

APPENDIX 2.14



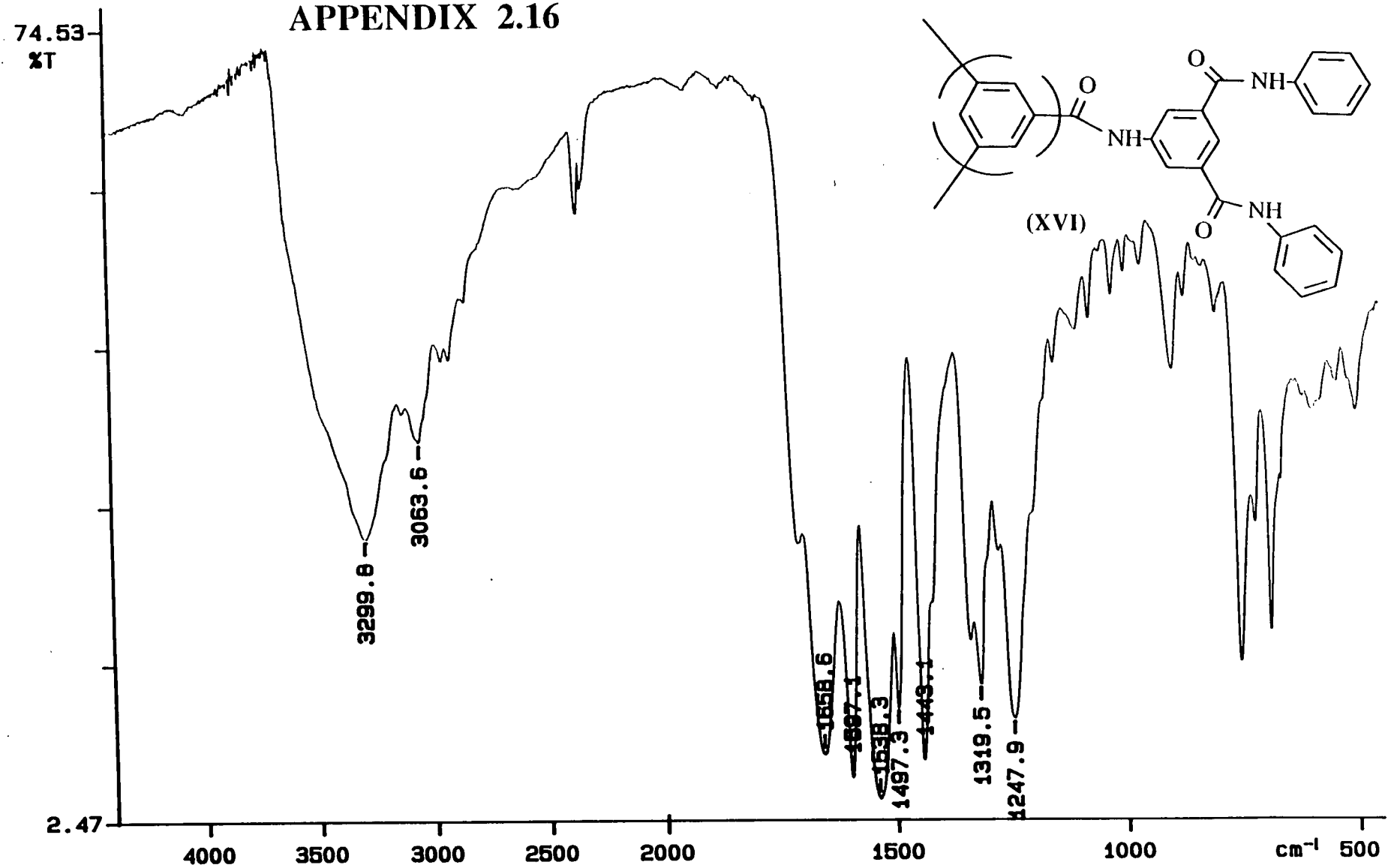
(XIV)

APPENDIX 2.15



(XV)

APPENDIX 2.16

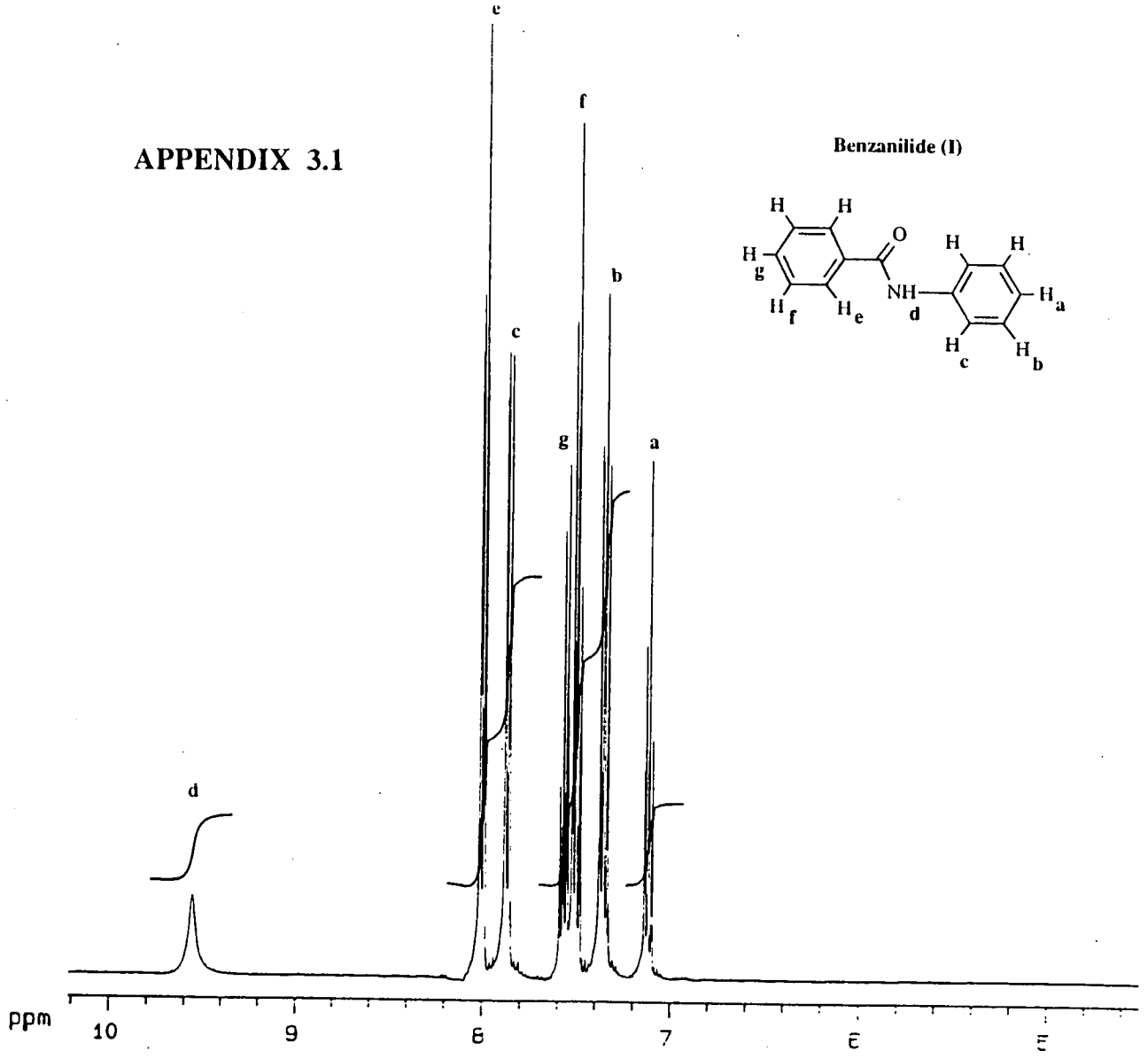


(XVI)

APPENDICES 3.1 to 3.12

^{1}H NMR SPECTRA

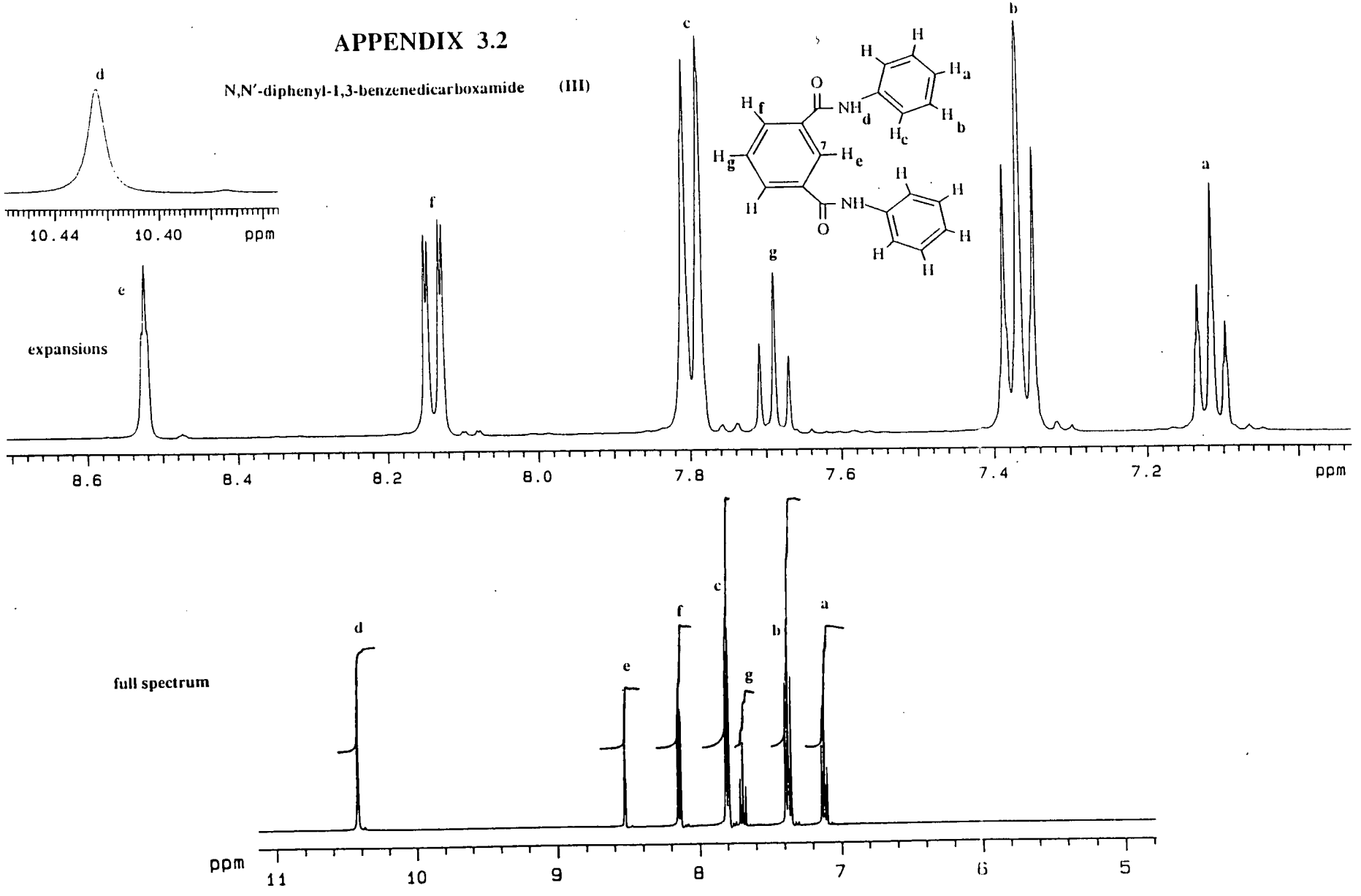
APPENDIX 3.1



Benzanilide (I)

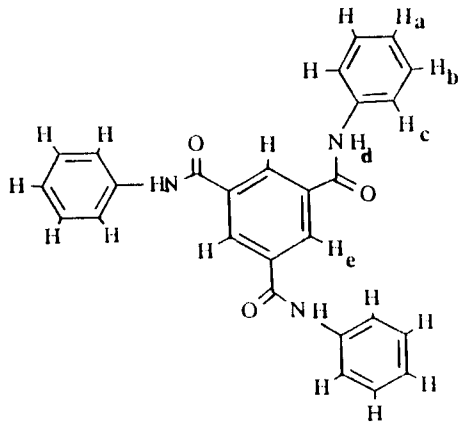
APPENDIX 3.2

N,N′-diphenyl-1,3-benzenedicarboxamide (III)



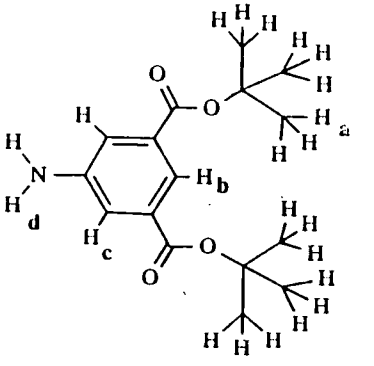
APPENDIX 3.3

N,N′,N″-triphenyl-1,3,5-benzenetricarboxamide (IV)

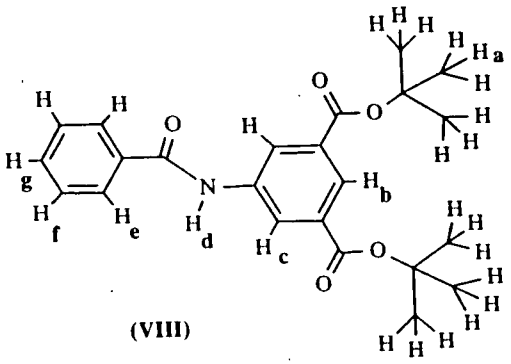


APPENDIX 3.4

Di-t-butyl-5-aminoisophthalate (VII)



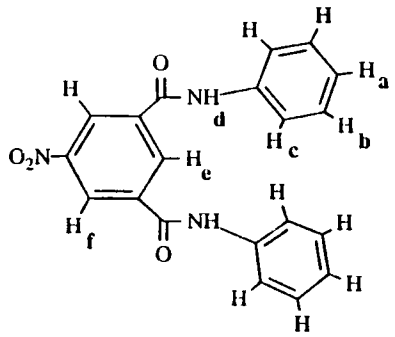
APPENDIX 3.5

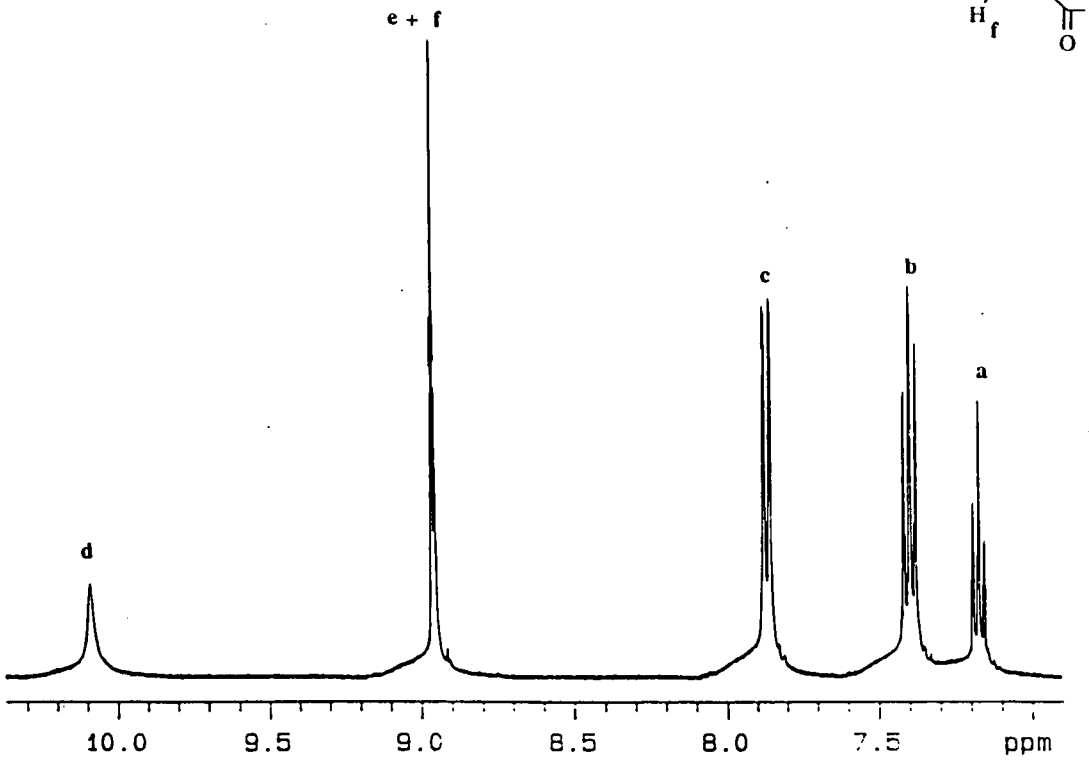


(VIII)

APPENDIX 3.6

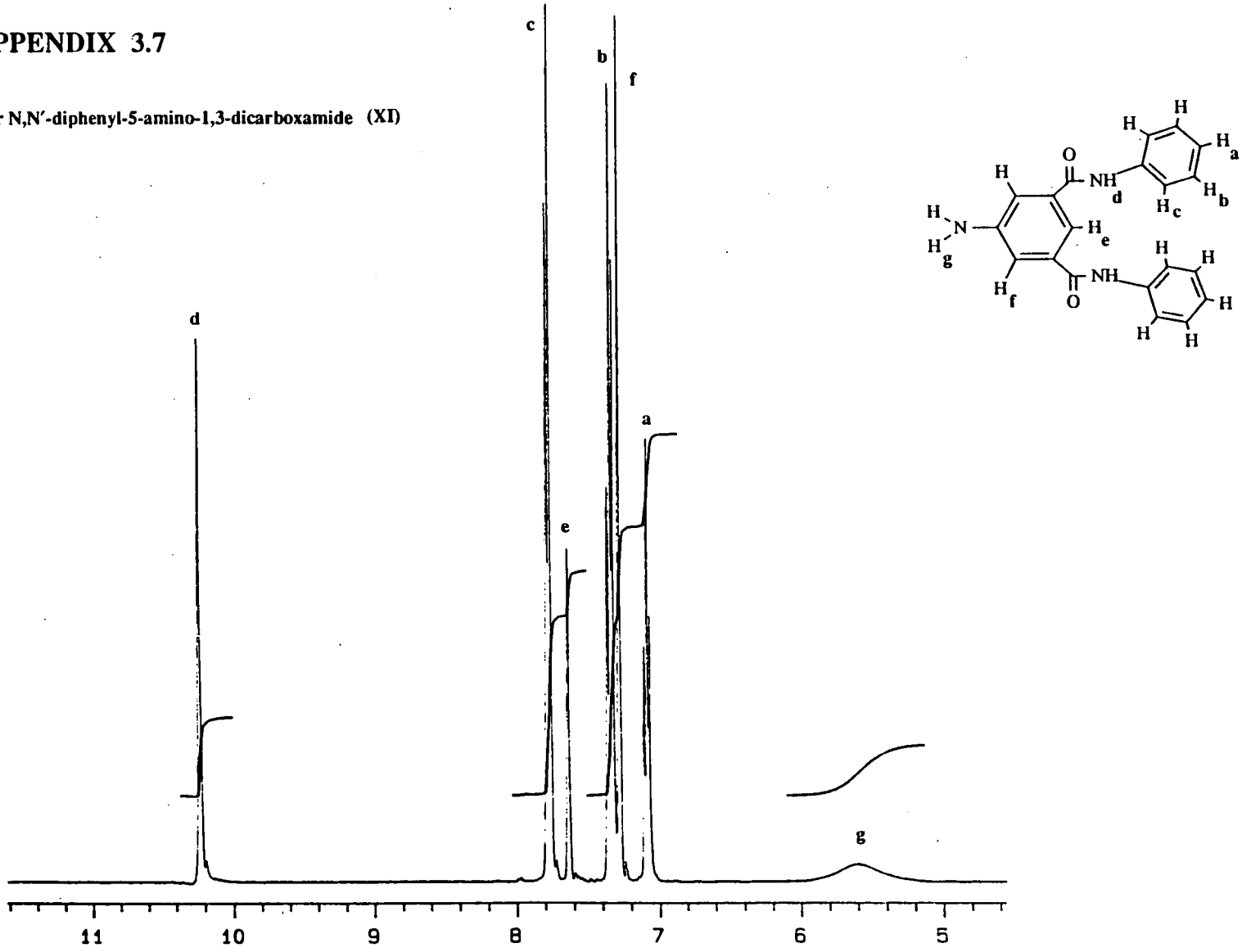
N,N′-diphenyl-5-nitro-1,3-benzenedicarboxamide (X)



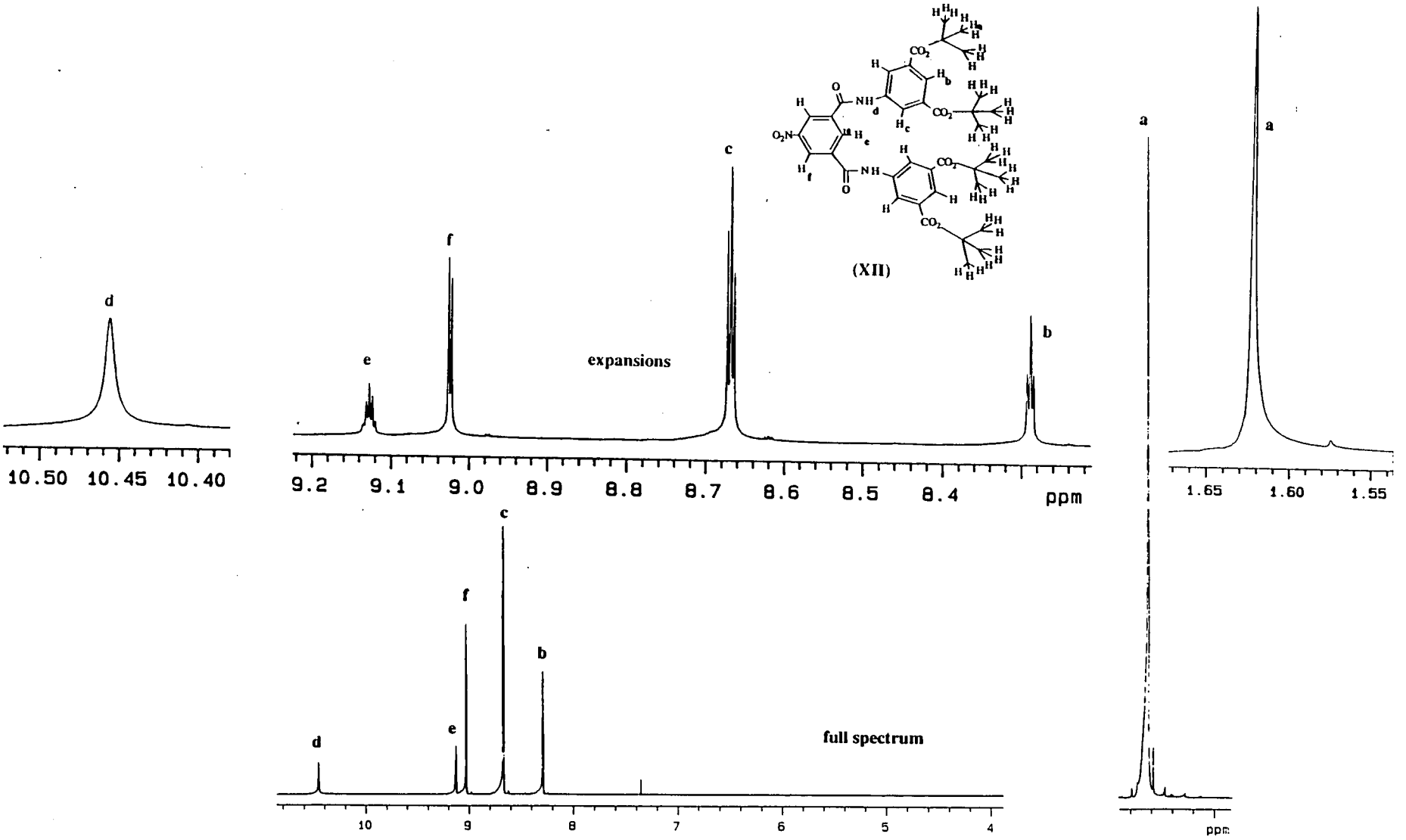


APPENDIX 3.7

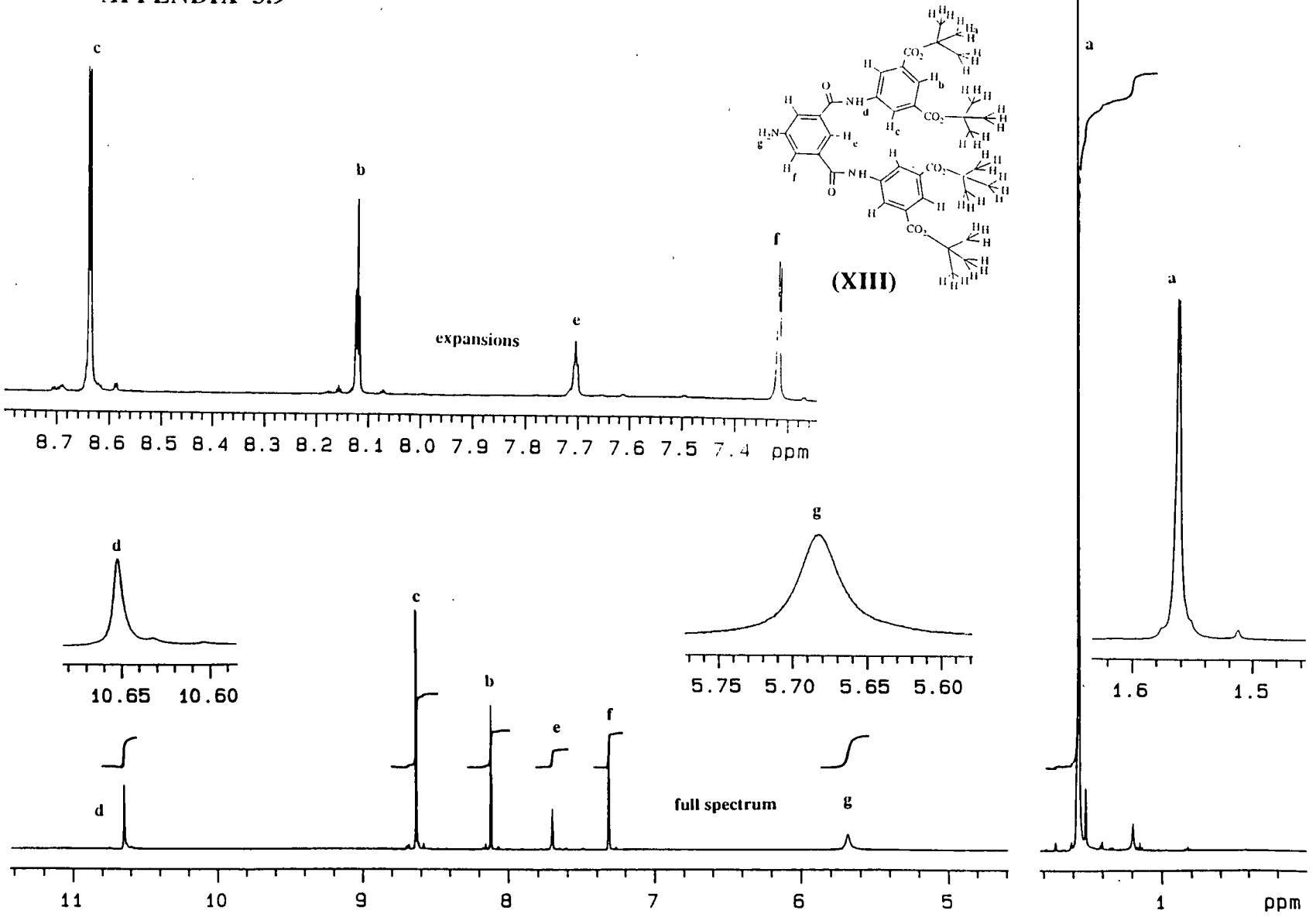
^{1}H NMR data for N,N′-diphenyl-5-amino-1,3-dicarboxamide (XI)



APPENDIX 3.8

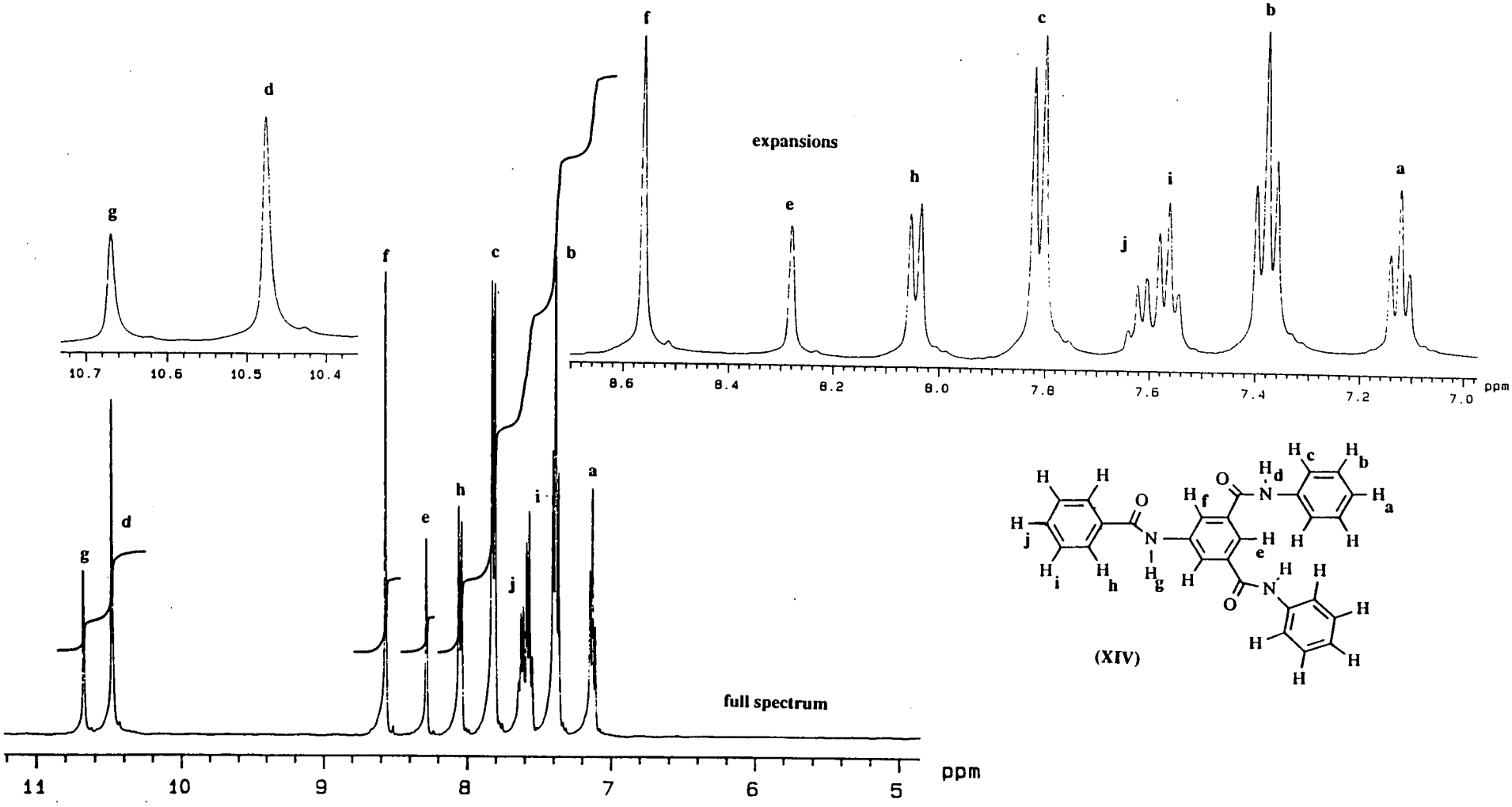


APPENDIX 3.9

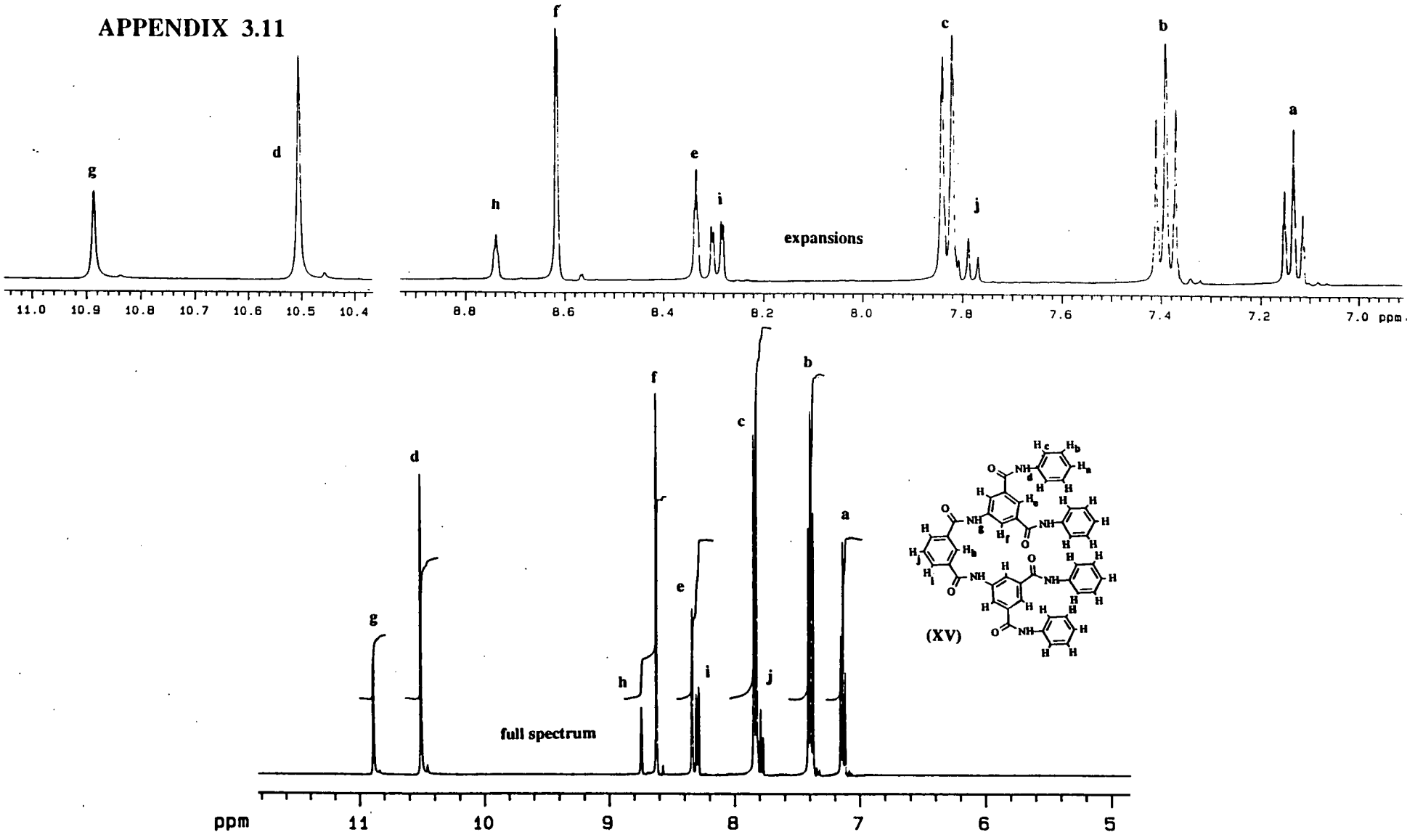


(XIII)

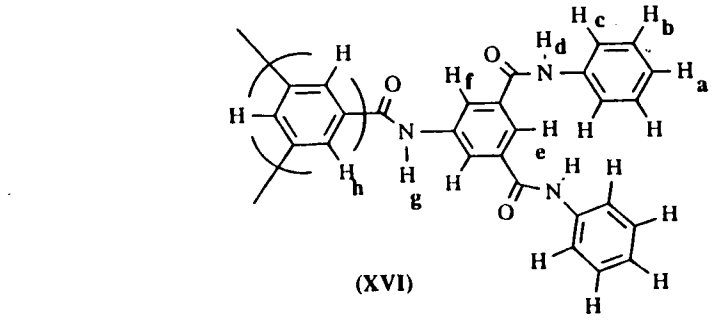
APPENDIX 3.10



APPENDIX 3.11



APPENDIX 3.12

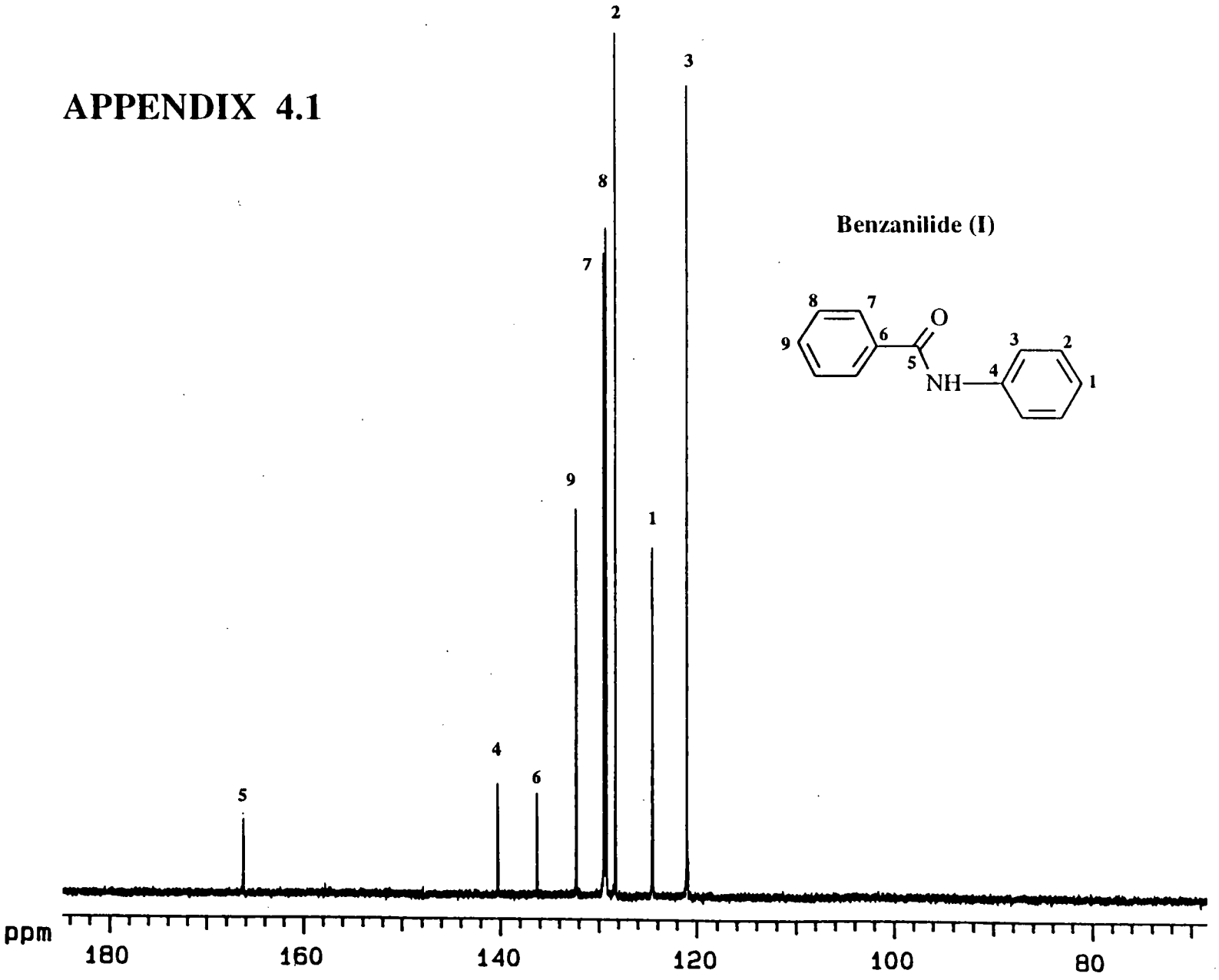


(XVI)

APPENDICES 4.1 to 4.12

^{13}C NMR SPECTRA

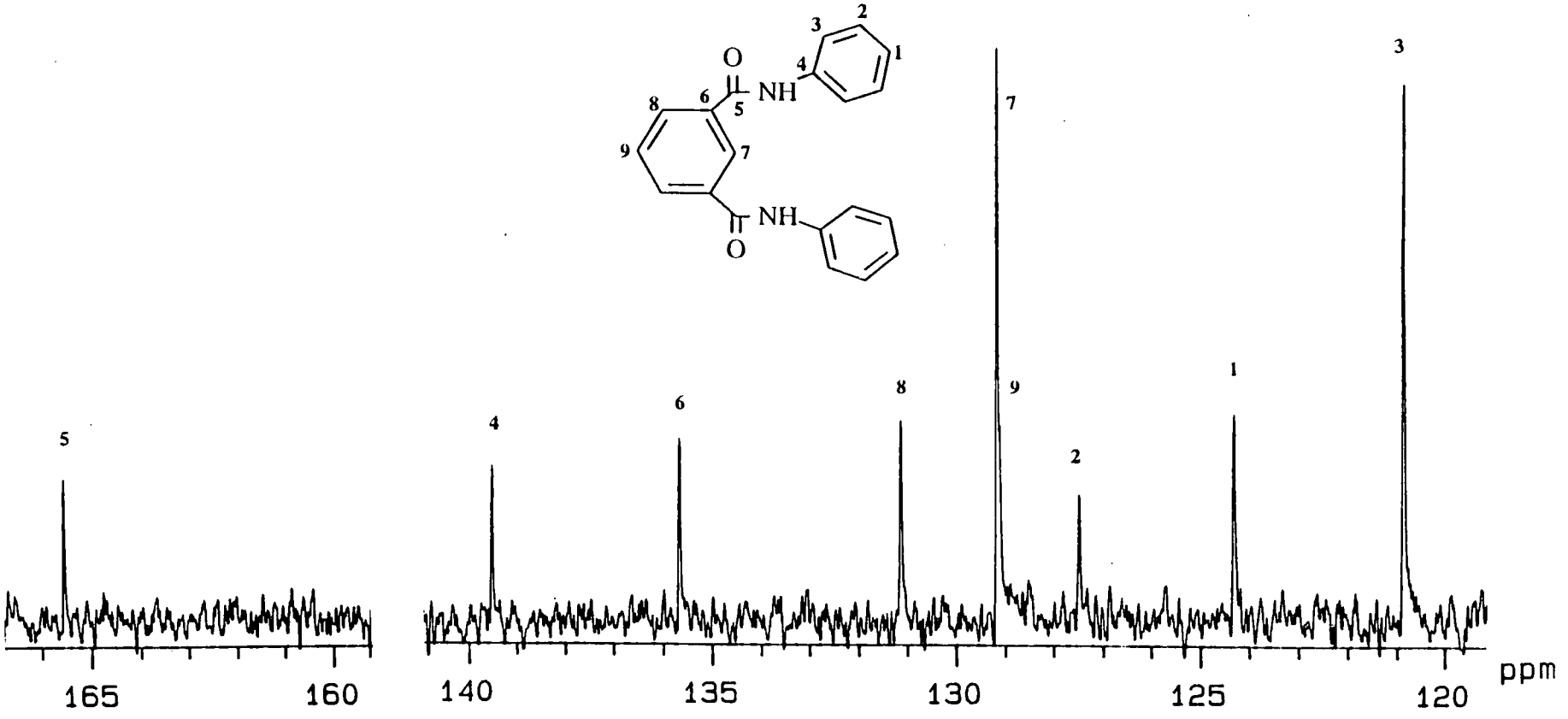
APPENDIX 4.1



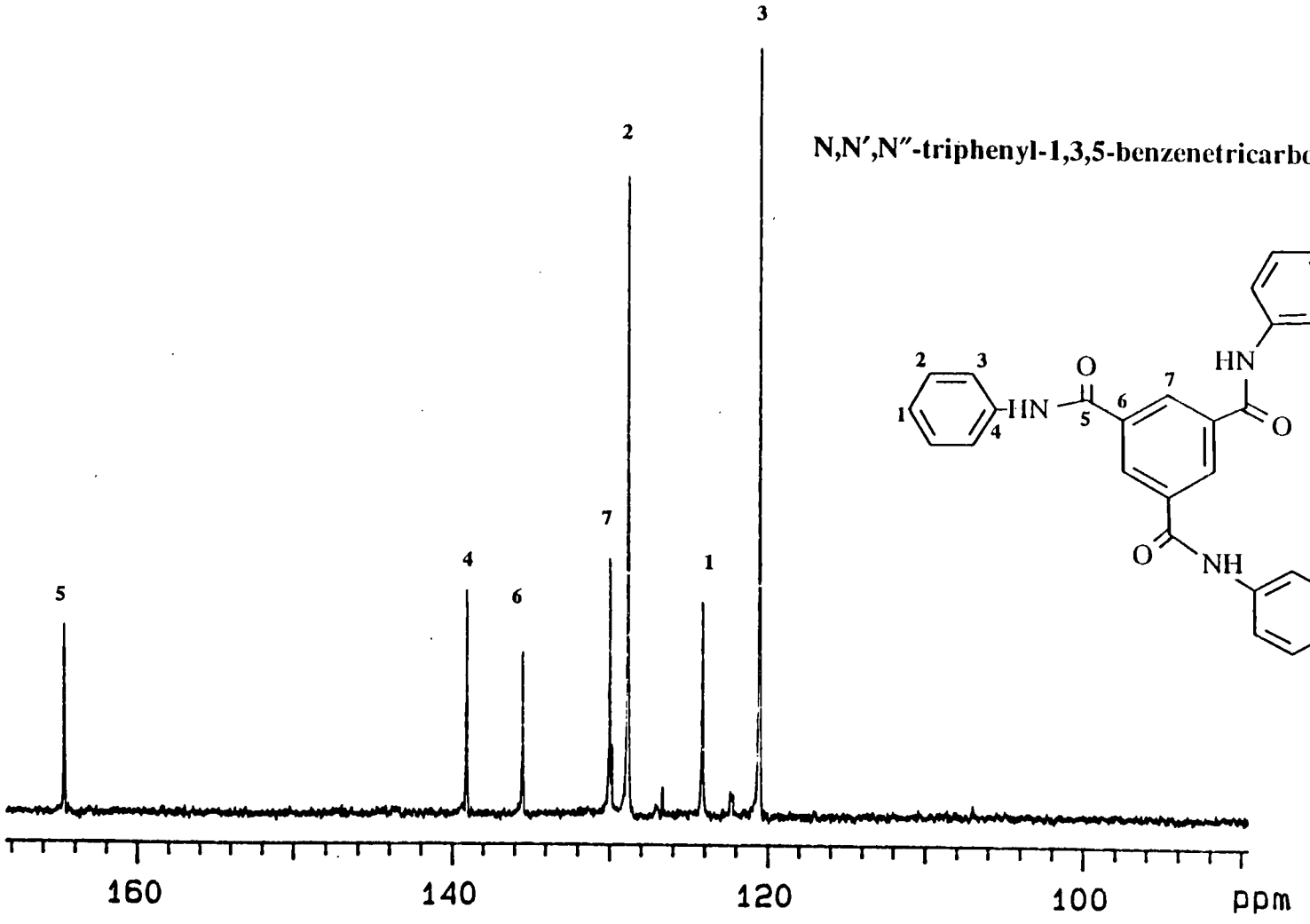
Benzanilide (I)

APPENDIX 4.2

N,N′-diphenyl-1,3-benzenedicarboxamide (III)



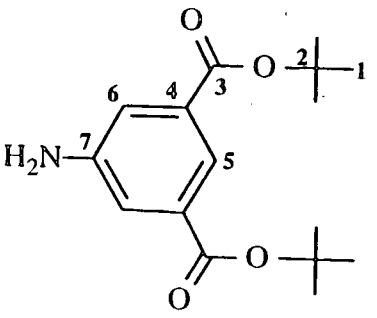
APPENDIX 4.3



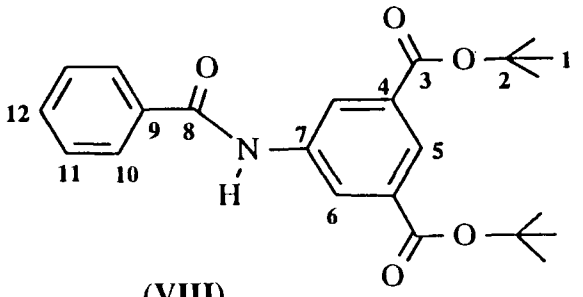
N,N′,N″-triphenyl-1,3,5-benzenetricarboxamide (IV)

APPENDIX 4.4

Di-t-butyl-5-aminoisophthalate (VII)



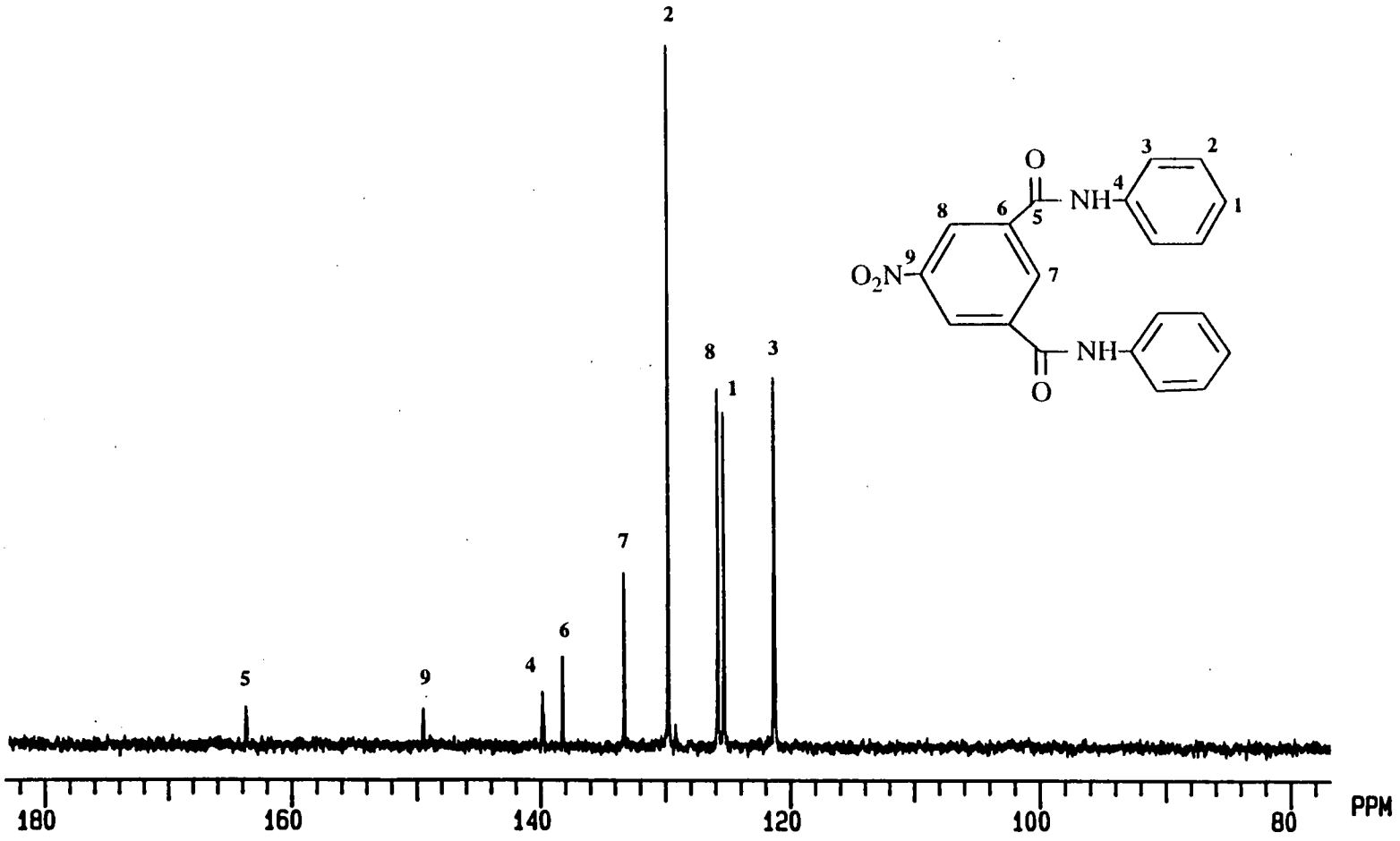
APPENDIX 4.5



(VIII)

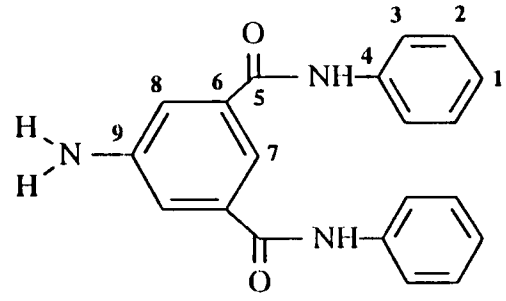
APPENDIX 4.6

N,N′-diphenyl-5-nitro-1,3-benzenedicarboxamide (X)

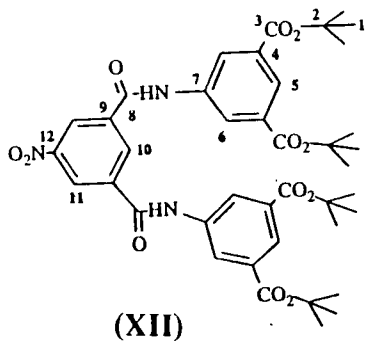


APPENDIX 4.7

N,N′-diphenyl-5-amino-1,3-dicarboxamide (XI)

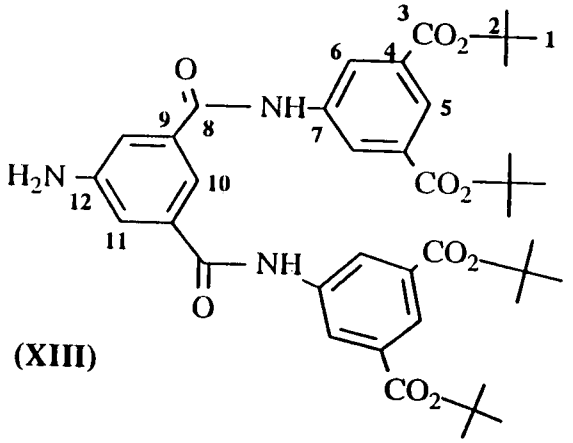


APPENDIX 4.8

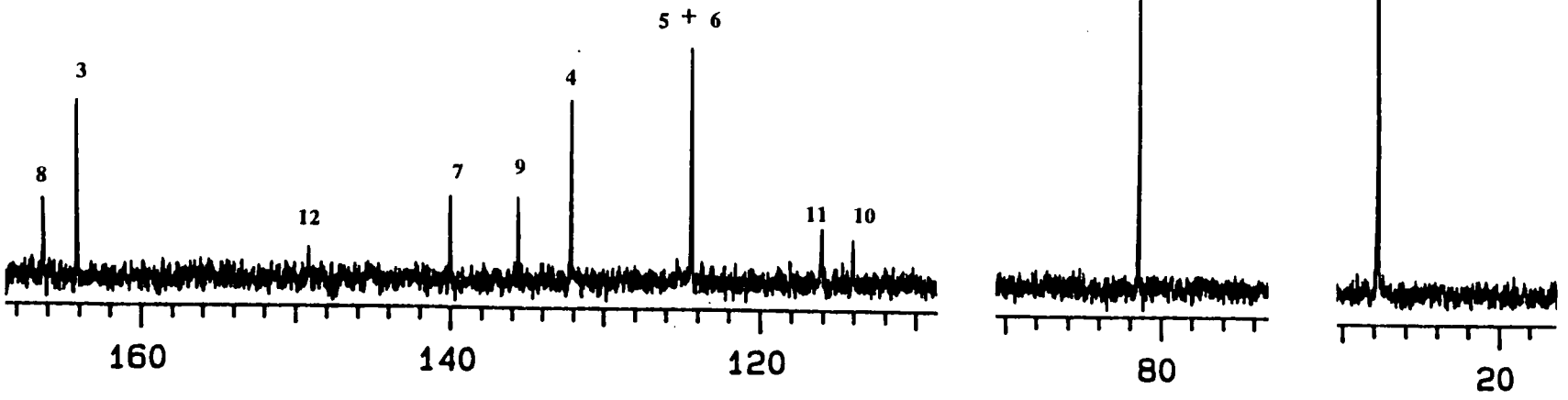


(XII)

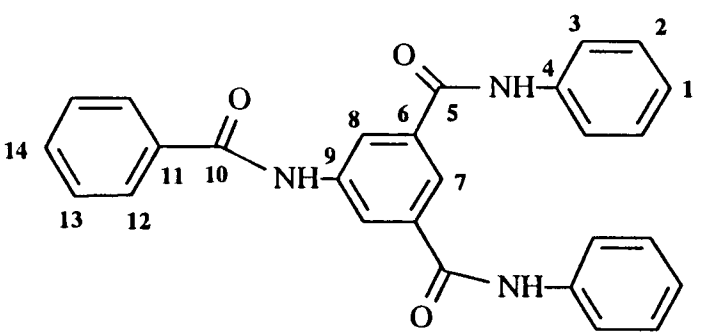
APPENDIX 4.9



(XIII)

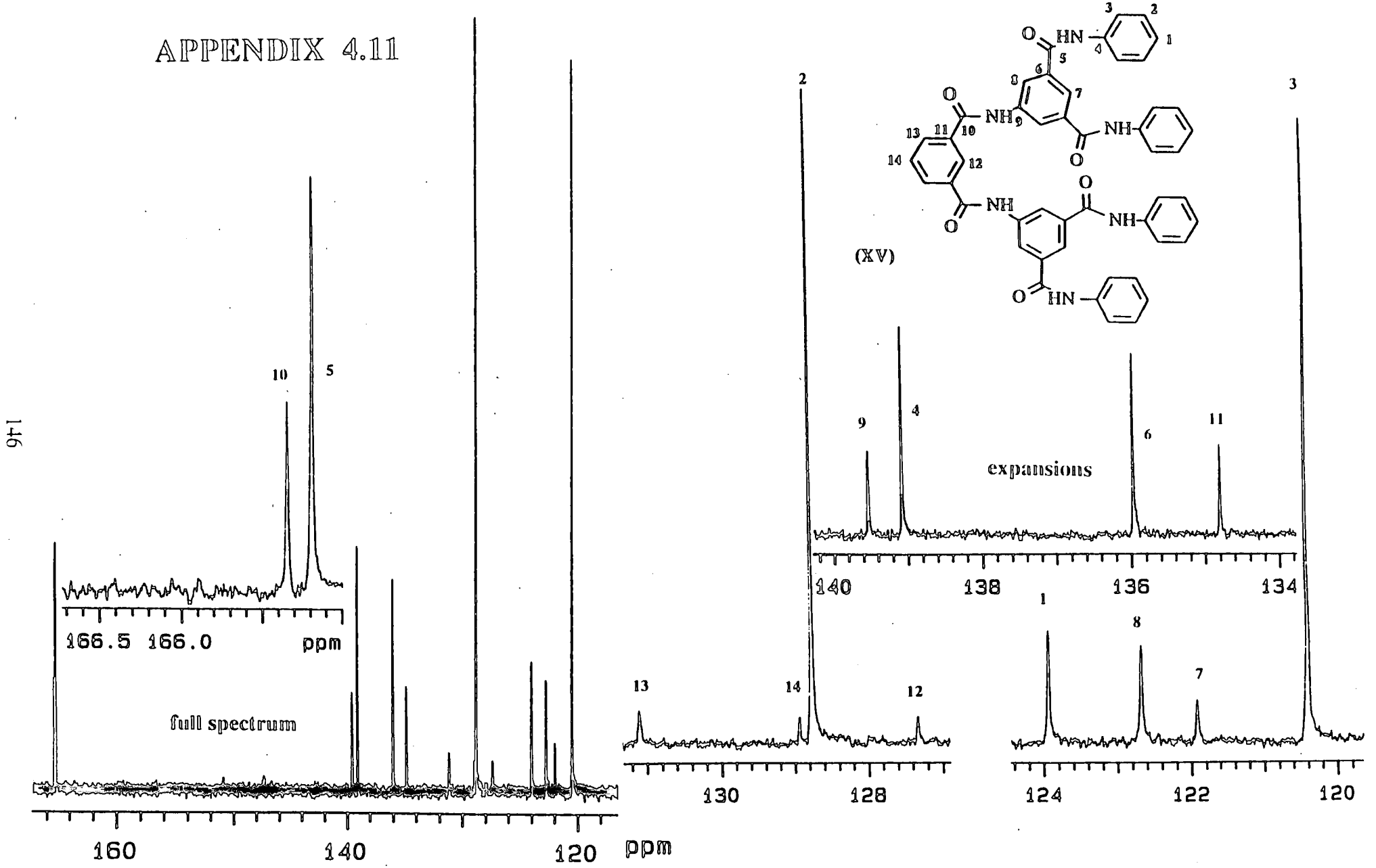


APPENDIX 4.10

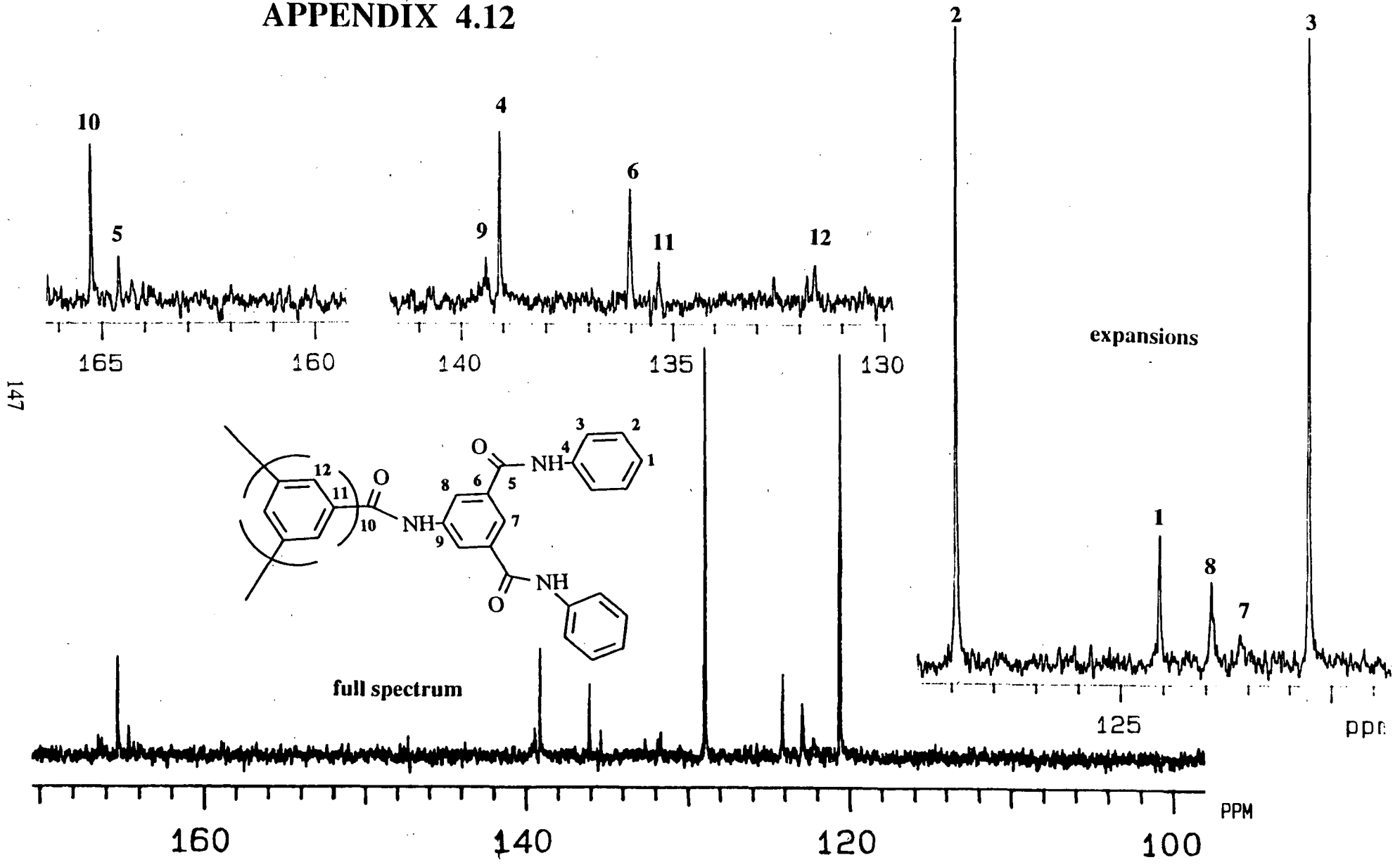


(XIV)

APPENDIX 4.11



APPENDIX 4.12

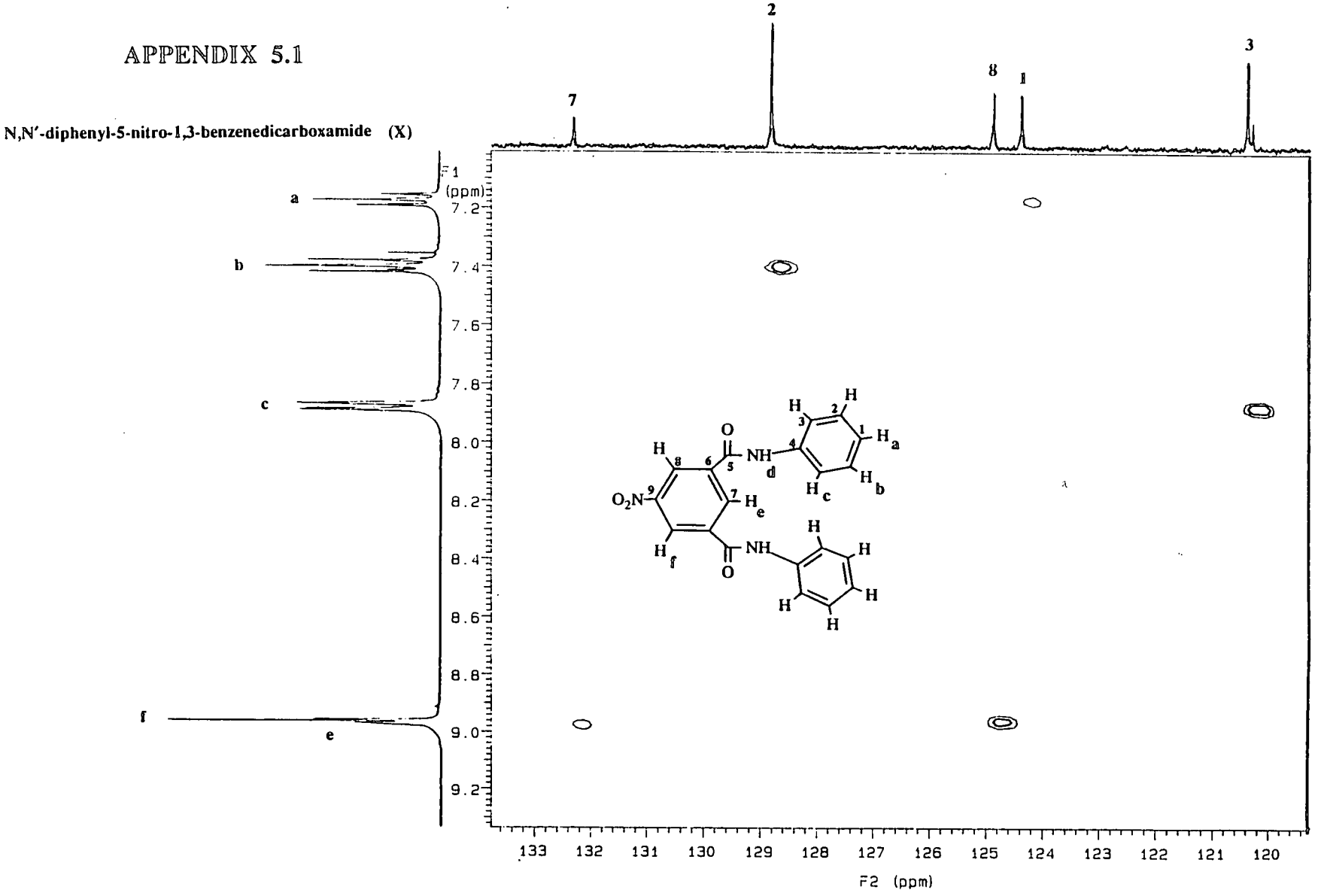


APPENDICES 5.1 to 5.5

^{1}H /^{13}C HETCOR SPECTRA

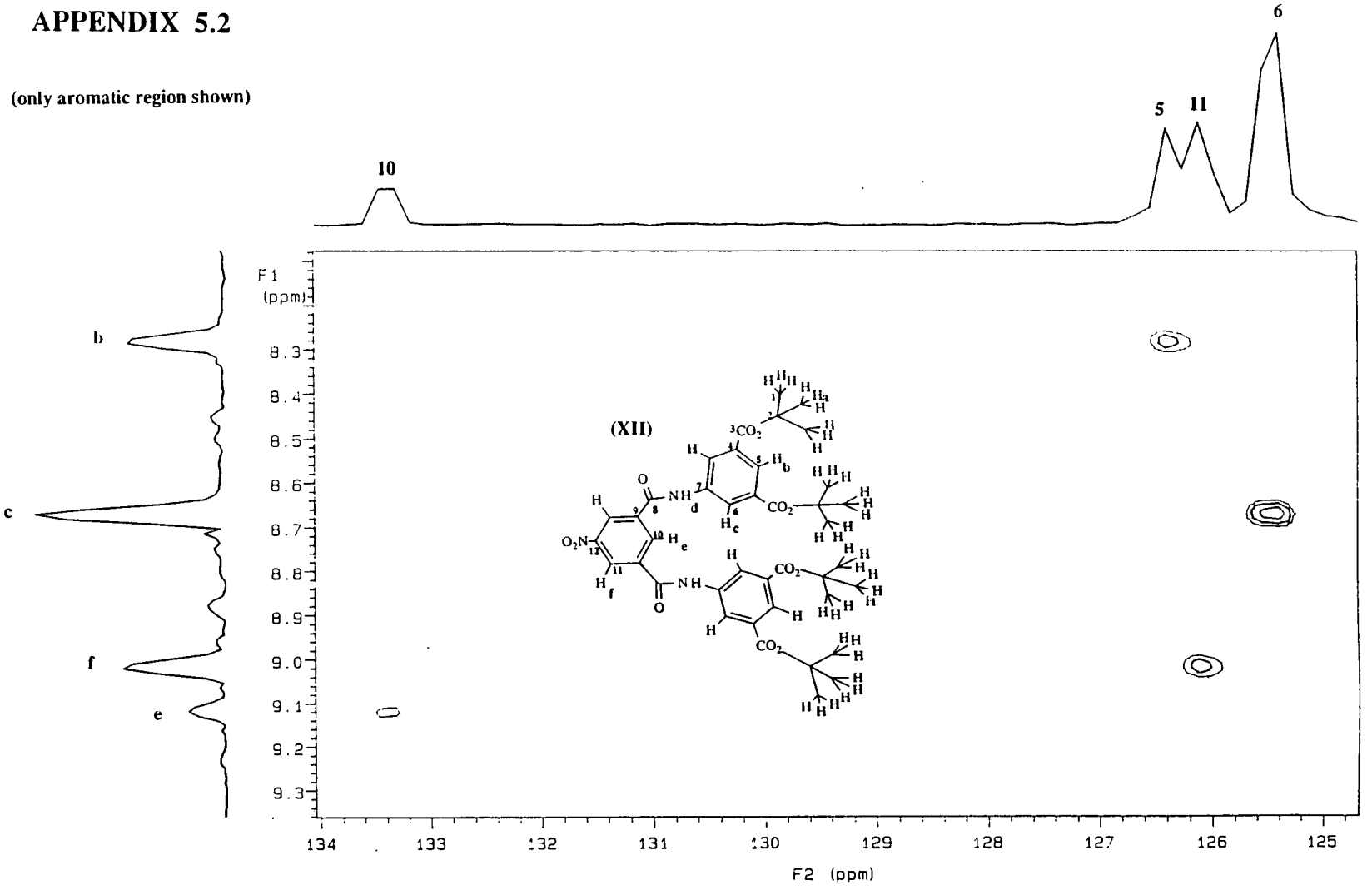
APPENDIX 5.1

N,N'-diphenyl-5-nitro-1,3-benzenedicarboxamide (X)

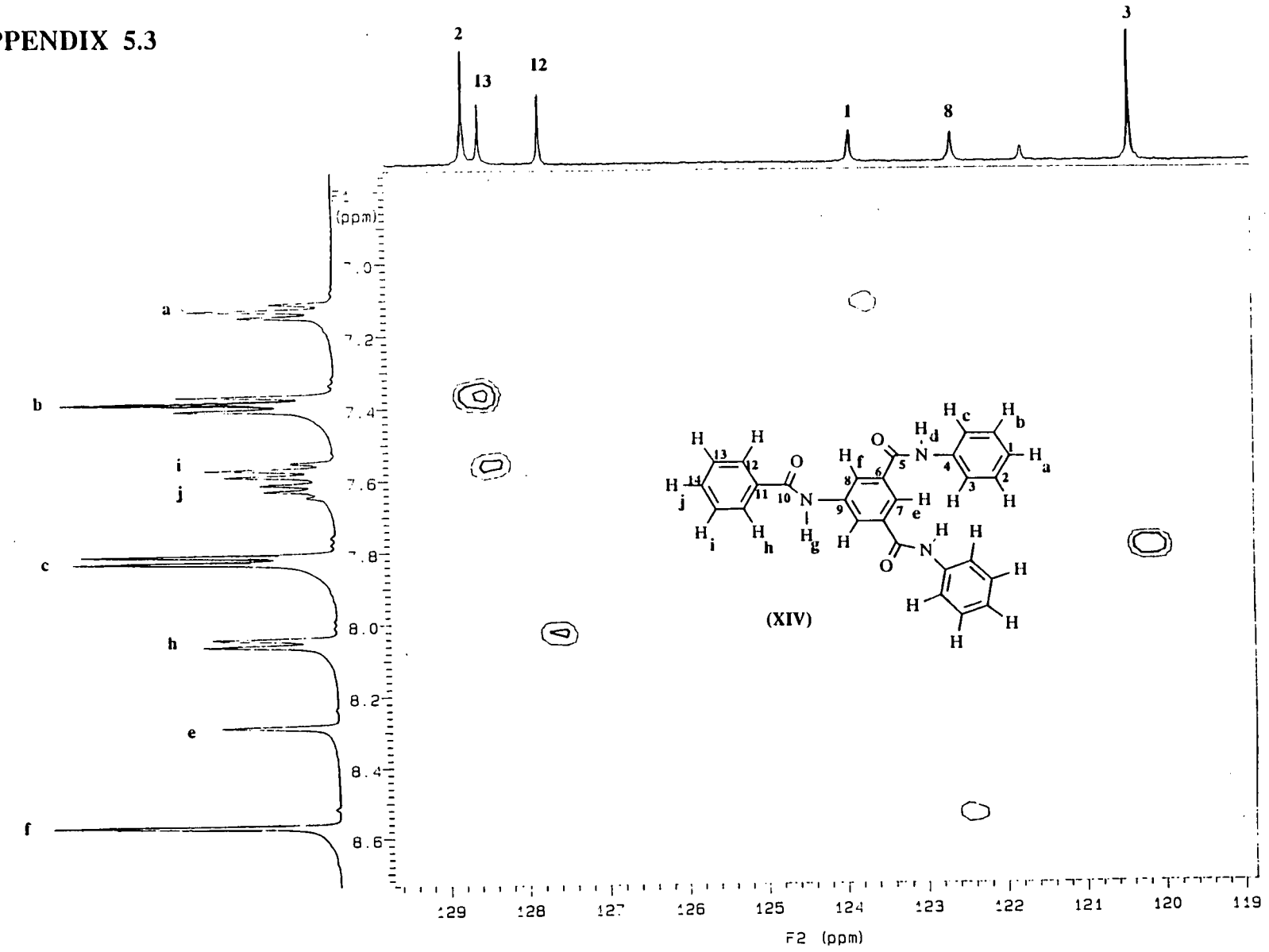


APPENDIX 5.2

(only aromatic region shown)

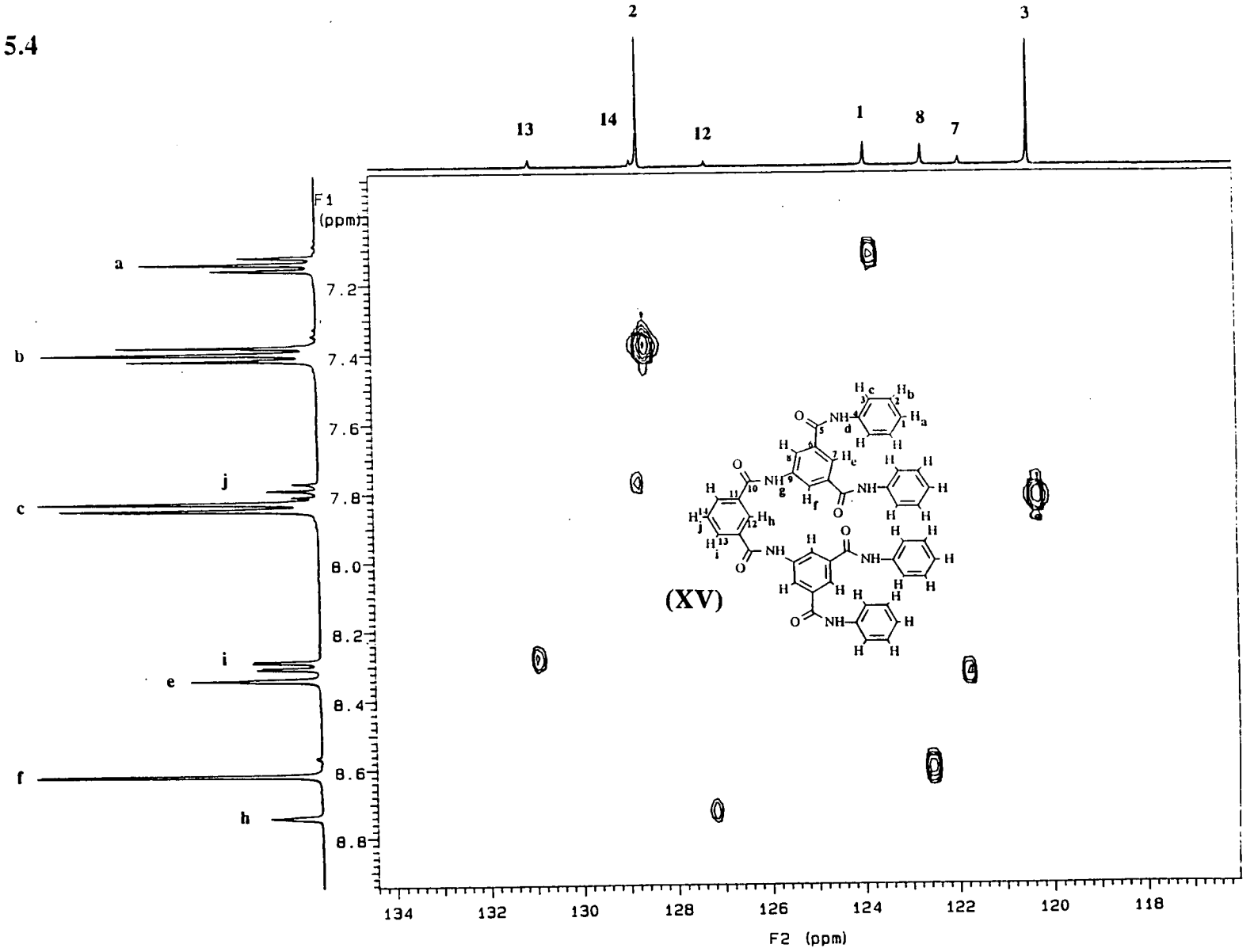


APPENDIX 5.3

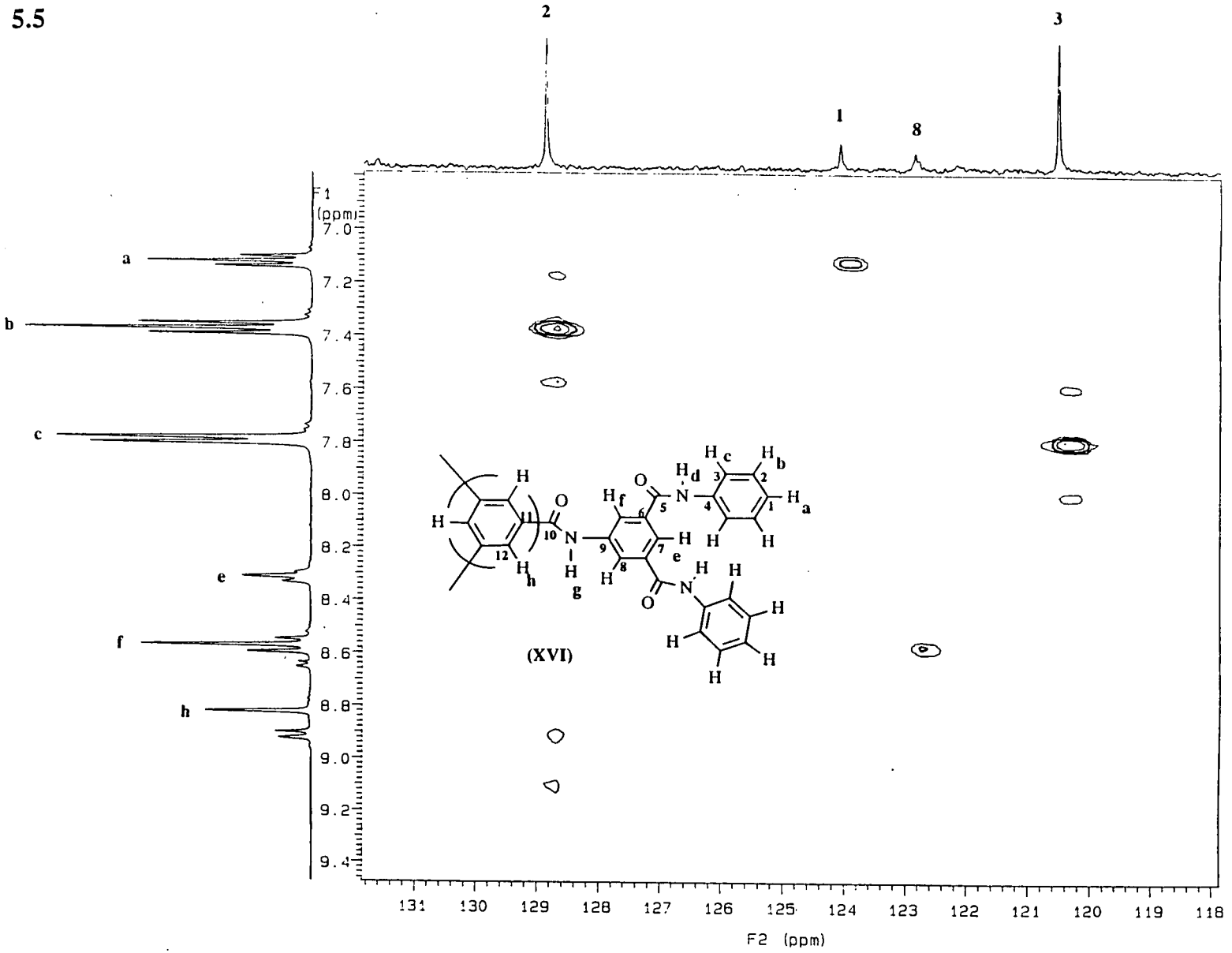


(XIV)

APPENDIX 5.4


2
3
13
14
12
1
8
7
F1
(ppm)
a
b
j
c
i
e
f
h
7.2
7.4
7.6
7.8
8.0
8.2
8.4
8.6
8.8
134
132
130
128
126
124
122
120
118
F2 (ppm)
(XV)

APPENDIX 5.5


2
3
1
8
F1 (ppm)
7.0
7.2
7.4
7.6
7.8
8.0
8.2
8.4
8.6
8.8
9.0
9.2
9.4
a
b
c
e
f
h
131
130
129
128
127
126
125
124
123
122
121
120
119
118
F2 (ppm)
(XVI)

APPENDIX 6

INSTRUMENTATION

Instrumentation

Mass spectra were recorded on a VG Analytical Model 7070E Mass Spectrometer.

Infrared spectra were recorded on a Perkin Elmer 1600 series Fourier Transform Infrared Spectrometer.

^{1}H and ^{13}C NMR spectra were recorded on a Varian VXR 400 NMR spectrometer at 399.952 MHz (^{1}H) and 100.577 MHz (^{13}C).

Thermogravimetric analysis was performed using a Stanton Redcroft TG760 thermobalance.

APPENDIX 7

RESEARCH COLLOQUIA, SEMINARS, LECTURES AND CONFERENCES

RESEARCH COLLOQUIA, SEMINARS, LECTURES AND CONFERENCES

The Board of Studies in Chemistry requires that each postgraduate research thesis contains an appendix listing:

(a) all research colloquia, seminars and lectures arranged by the Department of Chemistry during the period of the author's residence as a postgraduate student

(b) all research conferences attended by the author during the period of study.

UNIVERSITY OF DURHAM

Board of Studies in Chemistry

a) COLLOQUIA, LECTURES AND SEMINARS GIVEN BY INVITED SPEAKERS 1ST AUGUST 1989 TO 31ST JULY 1990

ASHMAN, Mr. A. (Durham Chemistry Teachers' Centre) — 11th October, 1989
The National Curriculum - an update

BADYAL, Dr. J.P.S. (Durham University) — 1st November, 1989
Breakthoughs in Heterogeneous Catalysis

BECHER, Dr. J. (Odense University) — 13th November, 1989
Synthesis of New Macrocylic Systems using Heterocyclic Building Blocks

BERCAW, Prof. J.E. (California Institute of Technology) — 10th November, 1989
Synthetic and Mechanistic Approaches to Ziegler-natta Polymerization of Olefins

BLEASDALE, Dr. C. (Newcastle University) — 21st February, 1990
The Mode of Action of some Anti-tumour Agents

BOLLEN, Mr. F.(Formerly Science Advisor, Newcastle LEA) — 27th March, 1990
Whats's New in Satis, 16-19

BOWMAN, Prof. J.M. (Emory University) — 23rd March, 1990
Fitting Experiment with Theory in Ar-OH

BUTLER, Dr. A. (St. Andrews University) — 7th December, 1989
The Discovery of Penicillin: Facts and Fancies

CAMPBELL, Mr. W.A. (Durham Chemistry Teachers' Centre) — 12th September, 1989
Industrial catalysis - some ideas for the National Curriculum

CHADWICK, Dr. P. (Dept. of Physics, Durham University) — 24th January, 1990
Recent Theories of the Universe (with Reference to National Curriculum Attainment Target 16)

CHEETHAM, Dr. A.K. (Oxford University) — 8th March, 1990
Chemistry of Zeolite Cages

CLARK, Prof. D.T. (ICI Wilton) — 22nd February, 1990
Spatially Resolved Chemistry (using Natures's Paradigm in the Advanced Materials Arena)

COLE-HAMILTON, Prof. D.J. (St. Andrews University) — 29th November, 1989
New Polymers from Homogeneous Catalysis

CROMBIE, Prof. L. (Nottingham University) — 15th February, 1990
The Chemistry of Cannabis and Khat

DYER, Dr. U. (Glaxo) — 31st January, 1990
Synthesis and Conformation of C-Glycosides

FLORIANI, Prof. C. (University of Lausanne, Switzerland) — 25th October, 1989
Molecular Aggregates - A Bridge between homogeneous and Heterogeneous Systems

GERMAN, Prof. L.S. (USSR Academy of Sciences - Moscow) — 9th July, 1990
New Syntheses in Fluoroaliphatic Chemistry: Recent Advances in the Chemistry of Fluorinated Oxiranes

GRAHAM, Dr. D. (B.P. Reserch Centre) — 4th December, 1989
How Proteins Absorb to Interfaces

GREENWOOD, Prof. N.N. (University of Leeds) — 9th November, 1989
Novel Cluster Geometries in Metalloborane Chemistry

HOLLOWAY, Prof. J.H. (University of Leicester) — 1st February, 1990
Noble Gas Chemistry

HUGHES, Dr. M.N. (King's College, London) — 30th November, 1989
A Bug's Eye View of the Periodic Table

HUISGEN, Prof. R. (Universität München) — 15th December, 1989
Recent Mechanistic Studies of [2+2] Additions

IDDON, Dr. B. (Univeristy of Salford) — 15th December, 1989
Schools' Christmas Lecture - The Magic of Chemistry

JONES, Dr. M.E. (Durham Chemistry Teachers' Centre) — 3rd July, 1990
The Chemistry A Level 1990

JONES, Dr. M.E. (Durham Chemistry Teachers' Centre) — 21st November 1989
GCSE and Dual Award Science as a starting point for A level Chemistry - how suitable are they?

JOHNSON, Dr. G.A.L. (Durham Chemistry Teachers' Centre) — 8th February, 1990
Some aspects of local Geology in the National Science Curriculum (attainment target 9)

KLINOWSKI, Dr. J. (Cambridge University) — 13th December 1989
Solid State NMR Studies of Zeolite Catalysts

LANCASTER, Rev. R. (Kimbolton Fireworks) — 8th February, 1990
Fireworks - Principles and Practice

LUNAZZI, Prof. L. (University of Bologna) — 12th February, 1990
Application of Dynamic NMR to the Study of Conformational Enantiomerism

PALMER, Dr. F. (Nottingham University) — 17th October, 1989
Thunder and Lightning

PARKER, Dr. D. (Durham University) — 16th November, 1989
Macrocycles, Drugs and Rock 'n' roll

PERUTZ, Dr. R.N. (York University) — 24th January, 1990
Plotting the Course of C-H Activations with Organometallics

PLATONOV, Prof. V.E. (USSR Academy of Sciences - Novosibirsk) — 9th July, 1990
Polyfluoroindanes: Synthesis and Transformation

POWELL, Dr. R.L. (ICI) — 6th December, 1989
The Development of CFC Replacements

POWIS, Dr. I. (Nottingham University) — 21st March, 1990
Spinning off in a huff: Photodissociation of Methyl Iodide

RICHARDS, Mr. C. (Health and Safety Executive, Newcastle) — 28th February, 1990
Safety in School Science Laboratories and COSHH

ROZHKOV, Prof. I.N. (USSR Academy of Sciences - Moscow) — 9th July, 1990
Reactivity of Perfluoroalkyl Bromides

STODDART, Dr. J.F. (Sheffield University) — 1st March, 1990
Molecular Lego

SUTTON, Prof. D. (Simon Fraser University, Vancouver B.C.) — 14th February, 1990
Synthesis and Applications of Dinitrogen and Diazo Compounds of Rhenium and Iridium

THOMAS, Dr. R.K. (Oxford University) — 28th February, 1990
Neutron Reflectometry from Surfaces

THOMPSON, Dr. D.P. (Newcastle University) — 7th February, 1990
The role of Nitrogen in Extending Silicate Crystal Chemistry

COLLOQUIA, LECTURES AND SEMINARS GIVEN BY INVITED SPEAKERS
1ST AUGUST 1990 TO 31ST JULY 1991

ALDER, Dr. B.J. (Lawrence Livermore Labs., California) — 15th January, 1991
Hydrogen in all its Glory

BELL†, Prof. T. (SUNY, Stoney Brook, U.S.A.) — 14th November, 1990
Functional Molecular Architecture and Molecular Recognition

BOCHMANN†, Dr. M. (University of East Anglia) — 24th October, 1990
Synthesis, Reactions and Catalytic Activity of Cationic Titanium Alkyls

BRIMBLE, Dr. M.A. (Massey University, New Zealand) — 29th July, 1991
Synthetic Studies Towards the Antibiotic Griseusin-A

BROOKHART, Prof. M.S. (University of N. Carolina) — 20th June, 1991
Olefin Polymerizations, Oligomerizations and Dimerizations Using Electrophilic Late Transition Metal Catalysts

BROWN, Dr. J. (Oxford University) — 28th February, 1991
Can Chemistry Provide Catalysts Superior to Enzymes?

BUSHBY†, Dr. R. (Leeds University) — 6th February, 1991
Biradicals and Organic Magnets

COWLEY, Prof. A.H. (University of Texas) — 13th December, 1990
New Organometallic Routes to Electronic Materials

CROUT, Prof. D. (Warwick University) — 29th November, 1990
Enzymes in Organic Synthesis

DOBSON†, Dr. C.M. (Oxford University) — 6th March, 1991
NMR Studies of Dynamics in Molecular Crystals

GERRARD†, Dr. D. (British Petroleum) — 7th November, 1990
Raman Spectroscopy for Industrial Analysis

HUDLICKY, Prof. T. (Virginia Polytechnic Institute) — 25th April, 1991
Biocatalysis and Symmetry Based Approaches to the Efficient Synthesis of Complex Natural Products

JACKSON†, Dr. R. (Newcastle University) — 31st October, 1990
New Synthetic Methods: α-Amino Acids and Small Rings

KOCOVSKY†, Dr. P. (Uppsala University) — 6th November, 1990
Stereo-Controlled Reactions Mediated by Transition and Non-Transition Metals

LACEY, Dr. D. (Hull University) — 31st January, 1991
Liquid Crystals

LOGAN, Dr. N. (Nottingham University) — 1st November, 1990
Rocket Propellants

MACDONALD, Dr. W.A. (ICI Wilton) — 11th October, 1990
Materials for the Space Age

MARKAM, Dr. J. (ICI Pharmaceuticals) — 7th March, 1991
DNA Fingerprinting

PETTY, Dr. M.C. (Durham University) — 14th February, 1991
Molecular Electronics

PRINGLE[+], Dr. P.G. (Bristol University) — 5th December, 1990
Metal Complexes with Functionalised Phosphines

PRITCHARD, Prof. J. (Queen Mary & Westfield College, London University) — 21st November, 1990
Copper Surfaces and Catalysts

SADLER, Dr. P.J. (Birkbeck College London) — 24th January, 1991
Design of Inorganic Drugs: Precious Metals, Hypertension + HIV

SARRE, Dr. P. (Nottingham University) — 17th January, 1991
Comet Chemistry

SCHROCK, Prof. R.R. (Massachusetts Institute of Technology) — 24th April, 1991
Metal-ligand Multiple Bonds and Metathesis Initiators

SCOTT, Dr. S.K. (Leeds University) — 8th November, 1990
Clocks, Oscillations and Chaos

SHAW[+], Prof. B.L. (Leeds University) — 20th February, 1991
Syntheses with Coordinated, Unsaturated Phosphine Ligands

SINN[+], Prof. E. (Hull University) — 30th January, 1991
Coupling of Little Electrons in Big Molecules. Implications for the Active Sites of (Metalloproteins and other) Macromolecules

SOULEN[+], Prof. R. (South Western University, Texas) — 26th October, 1990
Preparation and Reactions of Bicycloalkenes

WHITAKER[+], Dr. B.J. (Leeds University) — 28th November, 1990
Two-Dimensional Velocity Imaging of State-Selected Reaction Products

[+] Invited specifically for the postgraduate training programme.

b) RESEARCH CONFERENCES

NEW ORGANIC MATERIALS ***International Symposium***

University of Durham 10th -12th September 1990

Organized by the Royal Society of Chemistry

Perkin Division and Macro Group (UK)

POLYMER SURFACES AND INTERFACES II ***International Symposium***

University of Durham 22nd - 26th July 1991

Organized by the Macro Group (UK)

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