MELDOLA LECTURE: understanding the properties of urea and thiourea inclusion compounds*

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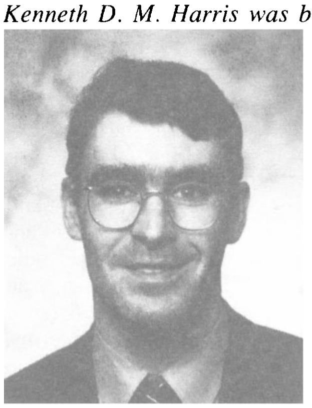
Much of the intrinsic appeal of structural science arises from the fact that structural behaviour at the molecular level often resembles macroscopic structures that we can see in the world around us. In the same way that we perceive beauty in the symmetries and forms of macroscopic objects, there is an equally enthralling beauty in the way that nature fashions symmetry and diversity within the architectures of crystalline solids. In the field of inclusion chemistry, for example, many direct analogies can be drawn between the concepts of inclusion in the microscopic and macroscopic worlds, but the scientific interest and importance of inclusion chemistry extends far beyond such structural comparisons. As this article demonstrates, solid organic inclusion compounds can exhibit a diversity of interesting and important fundamental properties, which can form the basis of a range of important applications.

1 Introduction

In general, inclusion compounds can be defined as systems in which one species (the 'guest') is spatially confined within another species (the 'host'). Inclusion phenomena are widespread throughout chemistry (see ref. 1 for a comprehensive survey of this field), and can be subdivided into two types. The first type comprises molecular host–guest complexes, in which the host is a molecule possessing an appropriate binding site or cavity for inclusion of the guest. Such complexes can usually exist as associated entities both in the solid state and in dispersed phases (for example, in solution). Examples of these hosts are crown ethers, cyclodextrins, cryptands, rotaxanes and catenanes.

In the second type of inclusion compound, guest molecules are located within the architecture of a solid host material, and in these cases the association of host and guest components is strictly a solid state phenomenon. The 'inclusion spaces' within these solid hosts encompass a wide variety of topologies, such as linear tunnels, isolated cages, networks of intersecting tunnels and/or cages, and two-dimensional inter-lamellar regions within layered hosts. Well known examples of solid host materials are aluminosilicates (such as zeolites and clay minerals), aluminophosphates, graphite, layered metal chalcogenides and layered metal phosphonates, as well as crystalline organic hosts such as urea, thiourea, tri-*ortho*-thymotide, perhydrotriphenylene and deoxycholic acid. In these host solids, the smallest dimension of the 'inclusion spaces' is of the order of molecular dimensions, and these host structures are therefore able to include individual guest molecules in a manner in which the spatial constraints on the properties of the guest molecules are imposed primarily by their host environment.



Kenneth D. M. Harris was born in Alexandria (Scotland) in 1963 and educated at the University of St Andrews (BSc, 1985) and the University of Cambridge (PhD, 1988), carrying out research for the PhD under the guidance of Professor Sir John Meurig Thomas. He then held lectureships at the University of St Andrews and University College London, before taking up his present position as Professor of Structural Chemistry at the University of Birmingham in 1995.

Within the broad range of solid inclusion compounds, there is an important subdivision between those for which the host structure remains stable when the guest component is removed and those for which the host structure undergoes substantial reorganization when the guest component is removed. For convenience, the terms 'hard' host (for the former category) and 'soft' host (for the latter category) may be used to distinguish these different types of behaviour. In the case of the soft hosts, the structural reorganization generally involves collapse of the low-density 'empty' host structure, with recrystallization to a more compact structure of higher density. Thus, for inclusion compounds of the soft hosts, the guest component generally acts as an essential template for the formation of the host structure as well as an essential buttress for maintaining the stability of the host structure; the collapse of the host structure on removal of the guest component is often an irreversible process. The exact structural nature of the soft hosts often varies substantially depending on the structural and chemical properties of the guest molecules. There is a greater synergy in properties between the host and guest components in the case of the soft hosts, and it is generally not satisfactory to attempt to rationalize the properties of these inclusion compounds in terms of the separate behaviour of the host and guest components.

This article describes some of the fundamental scientific issues associated with two particular families of solid organic inclusion compounds—the urea and thiourea inclusion compounds. These inclusion compounds exhibit a broad range of fundamental phenomena, and progress in understanding these phenomena has resulted from a substantial amount of work by many scientists over many years, as discussed in a recent comprehensive review.[2] Underpinning the research strategy that has allowed a detailed understanding of these solids to be established, has been the recognition that to understand fully the behaviour of a solid requires the combined application of a wide range of experimental, computational and theoretical approaches, each providing information on a different aspect of the solid. The present article aims to highlight some of the issues of contemporary interest for urea and thiourea inclusion compounds, with some emphasis on selected results from our own recent contributions to this field.

2 Urea inclusion compounds

2.1 An introduction to urea inclusion compounds

Urea inclusion compounds were first discovered in the 1940s by Bengen, who found by chance (while studying the effects of

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urea on proteins in pasteurised milk) that octanol forms a crystalline adduct with urea. Subsequently, it was found that a wide range of long-chain molecules can form similar adducts with urea, and X-ray diffraction studies carried out by Smith[3] provided direct evidence that these materials are based on a tunnel host structure. In the structure of the conventional urea inclusion compounds,[3,4] the urea molecules form an extensively hydrogen-bonded arrangement (Fig. 1) containing linear, parallel tunnels; the guest molecules are densely packed along these tunnels. The host structure is hexagonal ($P6_122$; $a = b \approx 8.2$ Å; $c \approx 11.0$ Å) at ambient temperature, with the effective tunnel 'diameter' between *ca.* 5.5 and 5.8 Å. It is important to note that $P6_122$ is a chiral space group, and aspects of the chirality of urea inclusion compounds are discussed in Section 2.5.

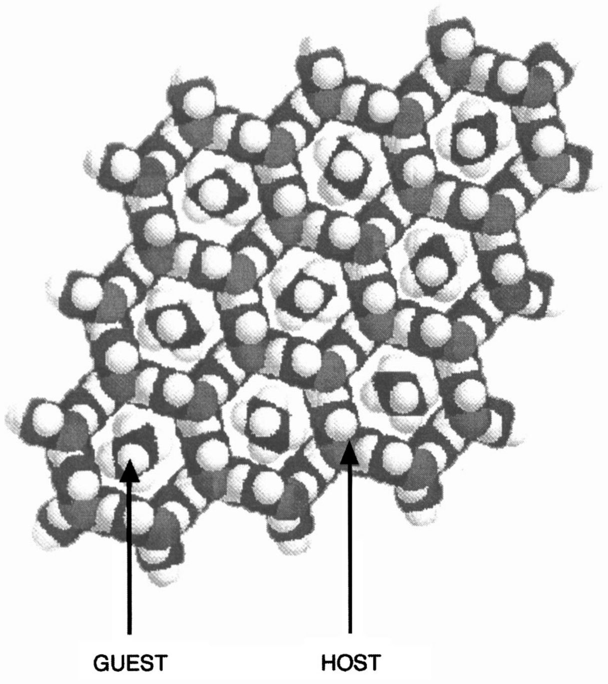


Fig. 1 The hexadecane–urea inclusion compound at ambient temperature, showing nine complete tunnels with van der Waals radii, viewed along the tunnel axis. The guest molecules have been inserted into the tunnels, illustrating orientational disorder (the positions of the guest molecules are not actually determined from X-ray diffraction data at ambient temperature).

Structural compatibility between host and guest components is fundamental to most inclusion phenomena, and as a consequence, urea only forms inclusion compounds with guest molecules that are based on a sufficiently long alkane chain with only a limited degree of substitution of this chain allowed. Examples of appropriate guest molecules (Fig. 2) are alkanes and derivatives such as α,ω-dihaloalkanes, diacyl peroxides, carboxylic acids, alkanones, α,ω-alkane dicarboxylic acids, $(\alpha + 1),(\omega - 1)$-alkanediones and carboxylic acid anhydrides. In general, molecules containing a benzene ring or a cyclohexane ring do not form inclusion compounds with urea, presumably because these structural components are too wide to fit inside the urea tunnel. On the basis of empirical observations, generalizations on the characteristic molecular features in the guest molecules that form inclusion compounds with urea have been established.[2,5,6] As a direct consequence of the requirement for size and shape compatibility between the host and guest components, urea inclusion compounds may be used in applications based on molecular separation, such as the separation of linear and branched alkanes from mixtures. Indeed, this was the motivation for much of the early research (particularly within the petrochemicals industry) on urea inclusion compounds, before the realization that zeolitic materials offer several advantages in such applications. Nevertheless, the use of urea inclusion compound formation as a method for isolating linear molecules is still used on the laboratory scale by synthetic organic chemists.

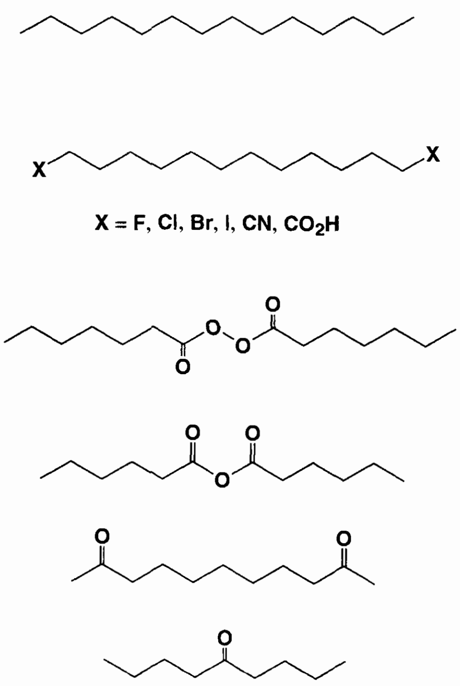


Fig. 2 Representative examples of guest molecules that form inclusion compounds with urea.

The urea tunnel structure is an example of a soft host structure, and it has been shown (both by experiment and computer simulation) that the tunnels collapse if the guest molecules are removed from the inclusion compound; the urea then recrystallizes in its 'pure' crystalline phase, which does not contain empty tunnels. Clearly the instability of the 'empty' urea tunnel structure provides some limitations on the scope for applications of urea inclusion compounds.

While we focus here on urea inclusion compounds that have the conventional urea tunnel structure (shown in Fig. 1) at ambient temperature, it is important to note that certain guest molecules induce significant changes in this host structure; in general, such changes occur when there is a commensurate relationship (see Section 2.2.1) between the host and guest substructures in the inclusion compound. Examples are the urea inclusion compounds containing 1,6-dibromohexane[7] and sebaconitrile[8] guest molecules. In a comprehensive series of investigations, Hollingsworth has shown[9] that urea inclusion compounds containing $(\alpha + 1),(\omega - 1)$-alkanedione guest molecules are also of this type, and exhibit an interesting diversity of commensurate superstructures.

2.2 Periodic structural properties

2.2.1 One-dimensional properties: the incommensurate structural nature

An important fundamental property of solid inclusion compounds is the degree of structural registry between the host and guest substructures. In general, the guest molecules in conventional urea inclusion compounds are arranged in a periodic manner (repeat distance c_g) along the host tunnels, with an incommensurate relationship between c_g and the repeat distance (c_h) of the urea molecules along the tunnel. In classical terms, the inclusion compound is incommensurate if there are no sufficiently small integers p and q for which $p\,c_h \approx q\,c_g$, and commensurate if sufficiently small integers p and q can be found to satisfy this equality. One consequence, with important physico-chemical implications, of an incommensurate structural relationship between the host and guest components is that different guest molecules within a given tunnel sample a range of different environments with respect to the host structure.

For several reasons, the classical (structural) definition of incommensurate and commensurate systems given above is far from satisfactory (a detailed discussion of this issue, and of commensurate and incommensurate behaviour in one-dimensional inclusion compounds in general, is given in ref. 10). To understand the commensurate *versus* incommensurate nature of one-dimensional inclusion compounds at a more fundamental level, new directions have led to the development[10] of a commensurate/incommensurate classification that reflects a division in the energetic behaviour of the inclusion compounds within each category. Specifically, the classification (Fig. 3) is based on the magnitude of fluctuations in the average host–guest interaction energy per guest molecule as the guest substructure is moved along the tunnel (keeping the guest periodicity c_g fixed). If these fluctuations are sufficiently small (*i.e.* within ±ε, where ε is some physically meaningful energy term) the inclusion compound is considered to exhibit incommensurate behaviour, whereas if these fluctuations are sufficiently large (*i.e.* larger than ±ε) the inclusion compound is considered to exhibit commensurate behaviour. In the commensurate case, a significant energetic 'lock-in' between the host and guest substructures will occur for a specific position of the guest substructure relative to the host substructure, whereas for the incommensurate case, the energy of the inclusion compound is essentially independent of the position of the guest substructure relative to the host substructure.

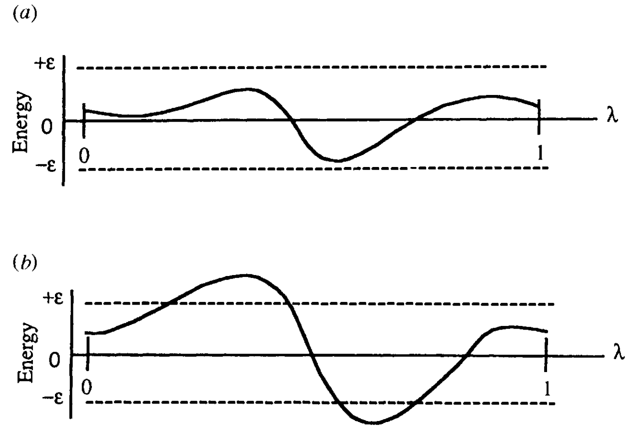


Fig. 3 Schematic graphs illustrating the fluctuation in average host–guest interaction energy per guest molecule on moving the guest substructure along the host tunnel for: (*a*) an inclusion compound that exhibits incommensurate behaviour; and (*b*) an inclusion compound that exhibits commensurate behaviour. See ref. 10 for full details.

Methodology has been developed[11] for applying these new concepts to predict structural properties of one-dimensional inclusion compounds from knowledge of potential energy functions for the inclusion compound (with known host structure and fixed c_h). Fundamental to this approach is the definition of an appropriate energy expression—the 'characteristic energy'—that directly indicates the relative energetic favourability of inclusion compounds with different guest periodicities. The characteristic energy $\hat{E}(\alpha,n)$ is defined by eqn. (1), where: n is the number of guest molecules within the

$$\hat{E}(\alpha,n) = \frac{1}{\alpha}\left(\inf_{\lambda}\left(\frac{1}{n}\sum_{k=0}^{n-1} E_h(k\alpha+\lambda)\right) + \hat{E}_{guest}(\alpha) + \hat{E}_{intra}\right) \qquad (1)$$

host tunnel; α is the scaled guest periodicity c_g/c_h; the first guest molecule is located at position $t = \lambda$ along the tunnel; $E_h(t)$ is the host–guest interaction energy for an individual guest molecule at position t along the tunnel; $\hat{E}_{guest}(\alpha)$ is the guest–guest interaction energy per guest molecule when the scaled periodicity of the guest molecules is α; and $\hat{E}_{intra}$ is the intramolecular potential energy of the guest molecule. The optimum guest structure for the inclusion compound corresponds to minimum characteristic energy, and the methodology allows the following structural properties to be established from the computed potential energy functions $E_h(t)$, $\hat{E}_{guest}(\alpha)$ and $\hat{E}_{intra}$ for the inclusion compound of interest: (*i*) the optimum guest periodicity (c_g); (*ii*) whether this value of c_g corresponds to commensurate or incommensurate behaviour; (*iii*) the optimum conformation of the guest molecules within the host structure. Importantly, the methodology can handle tunnels of finite length, allowing the properties of 'real' one-dimensional inclusion compounds to be predicted directly.

The methodology has been applied successfully[12] to predict structural properties of alkane–urea inclusion compounds, giving results in excellent agreement with experimental observations, and leading to new insights concerning the energetic properties of these inclusion compounds. *Inter alia*, the results demonstrate that, in the optimum structure of these incommensurate inclusion compounds, the interaction between neighbouring guest molecules in the same tunnel is repulsive, in agreement with inferences from X-ray diffraction data.[13,12]

We now consider the experimental investigation of incommensurateness in solid inclusion compounds, recalling that comparison of values of c_g and c_h measured from diffraction data is generally not a satisfactory approach. An alternative approach is based on recognizing that conventional crystals (including commensurate inclusion compounds) have three translation invariances, whereas an incommensurate one-dimensional inclusion compound has four translation invariances; the extra translation invariance corresponds to the shift of the guest substructure relative to the host substructure along the incommensurate direction (as discussed above, the energy of an incommensurate inclusion compound is, in principle, independent of the shift of the guest substructure relative to the host substructure along this direction). Corresponding to each translation invariance in a crystal there is an acoustic phonon, and therefore an incommensurate one-dimensional inclusion compound should have four acoustic phonons and a commensurate inclusion compound should have three acoustic phonons. The additional acoustic mode in the incommensurate system is called the 'sliding mode', and observation of the sliding mode can be taken as direct experimental evidence for incommensurate behaviour of the inclusion compound. With this motivation, Brillouin scattering investigations[14] of the heptadecane–urea inclusion compound have provided direct evidence for a fourth acoustic mode, assigned as the sliding mode, thus substantiating the incommensurate nature of this inclusion compound. It is interesting to reflect that the new (energetic) definition of commensurate *versus* incommensurate behaviour discussed above is directly akin to the concept of a sliding mode for an incommensurate material.

Before discussing the three-dimensional structural properties of urea inclusion compounds (Section 2.2.2), it is relevant to consider some of the wider consequences of the incommensurate structural relationship between the host and guest substructures along the tunnel. Although the host and guest substructures possess different structural periodicities (as a consequence of the incommensurate relationship), these two substructures are not independent, since each substructure will exert an incommensurate modulation upon the other. The three-dimensional host substructure is best considered in terms of a 'basic structure' which is subjected to an incommensurate modulation through its interaction with the guest substructure; the basic structure can be described using conventional crystallographic principles (*e.g.* three-dimensional space group symmetry). In a similar way, the guest substructure can be considered in terms of an incommensurately modulated 'basic structure'. The incommensurate modulations describe perturbations to the basic structures that arise as a result of host–guest interaction. A full discussion of these structural issues for the urea inclusion compounds is given elsewhere.[4,15,16]

2.2.2 *Three-dimensional ordering of guest molecules*

We now consider the ordering of guest molecules in three dimensions within the urea host structure, focusing first on the positional relationship between guest molecules in adjacent tunnels. The inter-tunnel ordering of the guest molecules in urea inclusion compounds is conveniently described in terms of two parameters (Fig. 4): c_g and Δ_g (Δ_g is the offset, along the tunnel axis, between the centres of mass of guest molecules in adjacent tunnels). Importantly, it is found that the nature of the inter-tunnel ordering depends critically on the functional groups present on the guest molecule, with different families of guest molecule exhibiting different characteristic modes of inter-tunnel ordering. Results for selected families of guest molecule at ambient temperature are summarized as follows: (*i*) alkane–urea inclusion compounds[17]— $\Delta_g = 0$ (independent of the value of c_g), with c_g increasing linearly with the number of CH_2 groups in the alkane molecule; (*ii*) diacyl peroxide–urea inclusion compounds[18]—$\Delta_g = 4.6$ Å (independent of the value of c_g); (*iii*) α,ω-dibromoalkane–urea inclusion compounds[19]—Δ_g depends on the value of c_g, with Δ_g and c_g related by the exact relationship $\Delta_g = c_g/3$; (*iv*) carboxylic acid anhydride–urea inclusion compounds[20]—$\Delta_g = 0$, with the exception of heptanoic anhydride–urea, for which $\Delta_g = 2.3$ Å. It is important to emphasize that these well-defined correlations between the positions of guest molecules in different tunnels (which are separated by more than 8 Å) exist despite the fact (arising from the incommensurate relationship between the host and guest substructures) that there is no well-defined positioning of guest molecules relative to the host substructure.

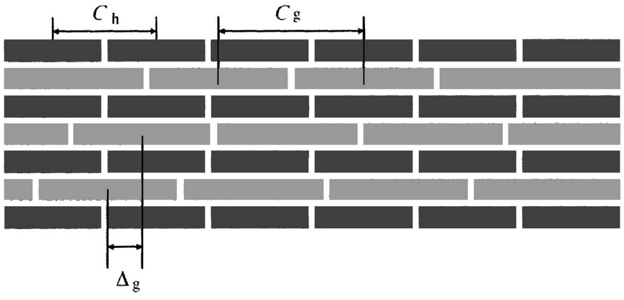


Fig. 4 Schematic two-dimensional representation of a urea inclusion compound, viewed perpendicular to the tunnel axis, indicating the definitions of c_g, c_h and Δ_g

The complete three-dimensional packing arrangement of guest molecules within the urea tunnel structure can be understood by extending the Δ_g concept into three dimensions. Thus, at ambient temperature, the basic guest structure in diacyl peroxide–urea inclusion compounds is monoclinic (probable space group *C*2), the basic guest structure in α,ω-dibromoalkane–urea inclusion compounds is rhombohedral (probable space group *R*32) and the basic guest structure in alkane–urea inclusion compounds is hexagonal (probable space group *P*622). In some cases, these symmetries require disorder of the guest molecules. In the case of the diacyl peroxide–urea and α,ω-dibromoalkane–urea inclusion compounds, the symmetry of the basic guest structure is lower than the symmetry of the basic host structure, and generally a given single crystal of these inclusion compounds contains different domains of the guest substructure—each domain has an identical packing of guest molecules, but has a different (although equivalent) orientation relative to the host structure, with the different domains related by rotation about the tunnel axis. It should be emphasized that while the diffraction data allow the average periodicity and symmetry of the basic guest structure to be determined, disorder of the guest molecules (see also Section 2.4) has made it impossible to actually solve the basic guest structure for any conventional urea inclusion compound at ambient temperature.

As a consequence of the incommensurate relationship between the host and guest substructures in urea inclusion compounds, the symmetry of the composite inclusion compound cannot be described by a three-dimensional space group, but instead requires a four-dimensional superspace group. Descriptions of the symmetry properties of urea inclusion compounds in superspace groups have been developed.[15]

The development of a fundamental understanding of the factors that control the three-dimensional ordering of guest molecules in urea inclusion compounds is an issue of particular importance at present. The incommensurate modulations are undoubtedly important in establishing well-defined positional correlations between the guest molecules in adjacent tunnels, with the relative positioning of guest molecules in adjacent tunnels thus controlled by their mutual interaction with the urea molecules in the 'tunnel wall' between these tunnels. However, so far it has not been possible to determine the extent of the modulations in the host and guest substructures (which would require the structure of the composite inclusion compound to be solved in a superspace group as discussed above). Thus, at present, our understanding of the structural properties of the urea inclusion compounds is confined to the separate knowledge of the basic structures of the host and guest subsystems.

2.2.3 *Structural properties at low temperature*

All structural properties described so far have been at ambient temperature. At sufficiently low temperature, most conventional urea inclusion compounds undergo a phase transition which is associated, *inter alia*, with a change in symmetry of the basic host structure [hexagonal in the high-temperature phase, usually becoming orthorhombic in the low-temperature phase (Fig. 5)] and a change in the dynamic properties of the guest molecules (see Section 2.4).

These phase transitions have been investigated extensively for alkane–urea and α,ω-dibromoalkane–urea inclusion compounds, both with regard to structural[21–24] and dynamic[25–29,23] aspects; in qualitative aspects, the behaviour of the alkane–urea and α,ω-dibromoalkane–urea inclusion compounds with respect to these transitions is very similar. There have been various attempts[30–32] to rationalize the phase transition in the alkane–urea inclusion compounds. The most recent of these approaches[32] embodies certain crucial features of the experimental behaviour, and draws an analogy between the phase transition in alkane–urea inclusion compounds and the order-disorder phase transitions in alkali cyanide crystals. Specifically, it has been proposed that, in the alkane–urea inclusion compounds, coupling between transverse acoustic phonons of the host structure and the orientational order of the guest molecules provides an indirect mechanism for orientational ordering of the guest molecules in the low-temperature phase. In spite of this recent progress, however, several aspects of these phase transitions remain to be understood, and the development of a fundamental understanding of the mechanism of these phase transitions is still one of the major challenges in this field.

While structural aspects of the low-temperature phase are essentially the same for alkane–urea and α,ω-dibromoalkane–urea inclusion compounds (with the low-temperature orthorhombic basic host structure based approximately on the orthohexagonal description of the high-temperature phase), we have found that other urea inclusion compounds, such as decane-1,10-dicarboxylic acid–urea[33] (Fig. 6), exhibit more complicated superstructures in the low-temperature phase. Clearly, the exact nature of the structural distortion in the urea inclusion compounds depends critically on the type of guest molecule.

Although the phase transitions studied so far for alkane–urea and α,ω-dibromoalkane–urea inclusion compounds involve a distortion of the host structure, they are not associated with

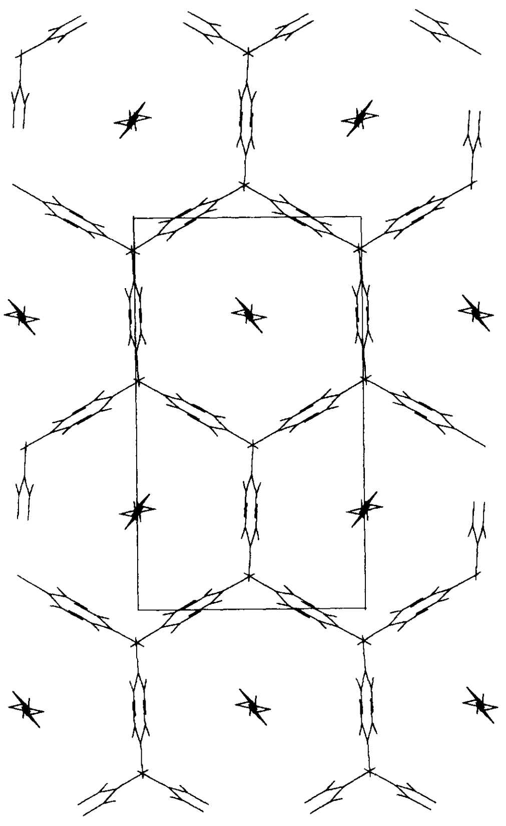


Fig. 5 Structure of the 1,10-dibromodecane–urea inclusion compound in the low-temperature phase at 108 K, viewed along the tunnel axis. There is a comparatively narrow distribution of guest molecule orientations, which correlates well with the distortion of the tunnel (see ref. 24 for full details).

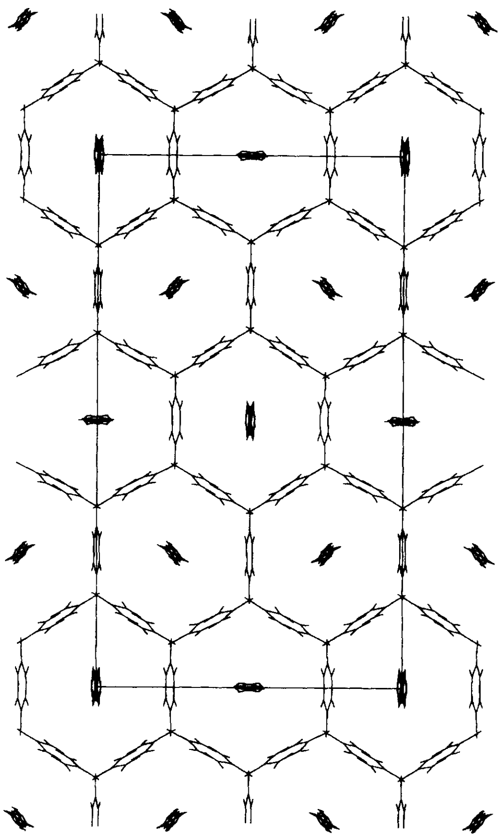


Fig. 6 Structure of the decane-1,10-dicarboxylic acid–urea inclusion compound, determined at 173 K (low-temperature phase), viewed along the tunnel axis. There are four independent types of tunnel, with different modes of distortion—within each type of tunnel, the distribution of guest molecule orientations correlates well with the distortion of the tunnel (see ref. 33 for full details).

changes in the mode of three-dimensional packing of the guest molecules. Other urea inclusion compounds exhibit more complicated behaviour, and as an illustration, heptanoic anhydride–urea exhibits two phase transitions on cooling below ambient temperature.[34] The first transition (at *ca.* 179 K on cooling) is associated only with a change in the three-dimensional packing of the heptanoic anhydride guest molecules (Δ_g = 2.3 Å above 179 K; Δ_g = 1.5 Å below 179 K), whereas the second transition (at *ca.* 122 K on cooling) is associated with a distortion of the host structure as well as a further change in the three-dimensional packing of the guest molecules (Δ_g = 0 Å below 122 K). Extrapolating from these preliminary observations, the structural characterization of urea inclusion compounds containing different families of guest molecules below ambient temperature is expected to reveal a great diversity of structural and phase behaviour.

In summary, the phase transitions described above reflect the cooperative behaviour of the host and guest components in the urea inclusion compounds. The guest molecules are usually dynamic at ambient temperature, and the average host structure (as determined from diffraction data) has a high symmetry that reflects the time-averaged distribution of guest molecules within it. At sufficiently low temperature, the extent of the dynamics of the guest molecules diminishes, and the guest molecules adopt a well-defined orientation with respect to the host; concomitantly, the host structure distorts to a lower symmetry that reflects the static distribution of the guest molecules (which may or may not be disordered). The intimate interplay of both host and guest components is crucial in controlling the overall behaviour of these phase transitions.

2.3 Local structural properties

The discussion in Section 2.2 assumed the ‘periodic approximation’ for the structural properties of crystalline solids. However, the periodic structural description (as probed by diffraction-based investigations) is only an averaged representation of the true system, as periodicity arises only on averaging the true structure over both space and time. To extend our understanding of the structural properties of a crystalline solid, it is necessary to go beyond this periodic description by investigating the distribution of local (spatial and/or temporal) structural features about this periodic average. In this regard, several experimental and computational approaches have been used to probe local structural aspects of urea inclusion compounds. Dynamic properties (*i.e.* temporal behaviour) are discussed in Section 2.4. Local structural properties that have been investigated include the conformational properties of the guest molecules and the interaction between adjacent guest molecules within the urea tunnel.

Bromine K-edge EXAFS experiments have been carried out[35] on urea inclusion compounds containing α,ω-dibromoalkane guest molecules [$Br(CH_2)_nBr$; n = 7–11] with the principal aim of determining the Br···Br distance between adjacent guest molecules in the urea tunnel (motivated by the expectation that the repulsive interaction between adjacent guest molecules within the tunnel predicted in Section 2.2.1 should lead to an uncharacteristically short intermolecular Br···Br distance). However, an accurate determination of the Br···Br distance was not possible from data collected at ambient temperature and at 77 K (and also at 9 K for 1,10-dibromodecane–urea), as a consequence of dynamic disorder at high temperature and static positional disorder at low temperature. It is interesting to note that, as a consequence of the incommensurate relationship between the host and guest substructures in these inclusion compounds, no well-defined features arising from backscattering by atoms in the host substructure were observed in the EXAFS spectra.

Raman spectroscopy has been used[36] to probe conformational properties of α,ω-dihaloalkane guest molecules [$X(CH_2)_nX$; $n = 8$ for X = Cl; $n = 7$–11 for X = Br; $n = 8$ for X = I] in urea inclusion compounds. In particular, the C–X stretching vibrations were used to assess the relative amounts of *trans* and *gauche* end-groups as a function of: (*i*) the length (n) of the guest molecule; (*ii*) the identity of the terminal substituent X; (*iii*) temperature; and (*iv*) pressure. *Inter alia*, these investigations have shown: (*i*) there is no well-defined relationship between the proportion of end-groups in the *gauche* conformation and the length of the $Br(CH_2)_nBr$ guest molecules (the proportion of *gauche* end-groups is in the range 7– 13% for $n = 7$–11 at ambient temperature); (*ii*) the proportion of end-groups in the *gauche* conformation at ambient temperature is *ca.* 51% for $Cl(CH_2)_8Cl$–urea, *ca.* 7% for $Br(CH_2)_8Br$–urea and *ca.* 1% for $I(CH_2)_8I$–urea—thus, the proportion of *gauche* end-groups decreases as the size of the terminal substituent increases; (*iii*) the proportion of *gauche* end-groups [for $Br(CH_2)_nBr$–urea inclusion compounds] increases slightly with increasing temperature; (*iv*) the proportion of *gauche* end-groups [for $Br(CH_2)_{11}Br$–urea] increases markedly with an increase in applied pressure.

A molecular dynamics simulation of the 1,10-dibromodecane–urea inclusion compound[37] has investigated several local structural properties of the 1,10-dibromodecane guest molecules at 300 K, providing results that corroborate well with the results from bromine K-edge EXAFS spectroscopy and Raman spectroscopy discussed above. The bromine radial distribution function (Fig. 7) determined from the molecular dynamics simulation indicates a broad distribution for the intermolecular Br···Br distance, but considerably narrower distributions for intramolecular Br···C distances, in support of the conclusions from the bromine K-edge EXAFS results.[35] The results from the molecular dynamics simulation also provide direct evidence that a small proportion of the 1,10-dibromodecane guest molecules contain a *gauche* end-group, and indicate that the interconversion between *gauche* and *trans* end-group conformations occurs on a timescale of the order of picoseconds within the urea tunnel structure.

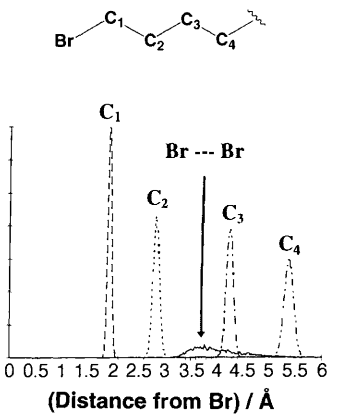


Fig. 7 Bromine radial distribution function for the 1,10-dibromodecane–urea inclusion compound, determined from the molecular dynamics simulation discussed in ref. 37. Note the broad distribution of intermolecular Br···Br distances.

The conformational properties of the guest molecules in alkane–urea inclusion compounds have also been probed using vibrational spectroscopy (ref. 2 contains a comprehensive review, with detailed referencing). IR spectroscopy of the isolated CD_2 rocking vibrations for selectively deuterated samples of tridecane–urea and nonadecane–urea suggest that the extent of *gauche* end-groups is below 3%. Similarly, Raman spectroscopy of the methyl group rocking modes [for alkanes $CH_3(CH_2)_nCH_3$ with even values of n between 12 and 20] suggest that the concentration of *gauche* end-groups is low (*ca.* 5%). A recent Raman study of the methyl group rocking modes for alkane guest molecules ($n = 6$–10 and 17) has extended this work to encompass the low temperature phases, and has shown that the concentration of *gauche* end-groups (*gt*-conformation) is of the order of 5%, both at 298 and 90 K, independent of the length of the guest molecule. Evidence was also obtained for the existence of some amount (less than 5%) of end-groups with the *tg*-conformation. This paper also reported that the proportion of *gauche* end-groups increases significantly with increase of pressure. Interestingly, ^{13}C NMR and ^{2}H NMR studies of alkane–urea inclusion compounds have led to substantially higher estimates of the proportion of *gauche* end-groups in the alkane guest molecules.

In a general sense, the fact that guest molecules trapped within solid host structures may be constrained to exhibit unconventional conformational properties can be exploited as a means of spectroscopic characterization of these conformations. For example, the recent discovery that the guest molecules in the 1,6-dibromohexane–urea inclusion compound exist exclusively with the bromine end-groups in a *gauche* conformation has allowed the definitive characterization[38] of the vibrational properties of this end-group conformation. Similar examples for thiourea inclusion compounds are discussed in Section 3.2.

Finally, we consider end-group interactions for unsymmetric guest molecules [$X(CH_2)_nY$] in urea inclusion compounds. In principle, three different types of interaction between the end-groups of adjacent guest molecules are possible (Fig. 8): X···X (head–head), X···Y (head–tail) and Y···Y (tail–tail). For two linear guest molecules of the type $X(CH_2)_nY$ constrained to approach each other along the one-dimensional tunnel, it may be assumed that the guest–guest interaction is dominated by the interaction between the end-groups (*i.e.* X and/or Y); thus, as proposed by Hollingsworth,[39] experimental measurements of the relative numbers of these different types of end-group interaction in a given inclusion compound can provide fundamental information on the relative preferences for different types of functional group interaction. For many unsymmetrical guest molecules of the type $X(CH_2)_nY$ in urea inclusion compounds,[2,39] the ratio of the number of X···X interactions to the number of X···Y interactions and/or the ratio of the number of Y···Y interactions to the number of X···Y interactions in the $X(CH_2)_nY$–urea inclusion compound can be determined from high-resolution solid state ^{13}C NMR spectroscopy (in some cases both ratios can be measured from the NMR spectrum of a given inclusion compound, whereas in many cases only one of these ratios can be measured). An important advantage of this experimental strategy for deriving fundamental information on functional group interactions is the fact that the terminal functional groups on guest molecules in urea inclusion compounds are constrained to approach each other in a well-defined and controlled geometry, allowing interactions between the different types of functional groups to be compared on a systematic geometrical basis.

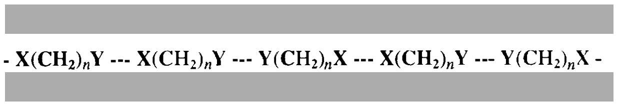


Fig. 8 Schematic illustration of the X···X, X···Y and Y···Y intermolecular interactions for unsymmetric guest molecules of the type $X(CH_2)_nY$ inside a host tunnel structure.

2.4 Dynamic properties

A wide range of techniques have been applied to investigate the dynamic properties of urea inclusion compounds, including solid state NMR spectroscopy, incoherent quasielastic neutron scattering, EPR spectroscopy, molecular dynamics simulation, Raman spectroscopy, IR spectroscopy, dielectric loss spectroscopy and X-ray diffraction. The vast majority of these investigations have probed the dynamic properties of the guest molecules, although some attention has also been given recently to the dynamics of the urea molecules.

Early studies of guest motion in alkane–urea inclusion compounds by solid state NMR focused on ^1H linewidth and second moment measurements and measurement of ^1H spin lattice relaxation times. While these methods yielded considerable insights into the guest mobility and its temperature dependence, it is difficult from these techniques to derive well-defined and unambiguous information relating to the mechanism for the motion. For this reason, subsequent NMR studies have focused on ^2H NMR spectroscopy of urea inclusion compounds containing fully deuterated or selectively deuterated guests. These experiments probe the ^2H quadrupole interaction parameters, and the technique can provide detailed mechanistic information for motions with characteristic timescales between *ca.* 10^{-3} and 10^{-8} s.

From variable-temperature ^2H NMR investigations of the $[^2H_{34}]$hexadecane–urea inclusion compound,[26] dynamic properties of the guest molecules have been established over a wide temperature range, with the following mechanism deduced at ambient temperature: (*i*) rapid ($\kappa \gtrsim 10^7\ s^{-1}$) reorientation of the whole molecule about its long molecular axis (which is coincident, on average, with the tunnel axis); (*ii*) rapid torsional libration (with approximate amplitude ± 25°) about the penultimate C–C bond; (*iii*) rapid rotation of the CD_3 group about the C–CD_3 bond. There is a substantial change in the ^2H NMR spectrum on crossing the phase transition temperature, suggesting that the phase transition is associated with an abrupt discontinuity in the motional freedom of the guest molecules; nevertheless, there is evidence for some amount of motion even below the phase transition temperature. Similar conclusions have also been reached from an independent ^2H NMR investigation[25] of $[^2H_{40}]$nonadecane–urea. For the $[^2H_{20}]$-1,10-dibromodecane–urea inclusion compound, the results from a ^2H NMR study[23] are in good agreement with those obtained for alkane–urea inclusion compounds with regard to the reorientational motion of the guest molecules about the tunnel axis; however, there are subtle differences with regard to both the change in dynamic properties on crossing the phase transition temperature and the extent of motion of the end-groups.

The NMR techniques discussed above provide information on reorientational motions of the guest molecules, but do not yield direct information on translational motions. Considerable progress in understanding translational motions (in addition to reorientational motions) of alkane[28] and α,ω-dibromoalkane[29] guest molecules in urea inclusion compounds has been made using incoherent quasielastic neutron scattering (IQNS), which probes motions with characteristic timescales between *ca.* 10^{-10} and 10^{-12} s. As a consequence of the large incoherent neutron scattering cross-section for ^1H, IQNS studies of urea inclusion compounds containing $[^2H_4]$urea and guest molecules with natural isotopic abundances ensure that the incoherent neutron scattering arises predominantly from the guest molecules. Translational motions along the tunnel axis have been investigated separately from reorientational motions about the tunnel axis by studying semi-orientated polycrystalline samples in which the tunnel axes of all crystals are aligned parallel to each other. Separate IQNS experiments performed with the neutron momentum transfer vector parallel ($Q_{\parallel}$ spectra) or perpendicular ($Q_{\perp}$ spectra) to the urea tunnel axis selectively probe translational motions of the guest molecules along the tunnel axis and reorientational motions of the guest molecules about the tunnel axis, respectively.

For alkane–urea[28] and α,ω-dibromoalkane–urea[29] inclusion compounds, quasielastic broadening is evident in the $Q_{\perp}$ spectra in the high-temperature phase, implying that the guest molecules undergo rapid reorientational motions. This reorientational motion is diffusive in character (rather than a discrete jump motion), and can be modelled as uniaxial rotational diffusion in a onefold cosine potential. Rotational diffusion coefficients (*ca.* $0.3 \times 10^{-12}\ s^{-1}$ for nonadecane–$[^2H_4]$urea at 306 K) and other parameters relating to this dynamic process have been elucidated as a function of temperature. The $Q_{\parallel}$ spectra also exhibit substantial quasielastic broadening in the high-temperature phase, assigned to translation of the alkane molecules along the tunnel. This motion has been modelled successfully as translational diffusion between rigid impermeable boundaries, and the diffusion coefficient and translation length have been determined as a function of temperature. For nonadecane–$[^2H_4]$urea, the translation length is *ca.* 2.7 Å at 306 K and *ca.* 1.1 Å at 160 K (just above the phase transition temperature); the translational diffusion coefficient at ambient temperature is *ca.* $1.5 \times 10^{-5}\ cm^2\ s^{-1}$. Quantitative details relating to this translational motion are in good agreement with information on longitudinal motions of alkane guest molecules determined from analysis of X-ray diffraction intensities[17] (specifically, it was proposed that the alkane molecules undergo large amplitude motions along the tunnel axis, with an average displacement of over 2 Å for hexadecane at ambient temperature). It is perhaps remarkable that, despite the appreciable amount of translation of the guest molecules along the tunnel at ambient temperature, X-ray diffraction patterns nevertheless indicate both long-range intra- and inter-tunnel ordering of the guest molecules; it is thus very likely that the translations of neighbouring guest molecules within a given tunnel are highly correlated and that the translations of guest molecules in adjacent tunnels are also highly correlated.

A detailed assessment of the dynamic properties of the guest molecules in the nonadecane–urea inclusion compound has been achieved recently from molecular dynamics computer simulations.[40] *Inter alia*, the results of these simulations indicate that the interaction between adjacent guest molecules in the tunnel exerts an important influence on the translational and reorientational motions of the guest molecules, and demonstrate that the reorientational motions of the guest molecules about the tunnel axis are coupled with movements of the host structure. An important strength of this work has been the establishment of links between the results from the molecular dynamics simulations and results from the IQNS experiments[28] on nonadecane–urea described above.

Although the alkane–urea and α,ω-dibromoalkane–urea inclusion compounds exhibit very similar dynamic behaviour, and apparently undergo the same type of phase transition, the dynamic behaviour of other urea inclusion compounds can differ substantially. Thus, the guest molecules in diacyl peroxide–urea inclusion compounds undergo a substantially different dynamic mechanism, and exhibit no evidence for a low temperature phase transition, at least down to liquid nitrogen temperature.

The vast majority of research on the dynamic properties of urea inclusion compounds has focused on the motion of the guest molecules, although some studies of the dynamics of the urea molecules have also been carried out. ^2H NMR investigations of alkane–$[^2H_4]$urea[41] and α,ω-dibromoalkane–$[^2H_4]$urea[42,23] inclusion compounds have demonstrated that, at sufficiently high temperature, the urea molecules undergo 180° jumps about their C=O axes. For 1,10-dibromodecane–$[^2H_4]$urea[23] the jump frequency is *ca.* $5 \times 10^6\ s^{-1}$ at 293 K. These ^2H NMR investigations provide no evidence for reorientation of the NH_2 groups about the C–N bond (on the ^2H NMR timescale). The timescale for the 180° jump motion of the urea molecules is substantially longer (at the same temperature) than the timescale for the motions of the guest molecules described above, confirming that the 180° jumps of the urea molecules and the reorientational and translational motions of the guest molecules are not correlated.

2.5 Host–guest chiral recognition

As discussed in Section 2.1, the host structure in the conventional urea inclusion compounds comprises a spiral hydrogen-bonded arrangement of urea molecules. The symmetry of the basic host structure in any given single crystal is either $P6_122$ (the inclusion compound contains only right-handed spirals of urea molecules) or $P6_522$ (the inclusion compound contains only left-handed spirals of urea molecules). This chirality of the urea tunnel structure is generated spontaneously during crystal growth of the inclusion compound, and represents an example of chirality being introduced into a crystal by spontaneous assembly of achiral molecules into a chiral packing arrangement. Clearly, chiral host structures can exert an important influence on the structural and chemical properties of chiral guest molecules. As the *R*-guest/($P6_122$)-host and *S*-guest/($P6_122$)-host inclusion compounds have a diastereoisomeric relationship, they should generally differ in energy, and a given crystal of a chiral host should therefore have a preference for incorporating one particular enantiomer of a chiral guest.

An extensive series of experimental investigations by Schlenk[43] has demonstrated that inclusion of chiral guest molecules within the urea tunnel structure can be associated with a significant degree of chiral recognition. In addition to experimental investigations of this phenomenon, computational investigations can provide detailed insights into the characteristics of host–guest interaction that underlie this chiral recognition in urea inclusion compounds. A recent computational study[44] of 2-bromoalkane–urea inclusion compounds has demonstrated (Fig. 9) a clear preference for the *R*-enantiomer of 2-bromoalkane guest molecules within the $P6_122$ urea tunnel structure, with the proportion of *R*-2-bromoalkane guest molecules at 300 K predicted to be *ca.* 0.75 for 2-bromotridecane–urea and *ca.* 0.82 for 2-bromotetradecane–urea. Interestingly, (see Fig. 9), for the lowest energy conformation (Br *trans*–CH_3 *gauche*) of the 2-bromotridecane guest molecule within the urea tunnel, the same enantiomer (*R*) of the guest is preferred at all positions along the tunnel [note that for other conformations (for example, Br *gauche*–CH_3 *trans*) of the 2-bromoalkane guest molecules, the *R* enantiomer is preferred at some positions and the *S* enantiomer is preferred at others (Fig. 9)]. It is important to note that, in assessing the enantiomeric excesses for incommensurate inclusion compounds, such as 2-bromoalkane–urea inclusion compounds, it is necessary to consider the characteristics of the host–guest interaction as a function of the position of the guest molecule along the host tunnel.

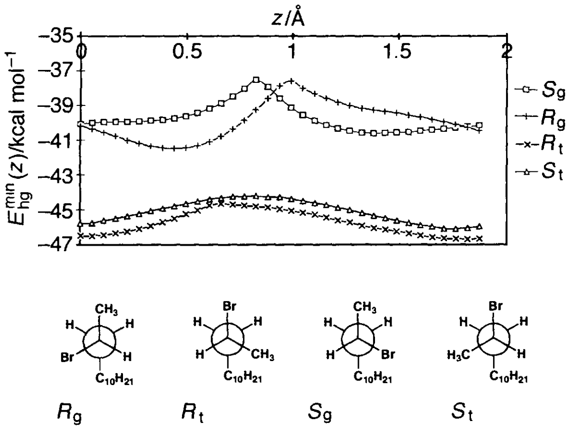
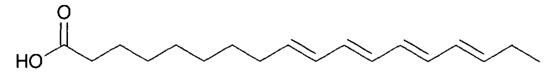


Fig. 9 Host–guest interaction energy $[E_{hg}^{min}(z)]$ for 2-bromotridecane guest molecules as a function of position (z) along the tunnel of the $P6_122$ urea host structure (for $0 \leq z < c_h/6$). The R_t, R_g, S_t and S_g types of 2-bromoalkane molecule are defined in the Newman projections [*R* and *S* enantiomers; Br *gauche*–CH_3 *trans* conformation (g) and Br *trans*–CH_3 *gauche* conformation (t)].

2.6 Generation of orientationally well-ordered molecular assemblies

Inclusion within one-dimensional tunnel structures may be exploited as a means of generating an orientationally well-ordered ensemble of molecules, which may be difficult to achieve in other phases. An example based on this fact concerns measurement of the orientation of the electronic transition dipole moment for conjugated polyenes; this property is important in relation to the use of these molecules in non-linear optoelectronics and other applications (including their use as probes of biophysical systems). Simple theoretical approaches to predict this property have generated differing results (some suggesting that the transition dipole moment is essentially parallel to the long axis of the molecule, others suggesting an angle of 30° with respect to this axis), and experimental verification of these predictions has been hindered by the difficulty of preparing perfectly orientated samples of the polyenes. This problem has been addressed[45] by constraining these molecules as guests within the urea tunnel structure, thus ensuring that the molecular axes of all guests in a given single crystal are parallel and orientationally well-defined with respect to the external morphology of the crystal. Specifically, octadeca-9,11,13,15-tetraenoic acid was considered as a dilute guest within the hexadecane–urea inclusion compound (dilution ensures that absorbance is low and that exciton effects are eliminated). Polarized fluorescence excitation spectra of a single crystal of this material have shown that the transition dipole does not lie strictly along the molecular axis, but at an angle of *ca.* 20 ± 1° with respect to this axis. On taking into account the effects of the surrounding medium for the guest in the urea inclusion compound, this value is modified to *ca.* 15 ± 1° for the isolated molecule. This result has important implications with regard to applications of these chromophoric materials. In general terms, it is clear that there are important prospects for exploiting uni-directional tunnel host structures in applications of this type, in which a highly anisotropic (uni-directional) orientation of guest molecules is required for the measurement of electronic or other properties.



3 Thiourea inclusion compounds

3.1 An introduction to thiourea inclusion compounds

Shortly after the discovery of urea inclusion compounds, it was found that thiourea also forms a tunnel host structure (Fig. 10) in the presence of appropriate guest molecules. The thiourea tunnels have a larger cross-sectional area than those in urea inclusion compounds, so the urea and thiourea host structures tend to incorporate different types of guest molecule. For example, thiourea forms tunnel inclusion compounds with cyclohexane and some of its derivatives, ferrocene and other organometallics, and certain compounds containing a benzene ring. Such guest molecules do not generally form inclusion compounds with urea.

In general, the host structure in thiourea inclusion compounds is either rhombohedral or monoclinic (structural properties of thiourea inclusion compounds are discussed in detail in ref. 2). For guest molecules that are substantially isotropic in shape [for example cyclohexane (see Fig. 10), chlorocyclohexane and ferrocene], the host structure is typically rhombohedral at ambient temperature, and the guest molecules usually exhibit substantial disorder. In many of these cases, the rhombohedral structure transforms to a monoclinic structure at low temperature. Planar guest molecules (for example, 2,6-diethylnaphthalene and cyclo-1,5-octadiene), on the other hand, tend to favour the monoclinic host structure at ambient temperature; within this structure, the guest molecules are constrained to adopt an ordered arrangement (lowering the symmetry from rhombohedral to monoclinic is associated with a deformation of the tunnel, which restricts the orientational freedom of the guest molecules).

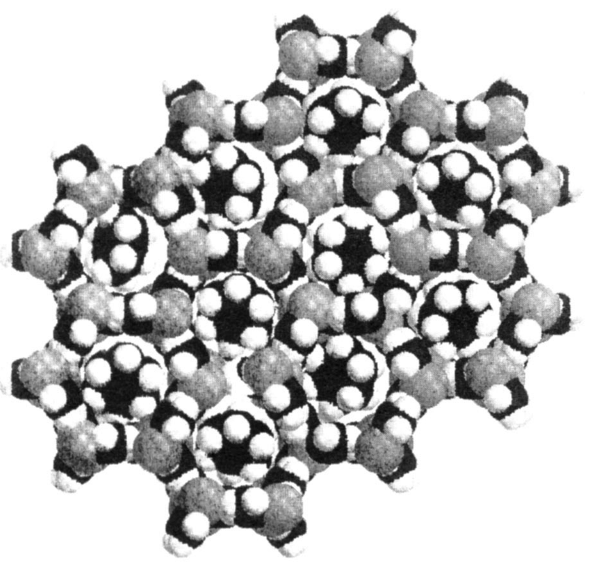


Fig. 10 The cyclohexane–thiourea inclusion compound at ambient temperature, showing ten complete tunnels with van der Waals radii, viewed along the tunnel axis. The guest molecules have been inserted into the tunnels, illustrating orientational disorder (the positions of the guest molecules are not actually determined from X-ray diffraction data at ambient temperature).

In contrast to the tunnel in conventional urea inclusion compounds, which is relatively cylindrical in the sense that there is only a small fluctuation in tunnel diameter on moving along the tunnel, the thiourea tunnel has prominent bulges (diameter *ca.* 7.1 Å) and constrictions (diameter *ca.* 5.8 Å) at different positions along the tunnel (Fig. 11). As a consequence, it is often more appropriate to regard the thiourea tunnel structure as a 'cage' type host rather than a 'tunnel' type host, and indeed many properties of thiourea inclusion compounds can be interpreted more directly on this basis. The guest molecules in thiourea inclusion compounds generally occupy preferred sites along the tunnel, corresponding to one guest molecule per cage (*i.e.* two guest molecules per unit repeat distance of the thiourea structure) and a stoichiometric guest/thiourea molar ratio of 1/3. This leads to the commensurate structural relationship c_g/c_h = 1/2 (see Section 2.2.1 for definitions of c_g and c_h).

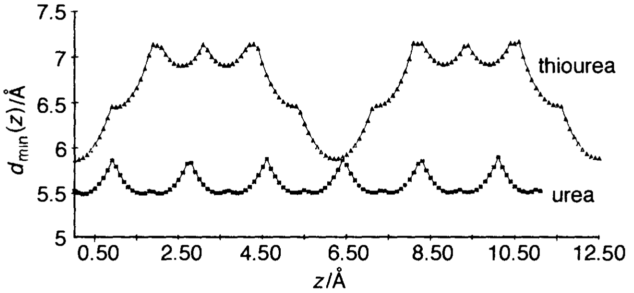


Fig. 11 Minimum tunnel diameter $d_{\min}$ as a function of position (z) along the tunnel for the urea and thiourea tunnel structures. In both cases, the range of z shown in the graph represents just over one lattice period of the host structure along the tunnel.

3.2 Conformational properties of guest molecules

As a consequence of the structural selectivity between the host and guest components, inclusion within a solid host structure can often serve to select an uncharacteristic conformation of the guest molecules. In general terms, this can be important in allowing spectroscopic characterization of conformations that may not be significantly populated in dispersed phases or in the 'native' crystalline state of the molecule. In addition, the attainment of uncharacteristic conformations may open up reaction pathways for constrained guest molecules that may be improbable for the same molecules in their normal conformational state.

A dramatic illustration of the constraints that a host structure can impose on the conformational properties of guest molecules is provided by monohalocyclohexane ($C_6H_{11}X$; X = Cl, Br, I) guest molecules in the thiourea tunnel structure. For monohalocyclohexanes in the liquid and vapour phases, the dynamic equilibrium between the equatorial and axial conformations favours the equatorial conformation, and in the solid state (at sufficiently low temperature or high pressure) these molecules exist almost entirely as the equatorial conformation. On the other hand, when included as guest molecules within the thiourea tunnel structure, $C_6H_{11}Cl$, $C_6H_{11}Br$ and $C_6H_{11}I$ exist predominantly in the axial conformation; these results have been established from IR, Raman and high-resolution solid state ^{13}C NMR techniques (ref. 2 contains a comprehensive list of references for this work). From ^{13}C NMR results,[46] the mole fractions of the equatorial conformations of these guest molecules in the thiourea tunnel structure are in the range 0.05–0.15, in contrast to the corresponding values (0.75–0.81) observed in $CFCl_3$–$CDCl_3$ (3 : 1) solution (the quoted values refer to temperatures of 159–220 K). The ^{13}C NMR results also demonstrate that a ring inversion process occurs for these guest molecules inside the thiourea tunnel structure at sufficiently high temperature. Bromine K-edge EXAFS spectroscopy, which provides a direct measurement of the intramolecular Br···C(3) distance (*ca.* 3.27 Å) [see Fig. 12(*a*)], confirms that the axial conformation of bromocyclohexane predominates within the thiourea tunnel structure.[47]

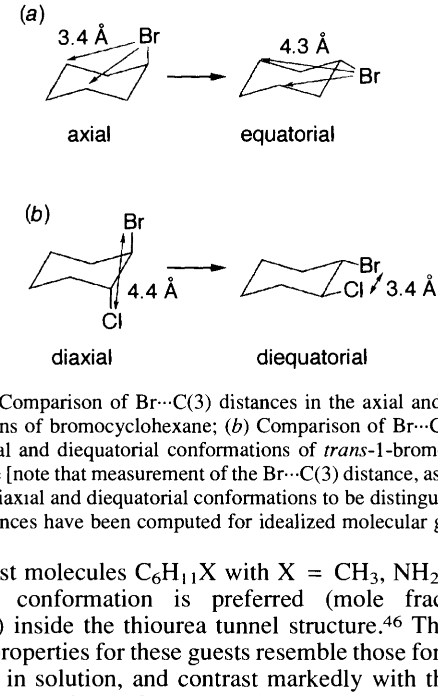


Fig. 12 (*a*) Comparison of Br···C(3) distances in the axial and equatorial conformations of bromocyclohexane; (*b*) Comparison of Br···Cl distances in the diaxial and diequatorial conformations of *trans*-1-bromo-2-chlorocyclohexane [note that measurement of the Br···C(3) distance, as in (a), also allows the diaxial and diequatorial conformations to be distinguished]. The quoted distances have been computed for idealized molecular geometries.

For guest molecules $C_6H_{11}X$ with X = CH_3, NH_2, OH, the equatorial conformation is preferred (mole fraction *ca.* 0.82–0.97) inside the thiourea tunnel structure.[46] The conformational properties for these guests resemble those for the same molecules in solution, and contrast markedly with the behaviour, discussed above, for monohalocyclohexane guest molecules in the thiourea tunnel structure. There is also a marked contrast between the conformational properties of monohalocyclohexane guest molecules in thiourea and in various zeolitic hosts, within which the equatorial conformation predominates.

Certain disubstituted cyclohexanes also exist in uncharacteristic conformational states within the thiourea tunnel structure. For the *trans*-1-bromo-2-chlorocyclohexane–thiourea inclusion compound [Fig. 12(*b*)], the intramolecular Br···Cl and Br···C(3) distances of *ca.* 4.50 and 3.27 Å determined from bromine K-edge EXAFS spectra[47] demonstrate clearly the preference for the diaxial conformation of the guest molecule.

In contrast, the diequatorial conformation is preferred in dispersed phases.

The theoretical approach discussed in Section 2.2.1 for investigating the structural properties of one-dimensional inclusion compounds has also been applied[48] to assess, from first principles, the preferred conformation of chlorocyclohexane guest molecules within the thiourea tunnel structure. For axial-chlorocyclohexane–thiourea, the optimum guest periodicity corresponds to $\alpha = \frac{1}{2}$, representing commensurate behaviour and corresponding to a lower characteristic energy than any guest periodicity for equatorial-chlorocyclohexane–thiourea. This predicted preference for the axial conformation is in direct agreement with the experimental results discussed above. In essence, axial-chlorocyclohexane can be packed more efficiently (smaller α) than equatorial-chlorocyclohexane within the constrained environment of the thiourea tunnel, and this contributes [through the factor $^1/_\alpha$ in eqn. (1)] to the more favourable characteristic energy for the axial conformation. The optimum guest period ($c_g = \alpha c_h = c_h/2 = 6.24$ Å) predicted for axial-chlorocyclohexane–thiourea is in good agreement with information inferred from X-ray diffraction data.

3.3 Application in non-linear optics

The potential to exploit inclusion phenomena in the field of non-linear optics has received considerable attention in recent years. We focus here on second harmonic generation (SHG), which involves doubling the frequency of light as it passes through a material. Materials that exhibit SHG are important in many device applications (including extending the frequency range of lasers) and have an important role in the field of optoelectronics. For a material to exhibit SHG, the component molecules must have a high value of the second order molecular hyperpolarizability (β), and in addition the molecules must aggregate in a non-centrosymmetric arrangement. Molecules with large β often have large degrees of intramolecular charge transfer and usually possess a large dipole moment in their ground state; however, there is a strong tendency for the crystal structures of such molecules to be centrosymmetric. There is therefore substantial impetus to develop ways to induce these molecules into non-centrosymmetric environments, and an attractive prospect is to include them as guest molecules within appropriate host materials. Thus, parallel alignment of guest molecules (with high values of β) within tunnel host structures has been particularly exploited in this regard, and has included successful applications involving thiourea inclusion compounds.[49] In this work, thiourea inclusion compounds containing appropriate organometallic guests [for example, $(\eta^6\text{-C}_6\text{H}_6)\text{Cr(CO)}_3$] were shown to exhibit pronounced SHG. These organometallics possess large values of β, but their 'native' crystalline phases are centrosymmetric and are therefore inactive for SHG. For the thiourea inclusion compounds, it was shown that the SHG arises predominantly from the organometallic guests rather than the thiourea molecules (which also have significant β). The structures of the inclusion compounds are non-centrosymmetric, in accord with the idea that dipole organization of the guest molecules should be favoured both within and between tunnels. It is interesting that the host structure in many other thiourea inclusion compounds (for example, cyclohexane–thiourea) is centrosymmetric, and the results here illustrate that the structure of a given host material can differ, often substantially, depending on the identity of the guest molecules within it. Such observations are particularly prevalent for hosts of the soft type.

4 Concluding remarks

It is clear that urea and thiourea inclusion compounds exhibit a wide range of interesting and important fundamental physicochemical phenomena, and that the application of a wide range of experimental and computational techniques has been essential in the endeavour to understand these properties. However, although significant progress has been made in recent years in expanding our fundamental understanding of these inclusion compounds, there is still a great deal to be learned.

It is now generally accepted that the properties of urea and thiourea inclusion compounds depend critically on the nature of both the host and guest components, and it is therefore not expected that universality will be observed in any particular property across all urea inclusion compounds or across all thiourea inclusion compounds. At best, a set of inclusion compounds with a given host and a closely related family of guest molecules (*e.g.* a homologous series, in the case of urea inclusion compounds) may be found to exhibit common behavioural trends, although even in these cases anomalous members of such families are often observed. When studied in sufficient depth, each particular inclusion compound of urea or thiourea is best regarded as an individual entity with its own characteristic set of properties, even though the host structures of many urea and thiourea inclusion compounds are essentially identical.

At present, materials applications based upon urea and thiourea inclusion compounds (and solid organic inclusion compounds in general) are comparatively scarce in comparison, for example, to the wide range of applications that exploit the properties of microporous inorganic materials. Nevertheless, the development of a fundamental understanding of the structural, dynamic and chemical properties of urea and thiourea inclusion compounds will lead the way towards the future design and development of applications of these materials. With the realization that urea and thiourea inclusion compounds exhibit a wide range of interesting properties and phenomena (with the interplay between these properties only at the very earliest stages of being understood) and the recognition that a detailed understanding of these systems will emerge only from the combined knowledge acquired from a wide range of experimental and computational techniques, there are exciting prospects for the continued study of these materials long into the future.

5 Acknowledgements

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