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Computer modelling studies of 18-crown-6 with urea and thiourea

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Computer modelling studies of 18-crown-6 with urea and thiourea

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Computer modelling studies have been carried out on the interaction of 18-crown-6 with a variety of guest molecules, including urea, thiourea and substituted ureas. The five known crystal structures of these host/guest systems were used as models. We were interested to establish whether the arrangement of guest molecules around a host molecule in the crystal was indicative of the lowest energy configuration for a host/guest fragment or was a consequence of packing effects. Two models were therefore considered for each structure and the structures minimised via molecular mechanics. In the first mode, the structure consisted of one unit cell and periodic boundary conditions were used in the calculation. Coulombic effects were calculated using the Ewald summation. In the second model, the structure consisted of an 18-crown-6 molecule surrounded by two hydrogen-bonded guest molecules. Both models were minimised using the CERIUS package using the DreidingII forcefield.

The crystal structure minimisations reproduced the structures very well with an average change in cell volume of 3.6% and a mean r.m.s. positional deviation of 0.20 Å. The fits for the fragment models were significantly larger for all structures (mean 0.30 Å) but even so it can be concluded that the arrangement in the crystal gave a good indication of the lowest energy configuration of the host/guest in vacuo.

INTRODUCTION

The computer modelling of host/guest complexes is a current problem of general interest.[1] However much molecular modelling and computational chemistry has been carried out on the structures of individual molecules where the covalent bond is of prime importance, but relatively little attention has been paid to the modelling of structure and properties of the entities formed by the interaction of two or more small molecules. This interaction is of supreme importance particularly in the area of molecular recognition.

In our work, we are particularly concerned with the interaction of guest molecules with small host molecules and in the role played by intermolecular hydrogen bonds and we have carried out several studies of these systems[2,3] but these have been theoretical studies for which little or no experimental data was available.

However we have also studied host/guest systems involving 18-crown-6 with guest molecules such as urea and thiourea and a brief report has been published.[4] Here there is a large amount of experimental data viz. 5 crystal structures. We simulated these structures by extracting a model from the crystal structures consisting of the host molecule surrounded by all the guest molecules with which it formed intermolecular hydrogen bonds. However the modelling proved unsatisfactory in that our model fragment proved not always to be at the minimum energy of the system[4] as a rearrangement of the positions of the guest molecules (and indeed the breaking of the observed hydrogen bonds and the formation of new ones) often gave rise to lower energies.

We concluded from this work, which is described here in detail, that the local arrangement of guest molecules around a host molecule as found in the crystal structures is not necessarily at an energy minima, although obviously this arrangement when positioned in a unit cell with all the other symmetry related molecules does define an energy minima for the system. Since it seems unlikely that this difference only occurs with hydrogen bonded systems, we conclude that any crystal structure cannot be assumed to necessarily indicate how a given guest molecule may interact with host molecules in the gas phase or in solution. The only exception could be provided when the guest is totally encapsulated within the host and therefore is screened from other hosts and guests.

It is often tempting to conclude that a crystal structure of a host/guest complex does indicate the existence of just one energy minimum structure. However crystal structures need to be treated with caution as models for two reasons. First because the position of the guest within the host is due not only to the interaction between the two but also to the packing of the hosts and guests within the unit cell. Thus the guest may not be positioned within the lowest energy position because this is precluded by the packing. Secondly because the crystal structure, unless disordered, gives just one position for the guest within the host. There may be more possible positions of similar energy that are not indicated by the crystal structure, although disorder or high thermal motion can often indicate broad energy minima. However, despite these comments, crystal structures do provide useful starting models and are a useful check on theoretical calculations.

We have now reinvestigated this problem using the CERIUS software package version 3.2[5]. This package permits routine molecular mechanics calculations but also allows minimisation of unit cells with periodic boundary conditions using the same forcefield. We have therefore repeated our calculations on small fragments but also refined the 5 structures as crystals using periodic boundary conditions. Results from the two systems are compared.

METHODS

Search of the Cambridge Crystallographic Database located five crystal structures containing 18-crown-6 with urea, thiourea and/or derivatives, and details are provided in Table 1. Two conformations of the 18-crown-6 host are observed, (a) with the symmetrical D_{3d} conformation and (b) with a C_i conformation. Conformational analyses of 18-crown-6[11,12,13] show that (a) and (b) are among the lowest energy conformations but there are other low energy conformations and some of these have been observed in structures of 18-crown-6. The prevalence of these two conformations in crystal structures of 18-crown-6 with urea and thiourea and indeed other guest molecules would seem to be due to the suitability of these conformations for the formation of multiple intermolecular hydrogen bonds or to the extra stability induced by the imposition of crystallographic symmetry which is found in four of the five examples. It is also noteworthy that the unit cells are complicated in that three contain two host molecules in the asymmetric unit and two contain extra guest molecules that are not hydrogen bonded to the host but instead take part in interconnected hydrogen-bonded layers.

Watson *et al.*,[10] in a study of six crystal structures of 18-crown-6 with various guests that formed hydrogen bonds, found that the conformation of 18-crown-6 was always either (a) or (b). This was rationalised as follows. In the D_{3d} conformation (a), the oxygen atoms are alternately above and below the mean plane. The three oxygen atoms on each side of this plane are available for hydrogen bonding with an O...O range of 4.71–5.17 Å. Bifunctional groups such as NH_2 (as in urea, thiourea) can efficiently form two hydrogen bonds with two oxygens on the same side of the plane and thus stabilize the D_{3d} conformation. In the (b) conformation, two symmetry related oxygens lie in the plane at ca 4.60 Å apart and the other adjacent oxygen pairs lie either above or below the mean plane. Bifunctional donors can interact only with the in-plane oxygen and one of the out-of-plane oxygen atoms. Usually this (b) conformation is less favourable.

However while this analysis is consistent with the six structures reported by Watson *et al.*,[10] it is not consistent with the five structures under review here for which the hydrogen bond pattern is summarised in Table 2. In DAYWIJ (18-crown-6)(thiourea)$_2$,[6] each thiourea forms four hydrogen bonds (Fig 1); one NH_2 group is bonded to three oxygen atoms, one hydrogen forming a single hydrogen bond to one oxygen atom at 2.14 Å, the other a bifurcated hydrogen bond to two oxygen atoms at 2.40, 2.47 Å, while in the other NH_2 group, only one hydrogen is involved in a single hydrogen bond at 2.38 Å. (Fig 1). This is a more complicated pattern (called here type a1) than that reported by Watson *et al.*[10] (called type a2) but is related to it in that type 1 does include the two

Table 1

Codename[a]	Reference	Formula[b]	Spacegroup	Z	imposed symmetry on crown
DAYWIJ	[6]	$H(tu)_2$	P-1	1	i
DAYWOP	[7]	$H(tu)_4$	$P2_1$	4	none (2 in asymmetric unit)
DIWMOL	[8]	$H(ClPhu)_2$	C2/c	4	i
CRWNUR	[9]	$H(u)_5$	$P2_1/c$	4	i (2 in asymmetric unit)
CEHGIF	[10]	$H(NMEtu)_2$	P-1	2	i (2 in asymmetric unit)

[a] from the Cambridge Crystallographic DataCentre files.

[b] H is the host 18-crown-6, u is urea, tu is thiourea, ClPhu is N-(m-chlorophenyl)urea, NMetu is N-methylthiourea

Table 2 Observed hydrogen bonds in the 5 crystal structures

Structure	Conformation of host	Hydrogen bond pattern
DAYWIJ	a	a1 (Figure 1)
DAYWOP:	b	b1 (Figure 2)
	b	b2 (Figure 3)
DIWMOL	b	b1 (Figure 7)
CRWNUR:	b	b2 (Figure 4)
	b	b3 (Figure 5)
CEHGIF:	a	* (Figure 8)
	b	b3 (Figure 8)

* Not comparable as the guest is N-methylthiourea

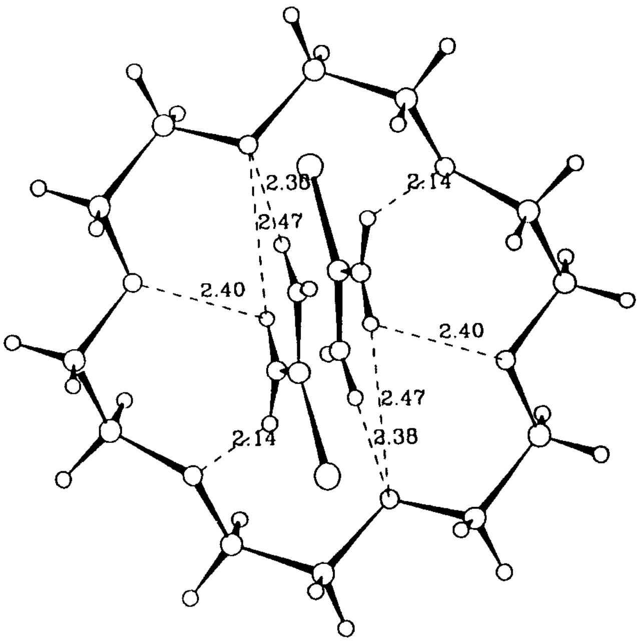

Figure 1 The structure of DAYWIJ, hydrogen bond type a1. Circles are sized according to atoms from S (largest) through C, N, O to H (smallest). Hydrogen bonds shown as dotted lines.

hydrogen bonds of type a2 (those at distances of 2.47, 2.14 Å in Fig 1). In addition in DAYWIJ, there is a hydrogen bond between the sulphur atom and an N–H group in an adjacent guest molecule.

In DAYWOP (18-crown-6) (thiourea)$_4$,[7] the two independent crowns (molecules 1 and 2) both have conformation (b) and are associated with two thioureas in an approximate centrosymmetric arrangement. As is apparent from Fig 2 (molecule 1) and Fig 3 (molecule 2), the hydrogen bond pattern in the two molecules is different. Neither pattern is equivalent to those indicated in ref 10. In molecule 1, while two hydrogens are hydrogen bonded to one oxygen to one side of the plane [2.08; 2.18 Å] and to the oxygen in the plane [2.37; 2.38 Å] in the manner described by Watson *et al.*,[10] in addition, this second hydrogen atom forms a second hydrogen bond to the other oxygen out of the plane [2.24; 2.33 Å] (Fig 2). In molecule 2, on the other hand, the two hydrogen bonds are formed to these oxygens out of the plane [1.98, 2.18; 1.96, 2.16 Å] and no hydrogen bonds are formed to the oxygen atoms in the plane (Fig 3). These two

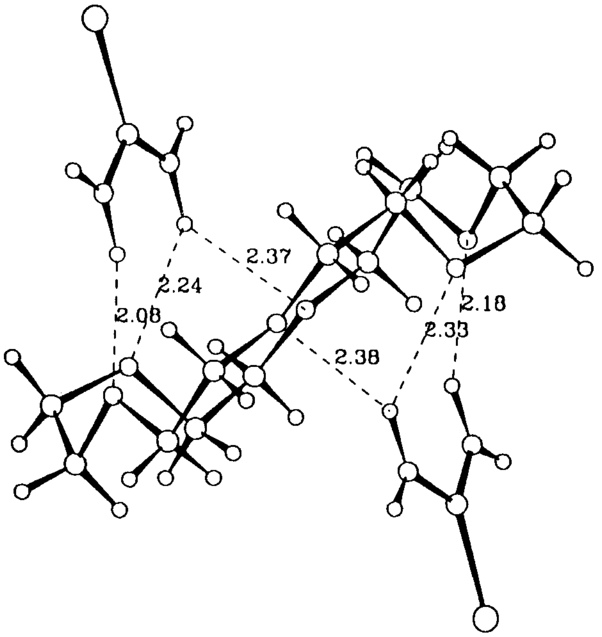

Figure 2 Part of the structure of DAYWOP, hydrogen bond type b1. Circles are sized according to atoms from S (largest) through C, N, O to H (smallest). Hydrogen bonds shown as dotted lines.

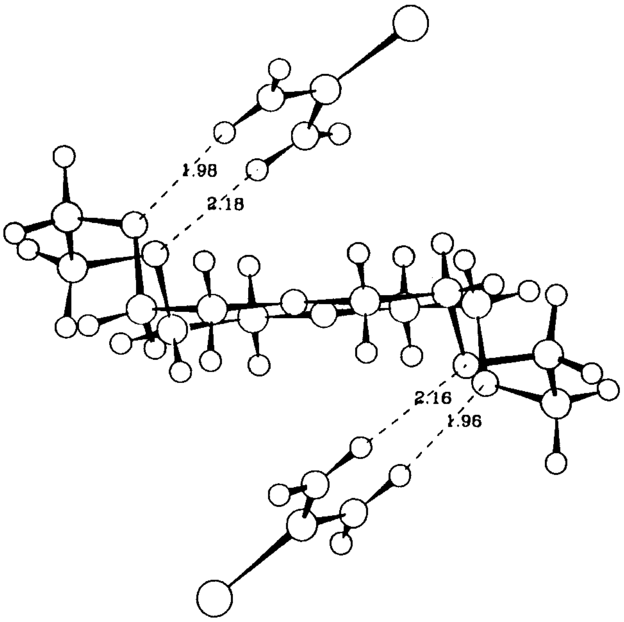

Figure 3 Part of the structure of DAYWOP, hydrogen bond type b2. Circles are sized according to atoms from S (largest) through C, N, O to H (smallest). Hydrogen bonds shown as dotted lines.

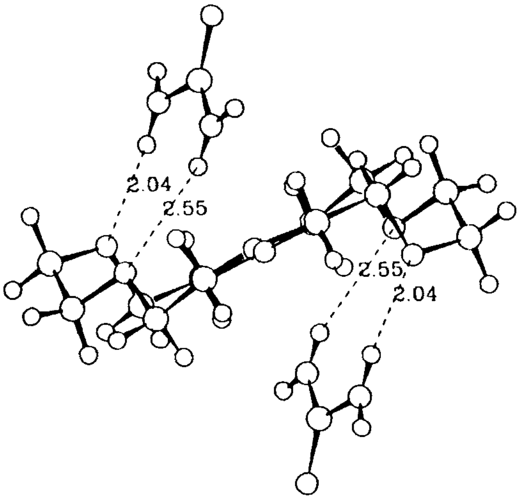

Figure 4 Part of the structure of CRWNUR, hydrogen bond type b2. Circles are sized according to atoms from C (largest) through N, O to H (smallest). Hydrogen bonds shown as dotted lines.

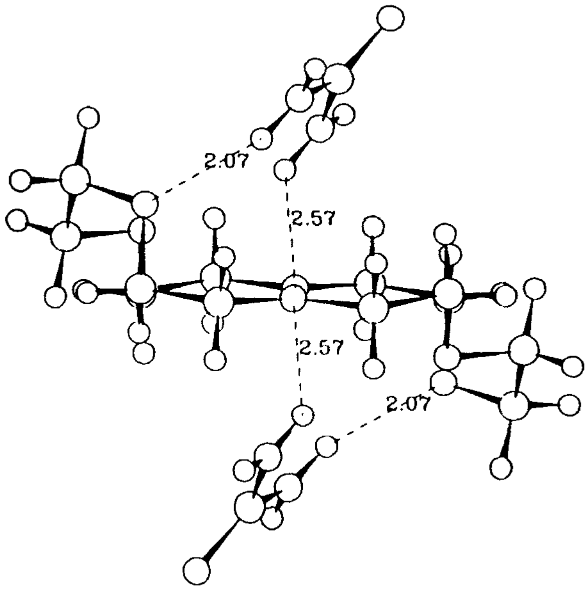

Figure 5 Part of the structure of CRWNUR, hydrogen bond type b3. Circles are sized according to atoms from C (largest) through N, O to H (smallest). Hydrogen bonds shown as dotted lines.

patterns are called type b1 and b2 respectively while that found by Watson *et al.* is identified as type b3. The unit cell also contains layers of thioureas forming hydrogen bonds to each other and to the other thioureas.

In CRWNUR (18-crown-6) (urea)$_5$,[8] the two independent centrosymmetric macrocycles are both hydrogen bonded to two ureas but molecule 1 (Fig 4) has type b1 bonding and molecule 2 (Fig 5) has type b2 bonding. However there is a slight distortion in both cases that one of the hydrogen bonds is strong and the other weak (molecule 1 2.04, 2.55; molecule 2 2.07, 2.57 Å). This is presumably due to the fact that these urea molecules are part of a layer of mutually hydrogen bonded urea molecules held together by a two-dimensional hydrogen-bonding network (Fig 6). It is interesting that neither the DAYWOP nor the DAYWIJ structure is observed for urea and the CRWNUR structure is not observed for thiourea. The remaining two structures contain substituted ureas as guest molecules. In DIWMOL, (18-crown-6) {N(m-chlorophenyl)urea}$_2$,[9] the unsubstituted –NH$_2$ group of the N(m-chlorophenyl)urea guest is hydrogen bonded in type b2 (Figure 7) with distances of 2.11, 2.49 Å and hydrogen bonded to another guest molecule via two C=O...H–N interactions. In CEHGIF, (18-crown-6) (N-methylthiourea),[10] the two

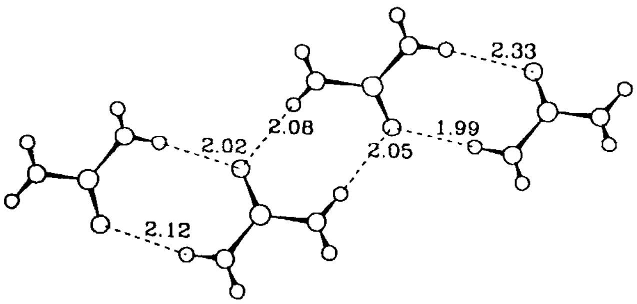

Figure 6 Part of the structure of CRWNUR, showing part of the layer structure of the urea molecules. Circles are sized according to atoms from C (largest) through N, O to H (smallest). Hydrogen bonds shown as dotted lines.

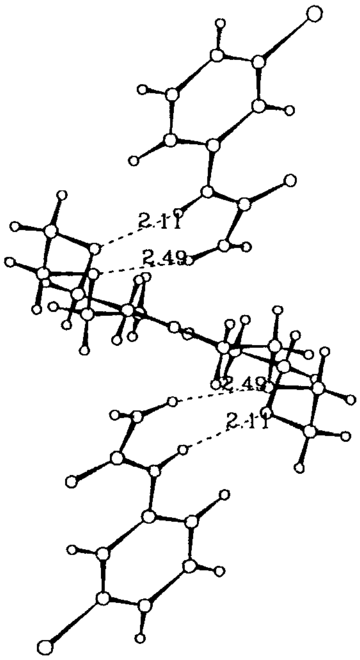

Figure 7 The structure of DIWMOL, hydrogen bond type b1. Circles are sized according to atoms from Cl (largest) through C, N, O to H (smallest). Hydrogen bonds shown as dotted lines.

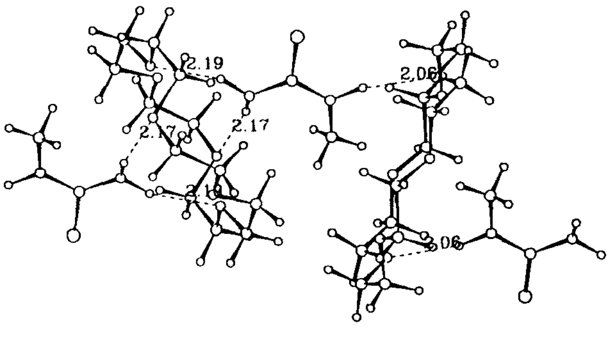

Figure 8 The structure of CEHGIF, hydrogen bond type b3. Circles are sized according to atoms from C (largest) through C, N, O to H (smallest). Hydrogen bonds shown as dotted lines.

centrosymmetric 18-crown-6 molecules are each sandwiched between two host molecules (Fig 8). The N-methyl end of the thiourea is hydrogen bonded through the N–H group to one oxygen of the crown at 2.06 Å in conformation (a), while the other unsubstituted NH_2 group is hydrogen bonded, in type b3 to two oxygens of the crown at 2.19, 2.17 Å in conformation (b) (Fig 8).

In summary then, the structures show only two conformations of the 18-crown-6 host which in each case forms intermolecular hydrogen bonds to only two guest molecules. There is a wide variation in the number of hydrogen bonds formed and also in the distances involved.

The major difficulty in the simulation of host-guest compounds is the modelling of the electrostatic component.[1] The electrostatic potential method (ESP)[14,15] is currently used most frequently. However there are two major problems with this method. First the calculated charges are very dependent upon conformation[16], though this is not a significant problem in the current work as the conformation of the host and guest are relatively inflexible. The second problem with the ESP method is that the charges thus calculated are necessarily incompatible with the forcefields used in the molecular mechanics calculations. These forcefields are parameterised on the basis of charge templates and therefore non-bonded constants are not necessarily consistent with imposed charges. It can be argued that it is preferable to use 'correct' ESP charges rather than 'incorrect' charge templates even given this inconsistency. However as coulombic interactions in general and in hydrogen bonds in particular play the major role in host/guest interactions, it was decided to use the 'correct' ESP charges in this work rather than the charge templates. In this case, this choice was simpler to make as the conformations of both host and guest remained relatively unchanged during the calculations. ESP charges on the molecules were calculated using the MOPAC-ESP program.[17] We used the dipole option which constrains the atomic charges to reproduce the dipole moment. It has been established that the charges produced from MOPAC are less than comparable charges produced from *ab initio* calculations with a 6-31G** basis set by a factor that is constant for specific groups of molecules. This constant ranges from 1.28 for carbohydrates to 1.42 for small alcohols.[14,15] We decided to use this latter value. The charges used are listed directly in Table 3 and illustrated in Figs 9 and 10.

Calculations were carried out with the CERIUS package[5] using the DreidingII forcefield. In all cases default values for the forcefield parameters were used except where otherwise stated.

RESULTS AND DISCUSSION

Crystal structure

The same procedures were adopted for all 5 structures. The asymmetric units were obtained from the Cambridge Crystallographic Database. These were

Table 3 Atomic charges taken from the MOPAC-ESP program

Urea	
	O −0.68, C 1.04, N −1.35 and H 0.58
Thiourea	
	S −0.55, C 0.22, N −0.50 and H 0.33

For m-Chloro-phenylurea and N-methylthiourea see Figs 9 and 10.
18-crown-6: average values in conformations (a) and (b) O −0.26, C −0.07, H 0.10.

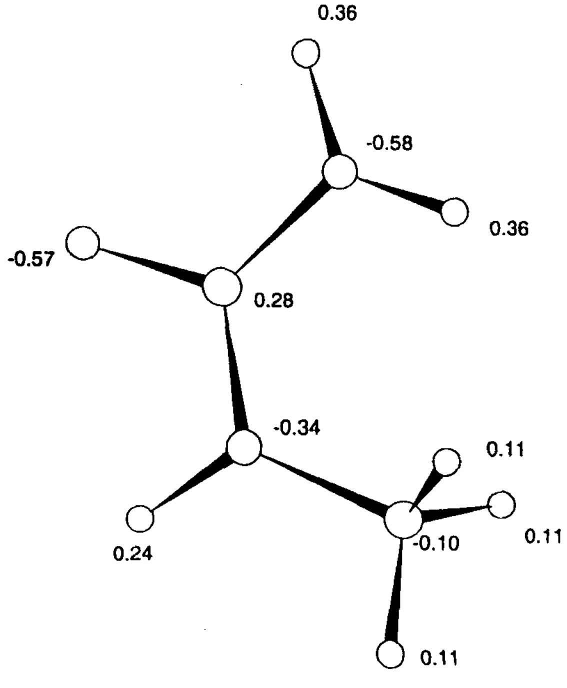

Figure 9 The atomic charges calculated for the N-methylurea guest molecule using the MOPAC-ESP program.

read into CERIUS and by using spacegroup symmetry the contents of one unit cell were obtained. The spacegroup of the unit cell was then changed to P1. MOPAC-ESP charges were added to the individual atoms as per Table 3. In the DreidingII force field, there is an option to include special terms to treat the hydrogen bonds. After various trials, we found that better results were obtained when these special terms were omitted and hydrogen bonds were treated only via electrostatic and van der Waals non-bonded terms.

The Ewald summation method[18,19] was used to sum the coulombic interactions. Here $V_{coul} = V_R + V_k$, where V_R is a quickly converging modified real-space sum and V_k is a summation in reciprocal space. Three parameters are variable, the real sum limit, the reciprocal sum limit and the Ewald sum constant and these were optimised using the CERIUS software for each structure. The cut-off in van der Waals interactions was set at 7.0 Å.

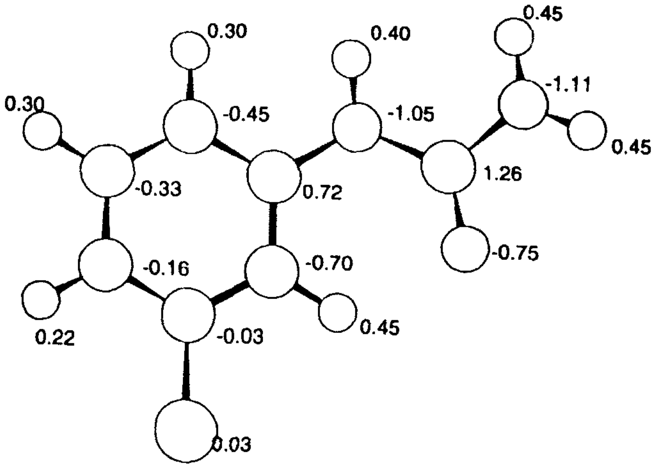

Figure 10 The atomic charges calculated for the m-chlorophenylurea guest molecule using the MOPAC-ESP program.

The energies of each unit cell were then minimised until convergence, the energy changing by less than 10^{-5} kcal mol^{-1}. All atom coordinates were allowed to vary as indeed were all the six unit cell parameters. In Table 4 the cell dimensions and volume in the crystal structure before and after minimisation are compared. The changes in volume are all less than 5.5% with a mean of 3.7%, thus indicating that the modelling of unit cells has worked satisfactorily. The r.m.s. values calculated over all atoms in one unit cell are quoted in Table 4 for the five structures and show values ranging from 0.13 to 0.40 Å. We also calculated the r.m.s. deviation for the unique fragments of the structure containing one crown with two hydrogen-bonded guest molecules for comparison with the results from molecular fragments. The changes in hydrogen bond pattern after minimisation are detailed in Table 4. All the hydrogen bonds are retained but in the case of DAYWOP and CRWNUR, two further hydrogen bonds are formed. The results from unit cell minimisation will be compared to those from molecular fragments below.

Molecular systems

We first took fragments from the five crystal structures. Each fragment consisted of one crown and two

Table 4 Refinement of the five crystal structures using periodic boundary conditions. Dimensions in the crystal structure are followed by dimensions after refinement

	DAYWOP	CRWNUR	DAYWIJ	DIWMOL	CEHGIF
a(Å) obs(calc)	9.18(9.25)	17.87(17.19)	8.37(8.14)	25.59(25.02)	8.90(9.19)
b(Å) obs(calc)	19.28(19.29)	8.31(8.88)	8.69(8.62)	7.97(8.29)	9.31(9.35)
c(Å) obs(calc)	16.32(16.56)	20.70(19.74)	8.68(8.76)	15.24(15.52)	15.77(15.84)
α(°) (obs(calc)	90.0(90.0)	90.0(90.0)	114.9(116.3)	90.0(89.9)	120.7(119.4)
β(°) obs(calc)	90.8(90.8)	108.6(106.0)	106.8(100.5)	101.6(103.6)	94.6(96.5)
γ(°) obs(calc)	90.0(90.0)	90.0(89.7)	71.5(72.9)	90.0(90.2)	114.3(113.2)
U(Å^3) obs(calc)	2886.5(2911.7)	3041.8(2895.9)	534.1(553.1)	3041.8(3127.0)	951.8(1006.6)
cell r.m.s. (Å)	0.24	0.40	0.13	0.37	0.17
fragment r.m.s. (Å)	0.32, 0.18	0.22, 0.26	0.13	0.20	0.13, 0.13
% change in U(A^3)	0.9	−5.0	−3.4	−2.8	5.3
hydrogen bonds					
obs(calc)	1.98(2.03) 2.18(2.40) 2.08(2.20) 2.24(2.26) 2.37(2.27) 2.73(2.47)[b] 2.89(2.43)[b]	2.06(2.15) 2.46(2.46) 2.04(2.06) 2.55(2.35) 2.82(2.35)[b] 2.60(2.31)[b]	2.14(2.24) 2.40(2.28) 2.38(2.21) 2.47(2.57)	2.11(2.18) 2.49(2.50)	2.06(2.22) 2.17(2.28) 2.19(2.25)

[a] Unique values are given for the hydrogen bonding distance. In the optimisation, symmetry was removed. Average values of the hydrogen bonds are therefore quoted.

[b] These distances represent hydrogen bonds that were generated in the minimisation but were not observed in the crystal lattice.

Table 5 Results of molecular mechanics calculations on the five structure models

	energy (kcal mol^{-1})	no of hydrogen bonds		r.m.s. deviation (Å)	
		before	after	in model	in cell
DAYWOP	−69.2	6	8	0.53	0.32
	−62.5	4	5	0.27	0.18
CRWNUR	−332.9	4	8	0.35	0.22
	−332.9	4	8	0.51	0.26
DIWMOL	−301.6	4	4	0.23	0.20
CEHGIF	−35.9	4	4	0.17	0.13
	−29.1	2	2	0.16	0.13
DAYWIJ	−69.9	8	8	0.15	0.13

associated guest molecules. When a structure had two different crown molecules in the asymmetric unit, then two starting models were taken. Thus there was one starting model for DIWMOL, and DAYWIJ and two for DAYWOP, CRWNUR and CEHGIF. Each model was then optimised with molecular mechanics using the CERIUS software with the DreidingII force field. Results are shown in Table 5 and compared to the results from the crystal structure calculations.

Two trends stand out. First the number of hydrogen bonds in the structure always increases or stays the same on minimisation. Second the goodness of fit is lowest when the hydrogen bond pattern is restricted i.e. in DIWMOL and CEHGIF where the guest is a substituted urea. We compare the r.m.s. values with those calculated from the identical fragments in the crystal structures rather than from the unit cells which contain (with the one exception of DAYWIJ) many more atoms. As expected the r.m.s. deviations of fragments abstracted from the crystal structure minimisation are always lower (mean value 0.20 Å) than in the direct fragment calculations (mean vaue 0.30 Å). Changes in the hydrogen bond pattern are also less than in the fragment calculation.

We then considered the global minimum conformations of the complexes of 18-crown-6 with urea and thiourea. Our analysis of the hydrogen bond pattern in the five structures when combined to the analysis in ref 10 has identified five different types; these were types a1 (Fig 1), a2 (Fig 11), b1 (Fig 3), b2 (Fig 4) and b3 (Fig 5). Type a2 was taken from ref 10. For each study, only one 18-crown-6 host was taken together with two guest molecules. For each model unsubstituted urea and 18-crown-6 were similar but not identical in the structures but the variations were not significant and so average conformations were taken for the starting models.

The analysis showed that the (a) models came to similar minimum as indeed did the (b) models and these minima are illustrated in Figs 12 and 13. The minima from the various models are similar but not identical indicating that shallow broad minima exists for these systems. As can be seen, what has happened during the molecular mechanics minimisation is that the number of hydrogen bonds has been maximised. In both cases 8 strong hydrogen bonds are formed between the urea and the crown. This is clearly a manifestation of the molecular mechanics technique where the energy is minimised by having a maximum number of hydrogen bonds so that a bifurcated hydrogen bond is equal in energy to 2 single hydrogen bonds. This has been found[2] in previous studies with the MM2 force field.

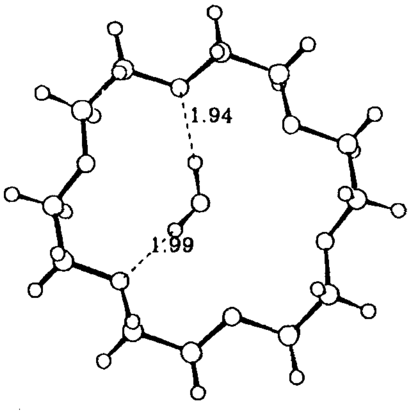

Figure 11 The structure of (18-crown-6) (H_2O), taken from ref 10 showing hydrogen bond type a2. Circles are sized according to atoms from C (largest) N, O to H (smallest). Hydrogen bonds shown as dotted lines.

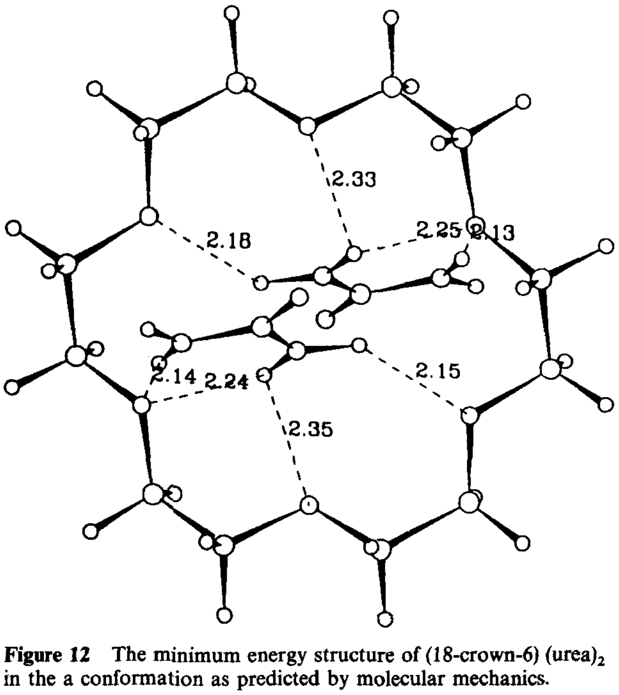

Figure 12 The minimum energy structure of (18-crown-6) (urea)$_2$ in the a conformation as predicted by molecular mechanics.

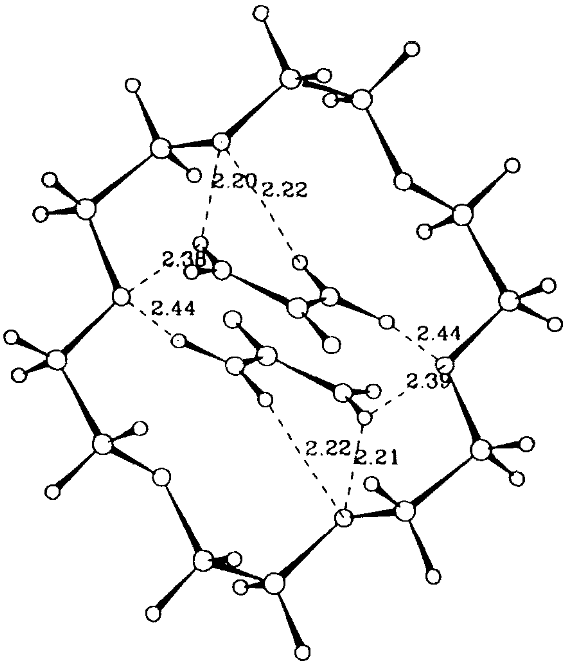

Figure 13 The minimum energy structure of (18-crown-6) $(urea)_2$ in the b conformation as predicted by molecular mechanics.

Table 6 Lowest energy structures of host/guest complexes (interaction energy in parentheses). All energies in kcal mol^{-1}

conformation	urea	thiourea
(a)	−335.0(−30.8)	−69.9(−28.5)
(b)	−332.9(−32.9)	−69.5(−32.3)

• calculated from $E_{interaction} = E_{host/guestc} - E_{host} - E_{guest}$ and using values for urea of −169.5 kcal mol^{-1}, thiourea −38.1 kcal mol^{-1}, conformation a 34.8 kcal mol^{-1}, conformation b 39.0 kcal mol^{-1}.

The minima found for conformation (a) (Fig 12) is similar in hydrogen bond pattern to that of DAYWIJ (Fig 1) but the dimensions are slightly different. The minima found for conformation (b) also contains 8 hydrogen bonds (Fig 13) and includes all the hydrogen bonds observed in models (b1), (b2) and (b3). The Figs illustrate the minima found with urea but those with thiourea are similar. The minimum energies of all the host-guest complexes are listed in Table 6. Results show that the association of the two guest molecules with the crown gives rise to an interaction energy of ca −30 kcal mol^{-1}.

CONCLUSIONS

For many host/guest systems, the interaction between host and guest is complicated and can only be described by simulating a large number of non-bonded interactions. Often the only guide to the likely arrangements of host and guest is provided by a crystal structure. In this work, we have investigated whether a crystal structure is an adequate guide to the likely arrangement of guests around the host in the gas or solvent phase.

Our modelling results show that a crystal structure which effectively contains an infinite number of host and guest molecules, can give a clear general indication of the likely arrangement of host and guest is non-crystalline phases. However from our computer modelling calculations on systems containing one host molecule and two hydrogen-bonded guest molecules, we have found energy minima conformations that correspond only approximately to those obtained in the crystal structure. There must remain some doubt as to the accuracy of these calculations as molecular mechanics calculations often lead to an excess of hydrogen bonds as compared with experimentally obtained structures. Clearly crystal packing forces play an important role and should be included in some form in any calculations on host/guest systems that involve using crystal structures as experimental data.

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