

## A Molecular Mechanics Study of 18-Crown-6 and its Complexes with Neutral Organic Molecules

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The flexibility of 18-crown-6 has been studied by the molecular mechanics method (MM2). Calculations on 190 different potentially favourable ('ideal') conformations reveal that the potential energy surface of the polyether has many minima with only small energy differences. The order of the conformational energies depends mainly on the contribution of the electrostatic energy. If no electrostatic interactions are present, the most favourable conformations are the ones occurring in complexes of 18-crown-6, as observed by X-ray crystallography. However, for larger contributions of the electrostatic energy the conformation adopted by uncomplexed 18-crown-6 in the crystalline state becomes the dominating conformation. Also results are presented for calculations on six experimentally observed conformations of 18-crown-6. It is shown that the calculated geometries correspond closely with the experimental ones, notwithstanding the omission of the guest molecules in the calculations, indicating that the minima in the potential energy surface of the polyether have steep slopes. Finally, results are given for calculations on the hydrogen-bonded complexes of 18-crown-6 with urea and formamide, both using the MM2 and the MM2HB force field. The latter is a modified version of MM2, incorporating an empirical N-H...O hydrogen-bond potential. MM2HB proves to be far superior over MM2 for calculations on this type of complexes, as well as for the conformation adopted by the macrocycles as regarding the hydrogen-bond geometries.

Molecular complexation and structural recognition are key processes in biological systems. For instance, enzyme catalysis, drug action, and ion transfer through lipophilic membranes all involve complexation between two or more distinct molecules. Since synthetic macrocyclic polyethers (crown ethers) show many features encountered in such biological processes<sup>1</sup> (complexing ability, flexibility, and selectivity), they may play an important role as substitutes for natural occurring molecules in living organisms. A possible field of application is in kidney dialysis, where the renal function (*viz.* the removal of noxious substances from the blood) is performed outside the body. A special problem hereby is posed by urea, which is toxic and very difficult to remove. Knowing that macrocyclic polyethers are capable of forming complexes with neutral molecules,<sup>2</sup> we are investigating the possibilities of using crown ethers as selective complexing agents for urea. To obtain an optimal receptor molecule for urea, some guidelines are wanted and a better understanding of the factors determining complexation is therefore necessary. The two main questions to be answered in this respect are *what is the nature of the complexation forces and what factors can influence them, and are most crown ethers flexible enough to fit their shapes to the geometrical and electronic requirements of a guest molecule, or are only certain 'fixed' conformations possible?*

Notwithstanding the presumed flexibility of medium and large crown ethers, only a very limited number of different crown ether conformations has been observed by X-ray crystallographic structure determinations.<sup>3,4</sup> In a previous publication<sup>4</sup> we presented a method for calculating the number of different conformations of 'ideal crown ethers' and to estimate their relative conformational energies. It was shown that 18-crown-6 can adopt 675 different ideal conformations, of which 190 (without CH...HC overlap) are classified as potentially favourable. A survey of the literature showed the experimentally encountered ideal conformations to be among the lowest-

energy ones. Observed non-ideal conformations were shown to be easily derivable from ideal ones.

To perform a more reliable study of the relative conformational energies of crown ethers and to investigate the factors determining complexation, we have used the molecular mechanics method. We present the results of calculations on 18-crown-6 for all 190 ideal conformations of 18-crown-6 without CH...HC overlap, for six experimentally encountered conformations, and for two complexes of this polyether with neutral organic guest molecules. Although some molecular mechanics calculations on 18-crown-6 (complexes) have been reported, only a few different conformations of the host molecule<sup>5-7</sup> and only complexes with alkali cations<sup>6</sup> have been investigated so far.

Although most parameters used in the potential energy functions of molecular mechanics programs are reasonably reliable owing to the large amount of experimental data to which they are fitted, this is not always the case for the parameters determining the contribution of the electrostatic energy to the total (steric) energy of a molecular system. This contribution, however, is very important for compounds with many heteroatoms [like crown ethers and urea(-like) molecules] and especially for complexes between such compounds. Bond dipole moments or net atomic charges are not easily obtainable and also the choice of the relative dielectric constant  $\epsilon_r$  is not straightforward, as the medium between the interacting charges or dipoles will not be uniform throughout the molecular system. Greenberg *et al.* investigated the necessity of some distance-dependency of  $\epsilon_r$  and obtained the best results when a small value is used (*ca.* 1) for short-range interactions (< 3.5 Å) and a larger value (*ca.* 2) for interactions over longer separations.<sup>8</sup> It was also reported that the neglect of the effect of induction and the polarizability of bonds may result in serious errors in the calculations of the electrostatic contributions and hence in the optimized geometries.<sup>9</sup> Therefore, all calculations

have been performed with different contributions of the electrostatic energies.

### Method

Calculations were performed using the MM2 program,<sup>10,11</sup> which is known to yield good results for ethers.<sup>11</sup> The electrostatic energy is calculated as the energy resulting from dipole-dipole interactions, using standard bond dipole moments (including 'lone pair dipoles'<sup>11</sup>). All parameters used in the present calculations have standard values, as incorporated in the MM2 program, with one exception. The standard bond length  $l_0$  for  $C_{sp^3}-C_{sp^3}$  bonds has a value of 1.523 Å, yielding C-C bond lengths in the range 1.52–1.61 Å.<sup>10</sup> However, the C-C bond lengths in crown ethers are always considerably shorter (average value *ca.* 1.495 Å<sup>3</sup>). Although the reason for this shortening may still not be fully understood,\* it is commonly agreed nowadays that it is a genuine phenomenon. Preliminary molecular mechanics calculations on 18-crown-6 indicated that a significantly smaller value for  $l_0(C_{sp^3}-C_{sp^3})$  had to be chosen to reproduce this shortening. A trial-and-error procedure yielded an optimal value of 1.48 Å.

Input co-ordinates for all ideal conformations were calculated assuming C-C and C-O bond lengths of 1.5 Å and C-H bond lengths of 1.113 Å (the standard C-H bond length in the MM2 force field). The calculations on experimental 18-crown-6 conformations and on the 18-crown-6 complexes started with co-ordinates for the non-hydrogen atoms obtained from X-ray structure determinations; initial hydrogen-positions were derived from the X-ray hydrogen co-ordinates by lengthening the experimental C-H and N-H bonds to the standard values of 1.113 and 1.011 Å, respectively. Lone pairs (LP) are included for the crown ether oxygen atoms in the bisecting planes of the C-O-C fragments, with O-LP bond distances of 0.6 Å and LP-O-LP bond angles of 130°. The exact values of the input co-ordinates proved not to be critical for the final optimized geometries and corresponding steric energies.

In the MM2 program  $\epsilon_r$  is introduced as a parameter. This facilitates calculations in which all dipole moments are scaled by a common factor and makes it easier to vary the contribution of the electrostatic energy to the total energy. To stress the point that it is not the dielectric constant that is changed, but rather the dipole moments that are being scaled,  $\epsilon_r^{-1}$  will be termed the 'electrostatic scale factor'.

It will be shown that the MM2 program is not well suited to deal with complexes of crown ethers with neutral organic molecules (*i.e.* in which hydrogen bonding is the main component of the binding between host and guest). To account in a better way for hydrogen bonding, an empirical hydrogen-bond potential was added to the MM2 force field. This potential is a slightly modified form of the empirical O-H...O hydrogen-bond potential developed for the MM2 force field by Kroon-Batenburg and Kanters,<sup>13</sup> who used it successfully in a molecular mechanics study of the influence of hydrogen bonds on the conformation of  $\alpha$ -D-glucose.<sup>14</sup> Following these authors, this modified molecular mechanics program will be called MM2HB.

There are two differences between the MM2HB and the MM2 force field. First, an additional energy term is used in MM2HB, called the *hydrogen-bond energy*  $E_{\text{HB}}$ , which is described by a Morse potential (1) in which  $r$  is the distance

$$E_{\text{HB}} = \sum D_0 \{ e^{-2\alpha_0(r-r_0)} - 2e^{-\alpha_0(r-r_0)} \} f(\delta) \quad (1)$$

\* It has been shown that part of this shortening may be due to inadequate treatment of thermal motion.<sup>12a,b</sup> Part of the shortening can also be explained by the electronegativity of the oxygen neighbour atoms.

between the acceptor atom (A) and the donor atom (D) in a hydrogen bond.  $D_0$ ,  $\alpha_0$ , and  $r_0$  are parameters, depending on the type of hydrogen bond. The function  $f(\delta)$  is an attenuation factor, introduced in a different form by Hagler *et al.*,<sup>15</sup> describing the angular dependence of the hydrogen bond. It has form (2) in which  $\delta$  is the supplement of the hydrogen-bond angle D-H...A and  $n$  is an empirical parameter.

$$f(\delta) = \cos^n \delta \quad \text{for } \delta \leq 90^\circ \quad (2a)$$

$$= 0 \quad \text{for } \delta \geq 90^\circ \quad (2b)$$

The second difference between MM2 and MM2HB is the use in the latter of an attenuation factor  $f'(\delta) = 1 - f(\delta)$  for the van der Waals interactions between the hydrogen atoms and the acceptor atoms (+ lone pairs) in hydrogen bonds. The necessity of this attenuation stems from the overestimated repulsive van der Waals forces for these atoms in a hydrogen bond in the MM2 force field.

The combined effect of  $f(\delta)$  and  $f'(\delta)$  is that the energy due to the interaction between the hydrogen atom and the acceptor atom in a hydrogen bond gradually changes from pure hydrogen-bond character to pure van der Waals character for  $\delta$  increasing from 0 to 90° or more.†

The hydrogen-bond potential in this form is almost equal to the one developed by Taylor<sup>16</sup> for use in the MMI program,<sup>17</sup> except for the use of the D...A distance in the Morse potential instead of the H...A distance.

There is no strong reason to adopt a particular form of the attenuation factor. McGuire *et al.*<sup>18</sup> even conclude that, for empirical hydrogen-bond potentials determined by them for various types of O-H...O and N-H...O hydrogen bonds, the introduction of an angular dependence for the potentials is unnecessary, the observed angular distribution being accounted for by the various intermolecular nonbonded and electrostatic interactions. Following Kroon-Batenburg and Kanters<sup>13</sup> and Taylor<sup>16</sup> a value of 2 for the power of the cosine terms in the expressions for  $f(\delta)$  and  $f'(\delta)$  is used. Although this choice is not critical for almost linear hydrogen bonds, it may become so for hydrogen bonds deviating considerably from linearity.

### Results and Discussion

(1) *Ideal Conformations of 18-Crown-6.*—The calculations reported in this section are carried out for two different values of  $\epsilon_r$ , arbitrarily chosen as 0.75 and  $\infty$ .‡ The calculated steric energies for the two values of  $\epsilon_r$  are collected in Table 1.§

The contribution of the electrostatic energy to the total steric energy has a large influence on the calculated relative energies of the conformations. If  $\epsilon_r$  0.75 is used in the calculations of the electrostatic interactions, the resulting values of the conformational energies suggest that almost 90% of 18-crown-6 molecules in the gas phase will adopt the  $g^+g^-ag^+aaa g^-g^+ag^-aaa$  conformation (*i.e.* the conformation of uncomplexed

† The differences between the given hydrogen-bond potential and the one used by Kroon-Batenburg and Kanters<sup>13</sup> is that they do not apply an attenuation factor to the Morse potential, nor do they use an attenuation of the van der Waals energy due to the H...LP interactions in a hydrogen bond (but have changed the van der Waals parameters  $\epsilon$  and  $r_0$  of the lone pairs on oxygen from 0.016 to 0.007 kcal mol<sup>-1</sup> and from 1.2 to 0.75 Å, respectively).

‡ The initial choice for the electrostatic scale factors is not very important, because it will be shown in the next section that the total steric energy of a conformation is nearly linear in  $\epsilon_r^{-1}$ . Steric energies of the conformations for other values of  $\epsilon_r^{-1}$  may therefore with reasonable accuracy be estimated by inter- or extra-polation.

§ To conform with the notations in refs. 4–7, we will use the units kcal mol<sup>-1</sup> for energy; 1 cal = 4.184 J.

**Table 1.** The 190 ideal conformations for 18-crown-6 (+, 0, and - stand for  $g^+$ ,  $a$ ,  $g^-$  respectively), and the calculated conformational energies (kcal mol<sup>-1</sup>) for two different contributions of the electrostatic energy

Conformation						Energy		Conformation						Energy	
						$\epsilon_r$ 0.75	$\epsilon_r$ $\infty$							$\epsilon_r$ 0.75	$\epsilon_r$ $\infty$
0 + 0	0 - 0	0 + 0	0 - 0	0 + 0	0 - 0	38.16	26.47	+ + 0	+ - 0	- + 0	+ 0 0	+ - -	0 + 0	44.97	40.89
+ + 0	0 - 0	0 + 0	0 - -	0 - 0	0 + 0	43.39	30.14	+ + 0	+ 0 0	+ 0 0	- - 0	- 0 0	- 0 0	46.53	40.97
+ + 0	0 - 0	0 - 0	- - 0	0 + 0	0 + 0	42.53	30.28	+ + 0	+ + 0	+ 0 -	- - 0	- + 0	+ 0 0	47.07	40.98
+ + +	0 + 0	0 + 0	+ + 0	0 - 0	0 + 0	44.24	31.98	+ + 0	0 - -	0 0 +	+ + 0	- + +	0 0 0	47.54	41.04
+ + 0	0 - -	0 + 0	+ - 0	0 + 0	0 + 0	42.60	32.49	+ + 0	0 + -	- + 0	0 + 0	0 + -	- 0 0	45.38	41.10
+ + 0	+ + 0	0 + 0	+ + 0	+ + 0	0 + 0	46.44	32.62	+ + 0	0 - +	0 + -	0 - +	0 0 -	- 0 0	43.00	41.11
+ - 0	0 + 0	0 - 0	0 + 0	0 - +	0 - 0	38.83	33.36	+ + 0	+ - 0	- 0 0	- 0 0	+ - 0	0 0 0	43.07	41.12
+ + 0	0 - 0	0 + 0	0 - +	0 + 0	- + 0	41.04	33.58	+ + 0	+ + 0	+ 0 0	+ + 0	+ - 0	- 0 +	47.59	41.15
+ + +	0 + 0	0 - 0	- - 0	0 - 0	0 + 0	46.08	33.87	+ 0 0	- 0 +	+ - 0	0 + 0	0 - 0	0 - +	44.86	41.18
+ - 0	0 + 0	0 0 0	- + 0	0 - 0	0 0 0	36.54	34.06	+ 0 -	0 - 0	0 + -	- 0 +	0 + 0	0 - +	45.49	41.25
+ + 0	+ + 0	0 0 0	- - 0	- - 0	0 0 0	41.84	34.17	+ + 0	+ 0 -	- + 0	0 + 0	+ - 0	- + 0	44.58	41.27
+ + 0	+ + 0	0 - 0	0 + 0	+ + -	0 - 0	45.06	34.25	+ + +	0 + +	0 0 -	- - 0	+ - -	0 - 0	48.46	41.27
+ + +	0 + +	0 - 0	- + 0	0 - 0	0 + 0	44.40	34.30	+ 0 0	- 0 +	0 0 0	- 0 0	+ - 0	0 0 0	41.00	41.28
+ + 0	0 - -	0 0 0	- - 0	0 + +	0 0 0	42.33	34.54	+ + 0	0 - 0	0 + -	- 0 0	0 + -	- 0 0	45.43	41.29
+ + 0	0 0 0	- + 0	0 - 0	0 - 0	- + 0	38.79	34.59	+ + 0	0 - +	0 0 +	0 + -	0 0 +	+ - 0	43.20	41.30
+ + 0	+ + 0	0 + 0	+ - 0	0 + +	0 0 0	42.18	34.80	+ + +	0 0 +	0 + 0	- + 0	0 0 -	0 - 0	44.87	41.38
+ + 0	0 - 0	0 + -	0 + +	+ - 0	0 + 0	41.11	35.17	+ + 0	0 + -	- + 0	- 0 +	+ - 0	0 + 0	46.91	41.42
+ + 0	+ + 0	0 - 0	0 - 0	- - +	0 - 0	43.82	35.28	+ + 0	+ 0 0	+ - 0	0 0 0	- + +	0 0 0	43.50	41.48
+ + 0	0 - +	0 - 0	- + +	0 + 0	0 + 0	43.73	35.32	+ + 0	+ + 0	+ 0 -	- 0 0	+ - 0	0 0 0	46.42	41.54
+ + +	0 + +	0 + 0	0 + 0	0 - +	0 0 0	42.30	35.41	+ + 0	0 + -	- + 0	0 0 -	- + 0	0 + 0	46.67	41.94
+ + +	0 + -	0 - 0	0 - -	0 - -	0 - 0	45.34	35.47	+ - 0	- 0 +	+ - 0	- + 0	+ - 0	- + 0	40.03	41.94
+ + +	0 + +	0 0 0	+ + 0	0 - -	0 - 0	45.52	35.50	+ + 0	+ - 0	- + 0	+ 0 0	- + +	0 0 0	43.51	41.97
+ + 0	0 + 0	+ + 0	0 - -	0 0 0	- + 0	43.70	35.53	+ + 0	+ 0 0	- - 0	- + 0	0 0 +	+ 0 +	47.45	41.97
+ + 0	+ + 0	0 0 0	- + 0	0 - -	0 + 0	44.22	35.74	+ + 0	0 + -	- - 0	+ - 0	0 0 0	- + 0	45.48	42.01
+ + 0	0 - +	0 + 0	- - 0	0 - -	0 - 0	43.28	35.89	+ + 0	0 0 +	+ 0 0	- - 0	0 0 -	- 0 0	47.61	42.04
+ + 0	+ + 0	0 + -	- - 0	- + 0	0 + 0	43.23	35.91	+ + 0	+ + 0	0 0 +	+ 0 0	- - 0	- 0 +	48.99	42.17
+ + 0	0 + 0	+ - 0	- - 0	0 - 0	- + 0	42.42	36.04	+ + 0	0 + -	- 0 0	0 - -	0 0 +	+ - 0	46.67	42.21
+ + 0	0 - 0	0 - +	+ + 0	- + 0	0 + 0	42.73	36.17	+ + 0	0 + -	- + 0	- 0 0	0 - +	+ - 0	48.65	42.26
+ + 0	0 - 0	0 + +	0 + +	0 0 0	- + 0	42.27	36.36	+ + +	0 + 0	0 + -	0 0 -	0 0 +	+ - 0	46.12	42.29
+ + 0	0 - +	0 - 0	+ - -	0 - 0	0 + 0	42.77	36.60	+ + 0	+ - -	0 - 0	- - +	0 + +	+ 0 +	48.10	42.31
+ + +	0 + +	0 + 0	- - 0	0 - -	0 - 0	48.38	36.67	+ + 0	+ + 0	+ 0 0	+ 0 0	- + 0	0 0 +	48.01	42.36
+ + +	0 + +	0 + 0	0 + +	0 + -	0 - 0	45.12	36.75	+ + 0	0 - 0	0 - +	+ 0 -	0 + -	- 0 0	46.56	42.36
+ + +	0 + 0	0 - 0	- - +	0 + 0	- + 0	45.76	36.83	+ + -	0 0 0	0 + -	- 0 +	0 + -	0 - 0	45.20	42.44
+ + 0	0 - +	0 0 0	+ + 0	0 - +	0 0 0	40.82	36.92	+ + +	0 + -	0 0 -	0 - +	0 0 -	- 0 0	44.73	42.53
+ + +	0 + -	0 0 0	0 + +	0 + +	0 0 0	42.53	37.08	+ + 0	+ + 0	+ - 0	- 0 0	+ - -	0 0 +	47.87	42.59
+ + 0	+ + 0	0 0 +	+ + 0	+ - 0	0 0 0	43.28	37.09	+ + 0	+ + 0	+ 0 -	- - 0	- - 0	- 0 +	50.89	42.60
+ + +	0 + +	0 0 0	+ - 0	- - 0	0 + 0	45.15	37.09	+ + 0	+ 0 0	+ 0 +	+ + 0	+ 0 0	- 0 0	49.24	42.64
+ + -	0 0 0	0 - 0	- - +	0 0 0	0 + 0	40.30	37.13	+ + +	+ - 0	0 + 0	0 - -	0 - 0	0 - +	48.08	42.74
+ + +	0 + +	0 0 0	+ + 0	+ + +	0 + 0	47.58	37.21	+ 0 0	0 + -	0 0 +	+ 0 0	0 + -	0 0 +	44.67	42.76
+ + -	0 0 0	0 + 0	+ + -	0 0 0	0 + 0	40.72	37.24	+ + 0	+ + 0	0 0 +	+ 0 +	+ + 0	+ 0 +	52.41	42.82
+ + 0	+ - 0	0 - 0	- + 0	0 - -	0 0 +	42.67	37.26	+ + +	0 + +	0 0 0	+ + -	0 + +	+ - 0	48.31	42.98
+ 0 0	+ - 0	0 + 0	0 0 +	+ - 0	0 + 0	40.11	37.40	+ + 0	+ + 0	+ - 0	- 0 0	- + +	0 - +	46.47	43.00
+ + 0	0 - 0	0 + -	0 0 0	0 - +	+ - 0	41.91	37.53	+ + 0	- + 0	0 + -	- - 0	+ - 0	0 - +	45.32	43.08
+ + +	0 + 0	0 + -	- - 0	+ - 0	0 + 0	43.81	37.57	+ + +	0 + -	0 - +	0 + -	0 0 +	+ - 0	44.57	43.09
+ + +	0 + -	0 0 0	- - 0	0 + -	0 - 0	42.26	37.62	+ + +	0 + 0	0 - +	+ 0 0	0 - +	+ - 0	48.36	43.27
+ + 0	0 - -	0 - +	0 - +	+ - 0	0 + 0	45.37	37.79	+ + 0	+ 0 -	- + 0	0 - -	0 + -	- 0 0	48.13	43.29
+ + 0	+ + 0	+ 0 0	+ + 0	+ + 0	+ 0 0	47.51	37.95	+ + -	0 + 0	0 0 0	+ + -	0 0 -	0 - 0	46.15	43.31
+ 0 0	+ - 0	0 - 0	- 0 0	- + 0	0 + 0	40.77	38.01	+ + 0	+ - -	0 + 0	+ + -	0 + +	+ 0 +	49.48	43.40
+ + +	0 + 0	0 + 0	+ + -	0 + 0	- + 0	44.00	38.11	+ + 0	+ - 0	0 0 -	- 0 0	+ - 0	- 0 +	46.44	43.61
+ + 0	0 - -	0 + -	- + 0	0 - 0	- + 0	44.60	38.14	+ + 0	+ 0 +	+ - 0	0 + +	0 - +	+ 0 +	47.60	43.82
+ 0 0	+ - 0	0 0 0	+ - 0	0 - 0	- + 0	39.31	38.18	+ + 0	- 0 -	- + 0	0 0 0	+ - 0	0 - +	45.28	43.83
+ + +	0 + -	0 - 0	+ + +	0 + -	0 - 0	44.34	38.29	+ + +	+ - 0	0 + 0	+ + +	0 + 0	0 - +	48.87	43.86
+ + 0	0 0 +	+ - 0	0 0 0	- + 0	0 + 0	42.12	38.40	+ + -	0 0 -	0 0 +	+ - 0	+ + -	0 - 0	47.18	43.97
+ + +	0 + -	0 - 0	+ + 0	0 - +	0 0 0	43.63	38.42	+ + +	0 0 -	- + 0	0 + +	0 - +	+ - 0	49.26	43.98
+ + 0	+ - -	0 + 0	+ + 0	0 - -	0 0 +	48.33	38.71	+ + +	0 0 -	- 0 0	+ + 0	0 0 +	+ - 0	48.80	44.08
+ 0 0	0 0 -	- + 0	0 + 0	0 - 0	0 - +	41.85	38.75	+ + +	0 - +	+ - 0	0 - 0	0 - +	+ - 0	49.56	44.09
+ 0 0	0 + 0	0 + -	- 0 0	0 - 0	0 - +	41.73	38.76	+ + 0	+ 0 0	- + 0	0 0 0	+ - -	0 0 +	47.25	44.18
+ + 0	- + +	0 - 0	- + 0	0 - 0	0 - +	42.96	38.78	+ + +	0 + 0	0 + -	- 0 +	0 - +	+ - 0	49.69	44.29
+ + 0	+ - 0	0 + 0	0 + 0	+ + -	0 + +	44.07	38.80	+ + 0	+ 0 +	+ - 0	0 0 0	+ - 0	0 - +	45.60	44.30
+ + 0	+ - -	0 0 0	- + 0	0 - 0	0 - +	42.42	38.81	+ + -	0 0 +	0 0 -	- + 0	- - +	0 0 0	46.03	44.33
+ + +	0 + +	0 + 0	0 - +	+ - 0	+ + 0	48.19	38.86	+ + 0	+ 0 0	- 0 -	- 0 0	+ 0 0	- 0 0	49.57	44.43
+ + 0	0 0 +	+ - 0	0 + 0	+ - 0	- + 0	42.03	38.88	+ + 0	+ - 0	- 0 +	+ + 0	+ - 0	- 0 +	48.08	44.43
+ + +	0 + -	0 - 0	0 - +	0 + +	+ - 0	43.23	38.90	+ + 0	+ - 0	0 0 0	+ 0 +	+ - 0	0 0 0	44.60	44.46
+ + 0	+ - -	0 - 0	0 + +	0 + -	0 0 +	44.78	38.96	+ 0 +	+ - 0	0 0 0	- 0 -	- + 0	0 0 0	44.67	44.47
+ + 0	+ - 0	0 + 0	0 - 0	- - +	0 + +	43.90	39.01	+ + 0	+ - -	0 + -	- - 0	- + +	0 - +	48.33	44.56
+ + 0	0 + -	- + 0	0 0 0	- + 0	0 + 0	43.54	39.07	+ + +	0 + -	- 0 +	0 + +	0 0 -	- 0 0	48.90	44.58
+ + +	0 + +	0 + -	0 - 0	0 + -	- 0 0	44.28	39.16	+ + -	0 0 -	0 0 0	- + 0	0 0 +	0 0 0	46.41	44.62
+ + 0	+ - 0	0 0 0	+ - 0	0 + +	0 - +	42.28	39.23	+ + 0	+ - 0	- 0 +	+ 0 0	- + 0	0 0 +	47.56	44.70

Table 1 (continued)

Energy									Energy								
Conformation						$\epsilon_r$ 0.75	$\epsilon_r$ $\infty$	Conformation						$\epsilon_r$ 0.75	$\epsilon_r$ $\infty$		
+ - 0	0 0 0	+ - 0	0 0 0	+ - 0	0 0 0	39.09	39.39	+ + 0	- + 0	0 + -	0 0 -	0 0 +	+ 0 +	48.97	44.71		
+ + +	0 + 0	0 - +	0 0 0	0 + -	- 0 0	42.81	39.44	+ + 0	0 + -	- 0 -	0 + +	+ 0 +	+ - 0	48.76	44.71		
+ + 0	+ - 0	- 0 0	- - 0	- + 0	+ 0 0	42.89	39.48	+ + 0	+ 0 0	- 0 -	- - 0	- 0 0	+ 0 +	51.66	44.76		
+ + 0	0 + -	- 0 0	+ 0 0	+ - 0	0 + 0	43.19	39.50	+ + 0	+ 0 0	- + 0	0 0 0	- + 0	0 - +	46.46	44.84		
+ 0 0	+ - 0	0 + 0	0 - 0	0 - +	+ - 0	42.82	39.56	+ + -	0 0 0	0 - +	+ 0 -	0 - +	0 0 0	45.76	44.91		
+ + 0	+ 0 0	+ - 0	0 0 0	+ - -	0 + 0	45.47	39.58	+ + 0	0 0 +	+ 0 +	+ + 0	- 0 -	- 0 0	53.03	44.91		
+ + -	0 0 -	0 - 0	0 - +	0 0 -	0 - 0	43.13	39.62	+ + +	0 + -	- 0 -	0 - -	- 0 -	- 0 0	50.24	45.01		
+ + 0	+ - -	0 + 0	+ - 0	- - 0	0 - +	44.92	39.64	+ + -	0 0 +	0 0 -	- 0 0	+ - -	0 0 0	48.08	45.25		
+ + +	0 + +	0 0 -	- - 0	- + +	0 + 0	47.74	39.70	+ + 0	+ - -	0 + -	- - 0	+ - -	0 0 +	49.89	45.26		
+ + +	0 + -	0 0 0	- - -	0 - +	0 0 0	42.63	39.79	+ + 0	+ 0 0	+ 0 0	- + 0	+ 0 -	- 0 0	48.59	45.36		
+ + 0	0 - 0	0 - +	+ - 0	+ - 0	- + 0	45.15	39.86	+ + +	0 0 -	- + 0	- - -	0 0 +	+ - 0	49.73	45.55		
+ + 0	+ + 0	0 + -	- 0 0	+ - 0	- + 0	43.43	39.86	+ + 0	+ 0 -	0 + -	- 0 -	- 0 -	0 + -	51.59	45.84		
+ 0 0	+ - 0	0 - 0	- + 0	+ - 0	- + 0	40.50	39.95	+ + 0	- + +	0 0 0	+ + -	0 + +	+ 0 +	51.82	45.99		
+ 0 0	0 + 0	0 - +	+ 0 -	0 - 0	0 - +	43.75	40.18	+ + 0	+ 0 0	- 0 0	+ - 0	- 0 +	+ 0 +	49.90	46.18		
+ + 0	+ - 0	0 0 -	- - 0	- + 0	0 0 +	43.77	40.20	+ 0 0	- 0 0	+ 0 0	- 0 0	+ 0 0	- 0 0	48.54	46.33		
+ 0 0	+ - 0	0 0 +	0 - -	0 - 0	0 0 +	43.60	40.25	+ + 0	- + +	0 0 -	- - 0	+ - -	0 0 +	52.09	46.35		
+ + 0	+ - 0	0 - +	+ + 0	+ - 0	0 - +	43.10	40.25	+ + +	0 0 -	- 0 -	- - 0	+ 0 +	+ - 0	52.41	46.46		
+ + +	0 + +	0 + -	0 + -	- + 0	0 + 0	48.00	40.34	+ + 0	+ 0 0	+ 0 +	+ 0 0	- 0 0	+ 0 +	52.77	46.58		
+ + -	0 0 +	0 + 0	0 + -	0 0 +	0 0 0	42.45	40.41	+ 0 +	+ 0 0	- 0 0	- 0 -	- + 0	- 0 +	53.74	46.70		
+ + 0	+ 0 0	+ + 0	+ - 0	0 0 -	- 0 0	45.08	40.48	+ + -	0 + 0	- + +	0 0 +	0 0 -	- 0 0	49.67	46.80		
+ + +	0 + -	0 0 0	0 + -	0 - -	- 0 0	43.89	40.51	+ + 0	- + 0	0 + -	- 0 +	0 - +	+ 0 +	49.22	46.99		
+ + 0	0 + 0	+ + -	0 + +	+ 0 0	- + 0	45.63	40.65	+ 0 +	+ 0 0	- 0 0	+ 0 +	+ - 0	- 0 +	50.78	47.81		
+ + +	0 + +	0 + 0	- - +	0 + +	+ - 0	48.65	40.66	+ 0 0	- + 0	+ 0 -	- 0 0	+ - 0	- 0 +	49.73	47.93		
+ + -	0 0 0	0 + -	- 0 0	0 - +	0 0 0	41.68	40.71	+ + 0	- 0 -	- 0 -	- 0 +	+ 0 +	+ 0 +	58.34	48.07		
+ + 0	+ + 0	0 0 +	+ 0 0	- + 0	+ 0 0	46.10	40.76	+ 0 +	+ 0 0	- 0 0	- 0 -	- 0 0	+ 0 0	54.18	48.40		
+ + -	0 0 0	0 - +	+ 0 0	0 + -	0 - 0	42.43	40.77	+ 0 +	+ 0 0	0 0 -	- 0 -	- 0 0	0 0 +	54.64	49.55		
+ + 0	0 - 0	0 - +	0 0 +	0 0 -	- 0 0	44.88	40.80	+ 0 +	+ 0 +	+ 0 0	+ 0 +	+ 0 +	+ 0 0	57.78	50.16		

18-crown-6 in the crystalline state<sup>19</sup>) at 298 K and only ca. 1% the  $D_{3d}$  conformation ( $ag^+a ag^-a ag^+a ag^-a ag^+a ag^-a$ ). However, if no electrostatic interactions would be present, the situation would be reversed with almost 98% of the polyethers adopting the  $D_{3d}$  conformation.

The spread in the steric energies among the 190 conformations, as calculated with MM2, is ca. 22 and 24 kcal mol<sup>-1</sup> for  $\epsilon_r$  0.75 and  $\infty$ , respectively. To estimate the effect that may be expected from complexation of a polyether with a guest cation, we have calculated the electrostatic interaction energy between a monovalent cation, located at the centre of the macro-ring, and the dipole associated with a lone pair directed to the centre. These terms are the major part of the electrostatic host-guest interactions. Assuming an average distance between the midpoint of the O-LP 'bond' and the centre of the cavity of 2.5 Å and a bond dipole moment along the O-LP direction of 0.9 D (the standard value in the MM2 program), the electrostatic energy is ca. 10 kcal mol<sup>-1</sup> for each ion-oxygen interaction. Differences in steric energies between the ideal conformations investigated may thus be well outweighed by the gain in energy due to the electrostatic interactions between host and guest. It can be concluded that the interaction between host and guest has to be included in the conformation calculations.

In studying the relative stabilities of crown ether complexes in solution solvation effects must be taken into account. It is expected that in polar solvents the sum of the solvation energies of the uncomplexed crown ether and of the guest will be larger than for the complex, in particular when the ligand adopts a conformation with a hydrophilic exterior in the uncomplexed state but with a hydrophobic exterior in the complex. Therefore, differences in electrostatic stabilizations in complexation may (partly) be cancelled by solvation effects.<sup>6</sup> This is in agreement with the observation that association constants for complexation of 18-crown-6 with several cations in different solvents decrease with increasing polarity of the solvent.<sup>20</sup> However, in apolar solvents the complexation energy will be determined

mainly by the difference in steric energy between the conformations of the uncomplexed and the complexed ligand and by the interactions between host and guest.

(2) *Experimental Conformations of 18-Crown-6*.—It is clear from the previous section that the choice of the electrostatic scale factor  $\epsilon_r^{-1}$  has a large influence on the relative stability of different conformations of 18-crown-6. To study this dependence in more detail and to compare calculated and observed geometries of 18-crown-6 conformations, we have performed molecular mechanics calculations on a number of experimental 18-crown-6 conformations, using various values of  $\epsilon_r^{-1}$ .

Six conformations (shown in Figure 1) were selected, which will be referred to by their (approximate) symmetry:

- $C_i$ , the 'biangular' conformation  $g^+g^+a ag^-a ag^-a g^-g^-a ag^+a ag^+a$ , adopted by the polyether in its 1:5 complex with urea;<sup>22</sup>
- $C_m$ , the  $g^+g^+a ag^-a ag^+a ag^-g^- ag^-a ag^+a$  conformation, which is the predominant conformation of 18-crown-6 in its 1:1 complex with *O*-*n*-butylisouronium picrate;<sup>23</sup>
- $C_2$ , the closely related  $g^+g^+a ag^-a ag^+a g^+g^+a ag^-a ag^+a$  conformation, found in the lowest occupied form of the last mentioned complex as well as in the 1:1 complexes of 18-crown-6 with uronium nitrate<sup>24</sup> and uronium picrate;<sup>23</sup>
- $D_{3d}$ , the well known  $ag^+a ag^-a ag^+a ag^-a ag^+a ag^-a$  conformation, found in the 1:1 complex of 18-crown-6 with uronium toluene-*p*-sulphonate<sup>23</sup> and in the 1:2 complex of 18-crown-6 with *S*-*t*-butylisothiouronium perchlorate;<sup>25</sup>
- $C_i'$ , the  $g^+g^-a ag^+a aaa g^-g^+a ag^-a aaa$  conformation, adopted by the uncomplexed 18-crown-6 molecule in the crystalline state,<sup>19</sup> which also has  $C_i$  symmetry;
- $C_1$ , the  $g^+g^+g^+ ag^+a g^+g^+a ag^-a ag^+a ag^-g^-$  conformation, found in the crystalline (18-crown-6)·NaNCS·H<sub>2</sub>O complex.<sup>26</sup>

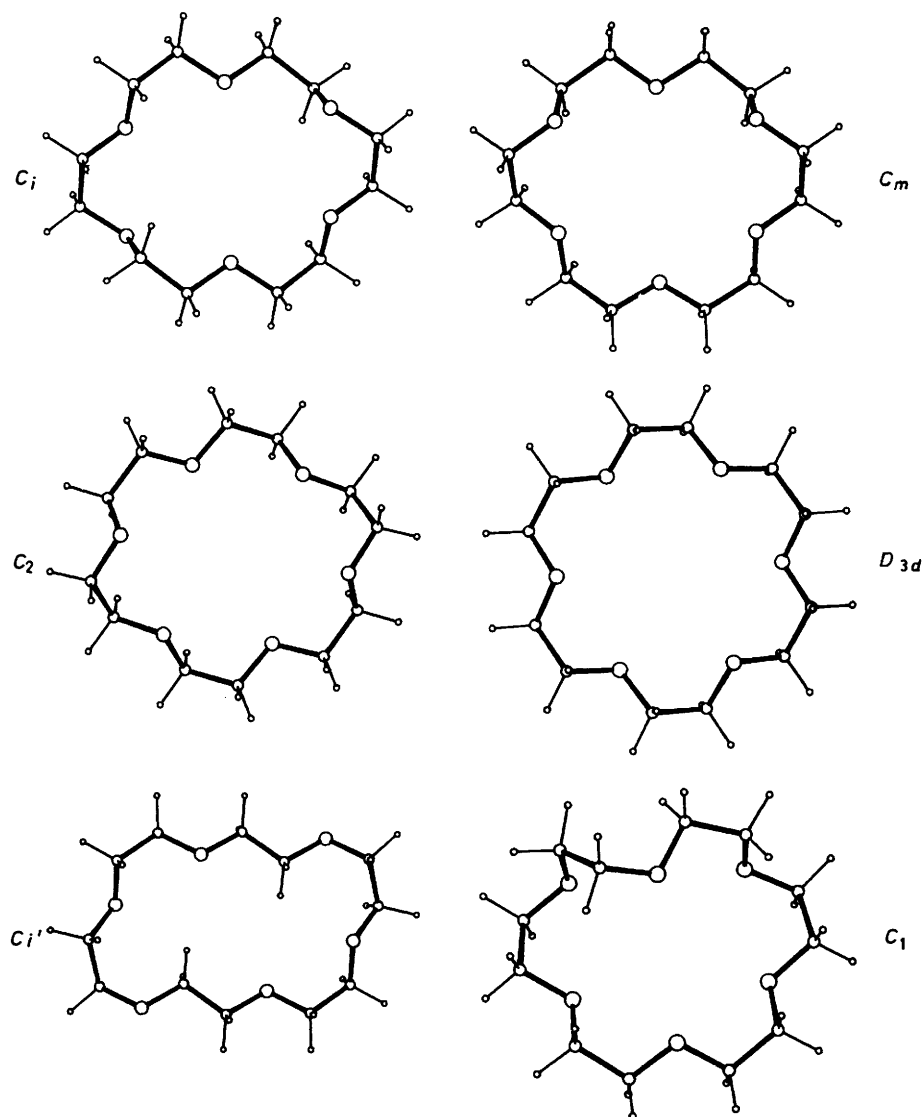


Figure 1. ORTEP views<sup>21</sup> of the  $C_i$ ,  $C_m$ ,  $C_2$ ,  $D_{3d}$ ,  $C_i'$ , and  $C_1$  conformations of 18-crown-6

The  $D_{3d}$ ,  $C_i$ ,  $C_m$ , and  $C_i'$  conformations correspond with the first three and the tenth in that order of the list of ideal conformations (Table 1).

The input co-ordinates for the molecular mechanics calculations were taken from the literature for conformations  $C_i$ ,<sup>22,\*</sup>  $C_2$ ,<sup>24</sup>  $C_i'$ ,<sup>19</sup> and  $C_1$ ,<sup>26</sup> and from the structures of the 1:1 complex of 18-crown-6 with *O*-*n*-butylisouronium picrate<sup>23</sup> (predominant conformation of the macro-ring) and of the 1:2 complex of 18-crown-6 with uronium toluene-*p*-sulphonate<sup>23</sup> for the  $C_m$  and  $D_{3d}$  conformations respectively. The six conformations were optimized for different values of  $\epsilon_r^{-1}$ , ranging from 0.0–2.5. The minima obtained in the case of the  $D_{3d}$ ,  $C_i$ ,  $C_m$ , and  $C_i'$  conformations were identical as found starting with the co-ordinates of the ideal conformations. The different energy terms contributing to the steric energies of the six conformations have been summarized in Table 2.

Conformations  $C_i$ ,  $C_m$ , and  $C_2$  have almost equal steric

energies, regardless of the contributions of the electrostatic energies. The  $D_{3d}$  conformation has an energy which is lower by ca. 4–5 kcal mol<sup>-1</sup>, whereas the  $C_1$  conformation is higher in energy by ca. 4–7 kcal mol<sup>-1</sup>. The steric energies are found to change in proportion to  $\epsilon_r^{-1}$ .

The net *electrostatic* term is repulsive for all six conformations, although it is much smaller for  $C_i'$  than for the other five conformations. The repulsion is mainly due to the interactions between the bond dipoles on the O–LP bonds directed to the centre of the macro-ring. In the  $C_i'$  conformation only two (non-neighbour) oxygen atoms have a lone pair pointing into the cavity, whereas in the other five conformations at least one lone pair at each oxygen atom is more or less centrally directed. The calculated energy differences between the  $C_i'$  conformation and the other five conformations are thus strongly dependent on the choice of  $\epsilon_r^{-1}$ .

The calculated geometries of the six investigated conformations are found to vary only slightly with the electrostatic scale factor, the main trend being an enlargement of the crown ether cavity on increasing  $\epsilon_r^{-1}$  to minimize the destabilizing dipole–dipole interactions.

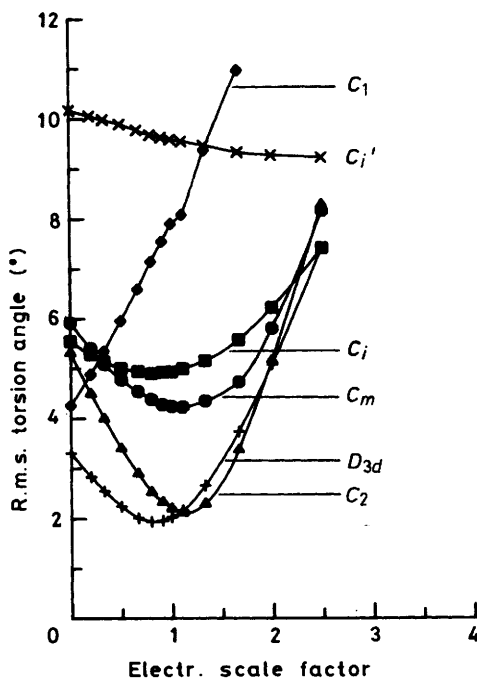
Notwithstanding the omission of the host–guest interactions in the calculations, the calculated structures are very similar to

\* As there are two independent macro-rings in the 1:5 complex of 18-crown-6 with urea<sup>22</sup> (both with the same  $C_1$  conformation), one of them was arbitrarily chosen as input for the calculations on the  $C_i$  conformation.

**Table 2.** Ranges of the energy terms for  $\epsilon_r^{-1}$  0.0–2.5 contributing to the final steric energies of the  $C_i$ ,  $C_m$ ,  $C_2$ ,  $D_{3d}$ ,  $C_i'$ , and  $C_1$  conformation of 18-crown-6

Term <sup>a</sup> (kcal mol <sup>-1</sup> )	$C_i$	$C_m$	$C_2$	$D_{3d}$	$C_i'$	$C_1$
Stretching	1.98–2.58	1.96–2.57	1.99–2.60	1.92–2.51	2.14–2.31	2.00–2.65
Bending	7.81–10.07	7.68–9.11	7.32–8.19	5.93–7.44	9.53–10.18	9.13–11.65
Stretch-bend	0.95–1.20	0.93–1.17	0.93–1.13	0.82–1.01	1.00–1.02	1.02–1.29
Torsional	-0.66–-0.27 <sup>b</sup>	-0.80–-1.07	-0.45–-2.59	-2.79–-0.77	1.26–2.02	2.64–5.18 <sup>c</sup>
van der Waals 1,4	~ 23.8	~ 24.0	~ 24.3	~ 24.5	~ 23.9	~ 24.0
van der Waals other	~ -3.9	~ -3.7	~ -3.8	~ -4.1	~ -4.0	~ -4.9
Electrostatic	0.00–18.07	0.00–17.57	0.00–15.74	0.00–15.83	0.00–2.77	0.00–18.70
Total	30.20–51.42	30.04–52.10	30.26–51.32	26.48–46.58	34.01–38.06	34.11–59.29

<sup>a</sup> According to the definitions given in ref. 10. <sup>b</sup> With a flat minimum of -0.77 kcal mol<sup>-1</sup> for  $\epsilon_r$  1.20. <sup>c</sup> With a flat minimum of 2.54 kcal mol<sup>-1</sup> for  $\epsilon_r$  2.00.

**Figure 2.** R.m.s. deviations between calculated and observed endocyclic torsion angles for the  $C_i$ ,  $C_m$ ,  $C_2$ ,  $D_{3d}$ ,  $C_i'$ , and  $C_1$  conformations of 18-crown-6 for various values of  $\epsilon_r^{-1}$ 

the corresponding observed ones. The close agreement between calculated and experimental conformations indicates that the potential energy surface around the experimental conformations is rather steep. Consequently omission of some terms in the force field does not drastically change the result of the energy minimization. To quantify the differences the root mean square (r.m.s.) deviations between the calculated and observed endocyclic torsion angles are used. As the choice of  $\epsilon_r$  is not obvious, we calculated the r.m.s. deviations for all calculations performed, the results of which are depicted in Figure 2.

In the region where the electrostatic scale factor corresponds with reasonable values of the dielectric constant (0.5–2.0), these r.m.s. deviations are only a few degrees for the  $C_i$ ,  $C_m$ ,  $C_2$ , and  $D_{3d}$  conformations. The  $C_1$  conformation, adopted by 18-crown-6 in its complex with NaNCS,<sup>26</sup> is less well reproduced, which may be due to the large deviations from ideal staggered torsion angles in the crystal structure to conform with the coordinating properties of the Na<sup>+</sup> ion. The even poorer agreement for the  $C_i'$  conformation is more surprising, since this is the only conformation for which the calculations are not

**Table 3.** Differences in steric energies (kcal mol<sup>-1</sup>) between conformations  $C_i$ ,  $C_m$ ,  $C_2$ ,  $D_{3d}$ , and  $C_1$  of 18-crown-6 and the corresponding steric energies of the  $C_i'$  conformation, for different values of  $\epsilon_r$ ; comparison with literature data

$\epsilon_r$	$C_i - C_i'$	$C_m - C_i'$	$C_2 - C_i'$	$D_{3d} - C_i'$	$C_1 - C_i'$
0.40	13.4	14.0	13.3	8.5	21.2
0.50	10.3	11.0	10.6	5.8	17.8
0.60	8.2	8.8	8.6	3.8	15.2
0.75	5.9	6.5	6.4	1.7	12.5
0.90	4.4	4.9	4.9	0.2	10.6
1.00	3.6	4.1	4.1	-0.5	9.6
1.10	3.0	3.4	3.4	-1.1	8.8
1.25	2.2	2.5	2.6	-1.9	7.8
1.50	1.2	1.5	1.6	-2.8	6.6
2.00	0.0	0.2	0.3	-3.9	5.0
3.00	-1.2	-1.2	-1.0	-5.1	3.4
5.00	-2.3	-2.3	-2.1	-6.1	2.1
$\infty$	-3.8	-4.0	-3.8	-7.5	0.1
literature					
a	$q_O - 0.3e$	5.0		7.8	4.4
b	$q_O - 0.6e$	14.8		11.9	20.9
	$q_O - 0.4e$	6.7		4.7	
	$q_O - 0.3e$	3.0		1.1	9.4
c	d		6.7	3.9	6.1
	e			-3.9	
f				-2.5	

<sup>a</sup> Bovill *et al.*,<sup>5</sup> charge-charge interactions;  $q_O = -2q_C$ ;  $\epsilon_r$  5.0. <sup>b</sup> Wipff *et al.*,<sup>6</sup> charge-charge interactions;  $q_O = -2q_C$ ;  $\epsilon_r$  1.0. <sup>c</sup> Perrin *et al.*,<sup>7</sup> using three methods with standard parametrization; dipole-dipole interactions;  $\epsilon_r$  1.5. <sup>d</sup> Force field MMI.<sup>17</sup> <sup>e</sup> Force field MM2<sup>10</sup> without explicit treatment of lone pairs. <sup>f</sup> As *e* with lone pairs.

influenced by the omission of guest molecules. However, it is believed that the large deviation for this conformation stems from the existence of close intramolecular C-H...O contacts across the cavity. The resulting short H...LP and H...O distances yield strong repulsions in calculations using the MM2 force field. The necessity for a special energy potential function for hydrogen bonds within the MM2 framework will be investigated in the next section.

In Table 3 the differences between the steric energies of the energy-minimized conformations  $C_i$ ,  $C_m$ ,  $C_2$ ,  $D_{3d}$ , and  $C_1$ , and the steric energies of the  $C_i'$  conformation of 18-crown-6, are collected for the  $\epsilon_r$  values used in the calculations, together with some results published earlier.<sup>5-7</sup> The results show that the  $C_i'$  conformation has only the lowest energy for values of  $\epsilon_r < ca.$  0.95, the  $D_{3d}$  conformation having the lowest energy otherwise. The  $C_i$ ,  $C_m$ , and  $C_2$  conformations are always less stable than the  $D_{3d}$  conformation, but become more stable than the  $C_i'$

conformation for  $\epsilon_r$ -values larger than *ca.* 2.0. The  $C_1$  conformation has the largest steric energy of all conformations, regardless of the electrostatic contribution. It is nearly as stable as the  $C'_1$  conformation, if no electrostatic interactions are taken into account.

These findings are not in accordance with the results of molecular mechanics calculations on the  $C_2$ ,  $D_{3d}$ ,  $C'_1$ , and  $C_1$  conformations of 18-crown-6 reported by Bovill *et al.*,<sup>5</sup> who used the WBFF2 force field, which is an extension of WBFF.<sup>27</sup> They used charge-charge interactions for the electrostatic component, with  $q_O = -0.3e$  and  $q_C = +0.15e$  ( $e$  being the elementary charge), based on a relative dielectric constant of 5.0. The order of steric energies of the conformations studied by them is totally different from our results, irrespective of the value of  $\epsilon_r$ . They calculate the  $C'_1$  conformation to be the most stable one and the  $D_{3d}$  conformation highest in energy (+7.84 kcal mol<sup>-1</sup>). They report the latter to be the lowest-energy conformation if the unfavourable electrostatic interactions of this conformation are ignored. This invalidates their statement that the value chosen for  $\epsilon_r$  'is not critical since electrostatic interactions represent a relatively small part of the interatomic non-bonded interactions'.<sup>5</sup>

The agreement between our results and those of Wipff *et al.*,<sup>6</sup> using the AMBER force field,<sup>28</sup> for the  $C_2$ ,  $D_{3d}$ ,  $C'_1$ , and  $C_1$  conformations of 18-crown-6 is quite satisfactory. They investigated the effect of the electrostatic scale factor by using three different sets of atomic charges (see Table 3). They found the same order in steric energies as we did and they observed the same trends for varying electrostatic interactions. Their results for  $q_O = -0.3e$ , which they judge the best value to use for uncomplexed 18-crown-6 on the basis of the calculated dipole moment of dimethyl ether with this charge set, are very similar to our results for  $\epsilon_r$  values between 0.75 and 1.10.

Perrin *et al.*<sup>7</sup> used the MMI force field<sup>17</sup> to compare the steric energies of conformations  $C_2$ ,  $D_{3d}$ ,  $C'_1$ , and  $C_1$  and the MM2 force field<sup>10,11</sup> for conformations  $D_{3d}$  and  $C'_1$  of 18-crown-6, the last method both with and without explicit treatment of lone pairs. They find surprising differences between the three methods, without, however, trying to judge the methods on their reliability. Allinger and his co-workers found that with the MM2 force field, and using lone pairs, far better results are obtained than with MMI, when applied to alcohols and ethers.<sup>11,29</sup> The results of Perrin *et al.*, using MM2, are in accord with our calculations, except for small differences originating in the fact that they, just as Bovill *et al.*<sup>5</sup> and Wipff *et al.*,<sup>6</sup> did not correct for the shortening of the C-C bonds, as we did.

(3) *Complexes of 18-Crown-6 with Neutral Molecules.*—To investigate the influence of the guests on the calculated geometries of the hosts and to study to what extent the hydrogen-bond geometry of a complex of 18-crown-6 with organic molecules can be reproduced, we performed molecular mechanics calculations (both using MM2 and MM2HB) on complexes of the polyether with neutral urea-like guests, in which host and guest are connected *via* N-H...O hydrogen bonds. Two test cases were chosen, the structures of which were determined by X-ray crystallography, namely (1) the 1:5

complex of 18-crown-6 with urea,<sup>22</sup> and (2) the 1:2 complex of 18-crown-6 with formamide.<sup>30\*</sup> These complexes are denoted the 'urea complex' and the 'formamide complex'. The host is hydrogen-bonded to two centrosymmetrical-related guest molecules in both complexes. In the calculations on the urea complex only the host and the two urea molecules bonded to it will be considered. The macro-ring in this complex adopts the  $g^+g^+ag^-ag^-ag^-ag^-ag^+ag^+ag^+ag^+$  conformation ( $C_2$ ) and each guest molecule forms two hydrogen bonds to neighbouring oxygen atoms of the macro-ring. The macro-ring in the formamide complex has the  $D_{3d}$  conformation ( $ag^+ag^-ag^+ag^-ag^+ag^-ag^+ag^-$ ) and accepts two hydrogen bonds from each guest at next nearest neighbour oxygen atoms.

A trial-and-error procedure for the urea and the formamide complexes yielded optimal values of 3.25 Å, 1.0 kcal mol<sup>-1</sup> and 1.5 Å<sup>-1</sup> for the Morse potential parameters  $R_0$ ,  $D_0$ , and  $\alpha_0$  respectively, to be used in the MM2HB calculations for the N-H...O hydrogen bond. The optimal values found for  $D_0$  and  $\alpha_0$  are equal to the corresponding values for the O-H...O hydrogen bond,<sup>13</sup> whereas the optimal  $R_0$  value is slightly larger for the N-H...O than for the O-H...O hydrogen bond<sup>13</sup> (3.25 versus 3.0 Å).

The r.m.s. deviations between calculated and observed endocyclic torsion angles and between calculated and observed N...O hydrogen-bond distances, both for the calculations using MM2 and MM2HB, for various values of  $\epsilon_r^{-1}$  are given in Figures 3 and 4 for the urea and for the formamide complex respectively. For comparison purposes, the corresponding curves for the torsion angles for the calculations without guests are also given.

The MM2 calculations show a significant improvement of the calculated geometry of the 18-crown-6 molecule in the urea complex when the host-guest interactions are included (lowest r.m.s. value for the endocyclic torsion angles 2.65° for  $\epsilon_r$  0.40;

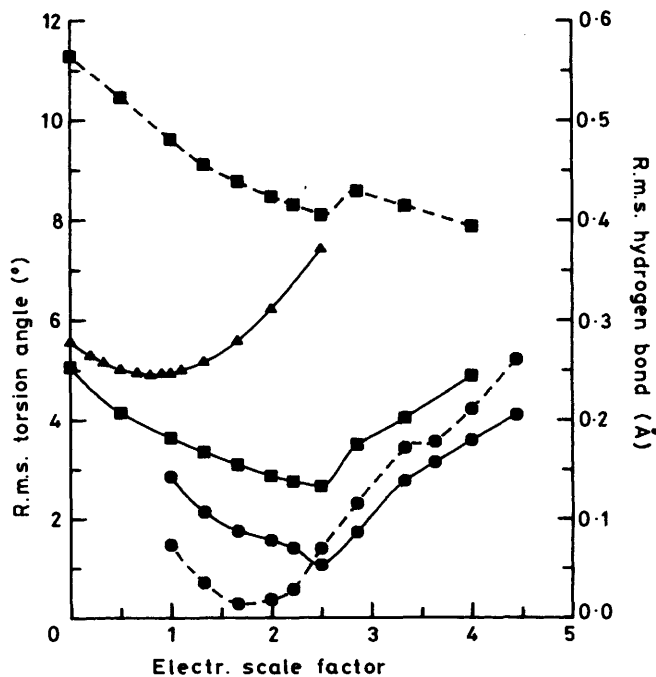


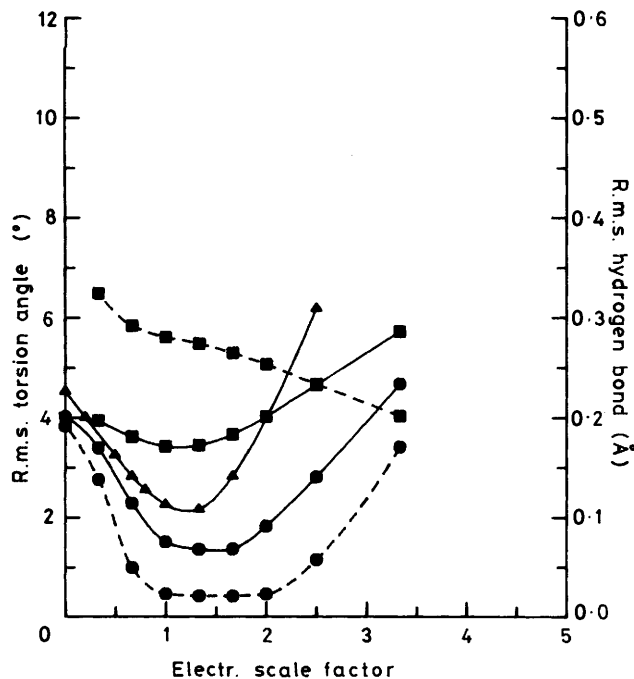
Figure 3. R.m.s. deviations between calculated and observed endocyclic torsion angles (solid lines) and between calculated and observed N...O hydrogen bond distances (dashed lines) for the complex of 18-crown-6 with urea, using MM2 (squares) and MM2HB (circles), for various values of  $\epsilon_r^{-1}$ ; the line through the triangles is the corresponding curve for the torsion angles if the guests are omitted in the calculations

\* The distances and angles for one of the two hydrogen bonds, as reported by Watson *et al.*<sup>30</sup> [H(10a)...O(7) 2.84 Å, N(10)...O(7) 3.133 Å, N(10)-H(10a)...O(7) 97.9°] are incorrect, as proven by recalculation using the co-ordinates given by the authors. These numbers correspond in fact with the distances and angle involving the (non-hydrogen bonded) O(4) atom. The correct figures are 2.04 Å, 2.996 Å, and 162.1°, respectively. Their description of the complex as having one strong hydrogen bond per guest and 'a much weaker interaction *via* O(7) or O(7')' is therefore invalid.

**Table 4.** Experimental and calculated endocyclic torsion angles<sup>a</sup> and hydrogen-bond parameters<sup>a,b</sup> (for optimal conformations of the macro-ring) in the complexes of 18-crown-6 with urea and formamide, using MM2 and MM2HB; units are Å for distances and degrees for angles

	Urea complex			Formamide complex		
	Observed	Calculated		Observed	Calculated	
		MM2	MM2HB		MM2	MM2HB
Φ(1)	-176.9	-179.6	-176.5	-179.3	179.9	179.0
Φ(2)	66.7	63.6	68.3	-73.3	-68.7	-71.3
Φ(3)	179.7	175.2	-179.3	177.9	-178.1	178.1
Φ(4)	170.9	172.1	169.5	-179.9	178.7	-179.5
Φ(5)	64.9	66.8	65.5	67.5	62.6	66.7
Φ(6)	172.3	174.9	171.7	-176.4	179.4	-178.0
Φ(7)	170.2	172.0	169.3	-176.6	-176.9	-178.4
Φ(8)	-59.3	-58.5	-58.0	-72.2	-67.5	-70.8
Φ(9)	-61.2	-64.3	-61.5	177.2	178.8	177.2
N...O	2.848	3.419	2.759	3.037	3.381	3.028
H...O	1.842	2.552	1.752	2.044	2.522	2.036
N-H...O	172.8	144.5	175.3	166.7	143.1	167.5
N...O	3.282	3.254	3.242	2.996	3.193	3.024
H...O	2.355	2.509	2.307	2.018	2.491	2.050
N-H...O	151.9	130.9	154.3	162.0	126.4	162.0

<sup>a</sup> Only the independent experimental parameters are given; the corresponding calculated parameters are each the average of the two centrosymmetrical similar parameters. <sup>b</sup> For the hydrogen atoms involved the positions after lengthening the N-H bonds to 1.011 Å were used for the experimental parameters.



**Figure 4.** R.m.s. deviations between calculated and observed endocyclic torsion angles (solid lines) and between calculated and observed N...O hydrogen-bond distances (dashed lines) for the complex of 18-crown-6 with formamide, using MM2 (squares) and MM2HB (circles), for various values of  $\epsilon_r$ ; the line through the triangles is the corresponding curve for the torsion angles if the guests are omitted in the calculations

corresponding r.m.s. value for the calculations on the crown without considerations of the guests  $4.90^\circ$  for  $\epsilon_r$  1.25). The agreement between the MM2-calculated and observed conformation of the macro-ring in the formamide complex,

however, is worse than with the guests omitted [lowest r.m.s. value of the torsion angles  $3.43^\circ$  for  $\epsilon_r$  1.0; corresponding r.m.s. value  $2.17^\circ$  (for  $\epsilon_r$  0.75), if the guests are not taken into account]. In both complexes, the N...O hydrogen-bond distances are not well reproduced using MM2, being invariably too long.

Using MM2HB on the other hand, a very good agreement between calculated and observed geometry of the 18-crown-6 molecule is obtained, both for the urea and the formamide complex. The lowest r.m.s. deviations of the endocyclic torsion angles are only  $1.06^\circ$  ( $\epsilon_r$  0.40) and  $1.37^\circ$  ( $\epsilon_r$  0.75), respectively. The corresponding r.m.s. values for the N...O hydrogen-bond distances are only 0.070 and 0.021 Å.

The experimental and calculated endocyclic torsion angles and hydrogen-bond geometries in both complexes are collected in Table 4 for the  $\epsilon_r$  values yielding optimal agreement with experiment for the calculated conformations of the macro-ring. Views of the observed and calculated (for optimal  $\epsilon_r$  values) complexes of 18-crown-6 with urea and with formamide are given in Figures 5 and 6, respectively.

In the MM2 calculations the hydrogen-bond geometries are badly reproduced. The H...O and N...O distances are much too long and the N-H...O angles deviate considerably from the observed values (up to  $36^\circ$ ). The main cause of these deviations is the strong repulsive van der Waals interactions between the hydrogen atoms and the lone pairs at the oxygen atoms in the hydrogen bonds. Consequently, the calculations show the guest molecules to shift and to rotate so as to turn the hydrogens away from the hydrogen-bond-acceptor atoms of the host. The bad agreement between calculated and observed hydrogen-bond geometries contrasts with the opinion of Allinger and his co-workers, who conclude that hydrogen-bonding is 'at least reasonably well accounted for in the (MM2) force field automatically, without any special "hydrogen-bond" having to be invoked'.<sup>11</sup> The overestimation of the repulsive van der Waals interactions between the atoms involved in hydrogen bonding is in agreement with the conclusion of Kollman and Rothenberg,<sup>31</sup> based on *ab initio* calculations of the hydrogen-bond affinities of simple amines and amides, that the uniqueness



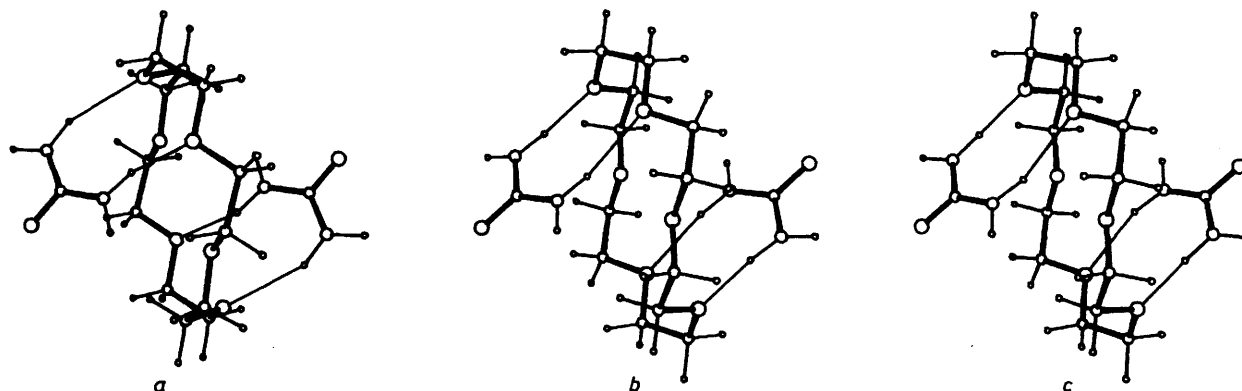


Figure 5. ORTEP views<sup>21</sup> of the urea complex as observed<sup>22</sup> (b) and calculated for optimal  $\epsilon_r^{-1}$  values, using MM2 (a) and MM2HB (c). The projections are such that the urea molecules in all three Figures are oriented the same as much as possible

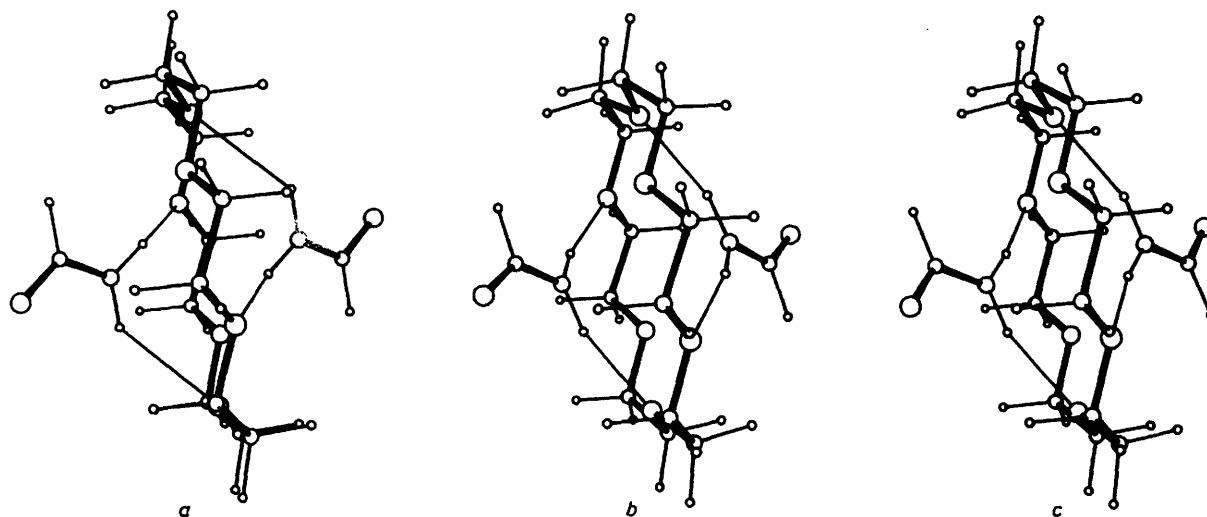


Figure 6. ORTEP views<sup>21</sup> of the formamide complex as observed<sup>30</sup> (b) and calculated for optimal  $\epsilon_r^{-1}$  values, using MM2 (a) and MM2HB (c). The projections are such that the formamide molecules in all three Figures are oriented the same as much as possible

of the hydrogen bond lies in the smallness of the exchange repulsion.

From inspection of Table 4 it may be seen that the calculated geometries of the hydrogen bonds using MM2HB, on the other hand, are in very good agreement with the observed geometries for both the urea and the formamide complex. This is especially surprising for the urea complex, in which the two hydrogen bonds have rather different geometries. It was supposed originally that this difference would be a result of the involvement of the urea molecules in hydrogen bonds other than to the macro-ring (*i.e.* with other urea molecules<sup>22</sup>). However, since the MM2HB calculations reproduce this difference in hydrogen-bond geometries, it must be attributed to the crown ether-guest interactions. In the formamide complex no such difference in hydrogen bonding is found, in agreement with experiment.

The influence of the Morse potential on the calculated geometry of the complexes has been studied by MM2HB calculations with different values of  $D_0$  [and unchanged  $R_0$  (3.25 Å) and  $\alpha_0$  (1.5 Å<sup>-1</sup>)]. The calculations revealed that the chosen value of  $D_0$  has virtually no influence on the calculated geometry of the macro-ring, even to the extent of complete omission of the Morse potential ( $D_0$  0.0 kcal mol<sup>-1</sup>). This indicates that the improvement in the calculated geometry of the macro-ring is mainly due to the attenuation of the van der

Waals interactions between the atoms involved in hydrogen bonding. However, the value of  $D_0$  has a large influence on the calculated hydrogen-bond geometries.

In the previous section MM2 calculations for the  $g^+g^-aag^+aaa g^-g^+a ag^-a aaa$  conformation ( $C'_i$ ), adopted by uncomplexed 18-crown-6 in the crystalline state,<sup>19</sup> were presented. It appeared that the agreement between calculated and observed endocyclic torsion angles for this conformation was significantly worse than in similar calculations for several conformations adopted by 18-crown-6 in complexes. It was assumed that this might be due to short intramolecular contacts. Since these contacts may have some hydrogen-bond character, it seemed worthwhile to repeat the calculations using the MM2HB program.

Two independent 'hydrogen bonds' are present in the  $C'_i$  structure. One is an almost linear hydrogen bond between a C-H unit and an oxygen atom seven positions further in the macro-ring (C...O distance 3.71 Å) and a second (strongly non-linear) hydrogen bond is formed between the same C-H unit and an oxygen atom, which is only four positions remote from the donor atom (*i.e.* a 1,5-C-H...O overlap situation due to the  $g^+g^-a$  pseudo-corner in the conformation), with a C...O distance of only 3.04 Å. Both hydrogen bonds are treated as such in the MM2HB calculations.

Preliminary calculations using MM2HB for the  $C'_i$

**Table 5.** Experimental and calculated endocyclic torsion angles<sup>a</sup> and hydrogen-bond parameters<sup>a,b</sup> (for optimal conformations of the macro-ring) in the  $C_i'$  conformation of 18-crown-6, using MM2 and MM2HB; units are Å for distances and degrees for angles

	Observed	Calculated	
		MM2	MM2HB
$\Phi(1)$	-80.3	-68.6	-72.6
$\Phi(2)$	74.7	82.9	80.6
$\Phi(3)$	-154.9	-165.9	-166.2
$\Phi(4)$	165.6	161.2	161.5
$\Phi(5)$	-65.1	-70.6	-65.3
$\Phi(6)$	175.2	179.5	178.1
$\Phi(7)$	172.4	-172.0	180.0
$\Phi(8)$	173.7	-176.5	180.0
$\Phi(9)$	169.2	169.5	172.8
C...O	3.037	2.979	3.003
H...O	2.449	2.514	2.421
C-H...O	111.4	103.5	110.7
C...O	3.710	3.732	3.713
H...O	2.604	2.756	2.657
C-H...O	172.4	145.9	157.6

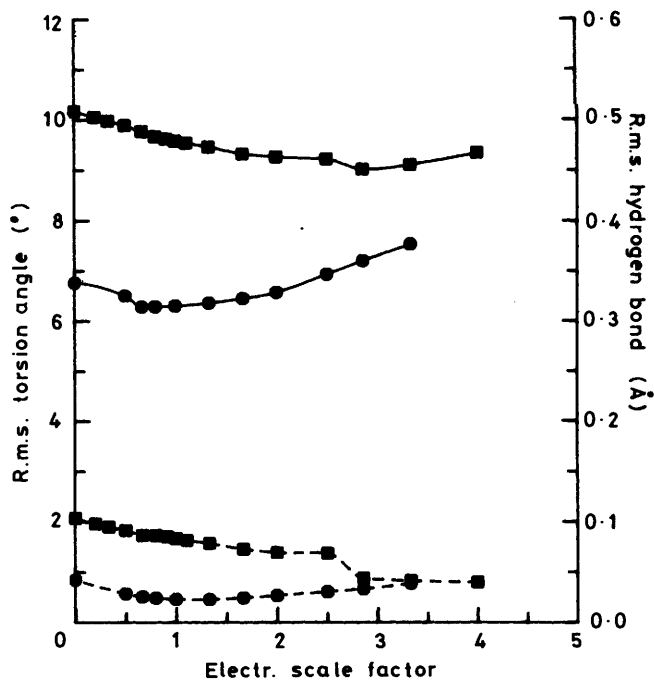
<sup>a</sup> Only the independent experimental parameters are given; the corresponding calculated parameters are each the average of the two centrosymmetrical similar parameters. <sup>b</sup> For the hydrogen atoms involved the positions after lengthening the C-H bonds to 1.113 Å were used for the experimental parameters.

conformation of 18-crown-6 yielded significantly better results for the endocyclic torsion angles than the results obtained with MM2. However, the hydrogen-bond geometry was still not well reproduced. The main cause of this seems to be the large deviation from linearity for the 1,5-C-H...O hydrogen bond, which results in nearly pure van der Waals character for the interaction involved and practically no hydrogen-bond character.

Although N-H...O<sup>32</sup> and O-H...O<sup>33</sup> hydrogen bonds in crystals show a strong preference for linearity, this is certainly not generally true for C-H...O<sup>34</sup> hydrogen bonds, especially for short intramolecular C-H...O contacts. For almost linear hydrogen bonds the functions  $f(\delta)$  and  $f'(\delta)$ , describing the angular dependence of the hydrogen bond and governing the amount of van der Waals or hydrogen-bond character, yield good results. It is suggested that this may be different for strongly nonlinear intramolecular C-H...O hydrogen bonds. To investigate this, MM2HB calculations on the  $C_i'$  conformation of 18-crown-6 with reduced values for the parameter  $n$  in the functions  $f(\delta)$  and  $f'(\delta)$  were done, giving the short 1,5-C-H...O contact more hydrogen-bond character and diminishing the strong repulsive van der Waals interactions. This indeed improved the calculated overall geometry of the  $C_i'$  conformation.

The best agreement with experiment was obtained for values for  $R_0$ ,  $D_0$ ,  $\alpha_0$ , and  $n$  of 3.5 Å, 1.0 kcal mol<sup>-1</sup>, 1.5 Å<sup>-1</sup>, and 0.5, respectively, although no exhaustive fitting of the parameters was performed. The r.m.s. deviations, for this calculation, between calculated and observed endocyclic torsion angles and between calculated and observed C...O hydrogen-bond distances for various values of  $\epsilon_r$  are given in Figure 7. For comparison the corresponding curves for the MM2 calculations (see Figure 2) are also given. The experimental and calculated torsion angles and hydrogen-bond parameters for optimal values of  $\epsilon_r$  (0.35 and 1.25 for the MM2 and MM2HB calculations, respectively) are collected in Table 5.

From inspection of Table 5 it is clear that MM2HB yields



**Figure 7.** R.m.s. deviations between calculated and observed endocyclic torsion angles (solid lines) and between calculated and observed C...O hydrogen-bond distances (dashed lines) for the  $C_i'$  conformation of 18-crown-6 for various values of  $\epsilon_r^{-1}$ , using MM2 (squares) and MM2HB (circles)

better results for this conformation than MM2, both with respect to torsion angles and the geometries of the hydrogen bonds. It is surprising that the geometry of the non-linear 1,5-C-H...O hydrogen bond is significantly better reproduced than of the second, almost linear, hydrogen bond, especially with respect to the C-H...O angle. The large deviation in this angle in the latter case is not caused by the choice of a small value of  $n$  in the expressions for the attenuation factors, as calculations with much larger values gave similar results. The reason for this is not clear.

**Conclusions.**—MM2 calculations, using two different values for the electrostatic scale factor  $\epsilon_r^{-1}$  and starting with the 190 ideal conformations of 18-crown-6 without CH...HC overlap, yield two rather different pictures of the potential energy surface of 18-crown-6. For large values of the electrostatic scale factor the  $g^+g^-a ag^+a aaa g^-g^+a ag^-a aaa$  conformation, adopted by uncomplexed 18-crown-6 in the crystalline state,<sup>19</sup> is calculated to be the most stable conformation. The relative conformational energies calculated with neglect of electrostatic interactions correspond with the frequency of occurrence of these conformations in complexes of 18-crown-6.<sup>4</sup>

MM2 calculations on some experimental conformations of 18-crown-6 show that the relative steric energies are strongly dependent on the value of the electrostatic scale factor. The agreement between calculated and observed conformations of the macro-rings is fair, notwithstanding the omission of the guest molecules in the calculations. This indicates that the potential energy surface of the polyether is not dominated by a few wide energy minima, but that many minima are present with steep slopes. Since these minima have only small energy differences, their relative order may be changed by electrostatic interactions with guest molecules. Regarding the flexibility of crown ethers we suggest that crown ethers choose from a large but limited number of more or less equivalent conformations so as to fit

their shapes to the geometric and electronic particularities of the guest molecule. Hence it is clear that, in investigating the geometries of crown ethers in complexes and in comparing stabilities of complexes for different conformations of the polyether, the host-guest interactions must be taken into account.

The calculations on the complexes of 18-crown-6 with urea and formamide using the MM2 program revealed that the MM2 force field is not very well suited to deal with these molecular systems. Similar calculations, using an empirical N-H...O hydrogen-bond potential incorporated in the MM2 force field (MM2HB), yielded much better results, both with respect to the conformation adopted by the macro-ring and to the geometry of the hydrogen bonds. MM2HB is thus a significant improvement over MM2 for the calculations on this type of complexes. The calculations confirm that the essential element of the hydrogen bond is the attenuation of the repulsive van der Waals interactions between the atoms involved, in agreement with quantum mechanical studies of hydrogen bonding.<sup>31</sup>

The large  $\epsilon_r^{-1}$  value necessary to obtain the best agreement between calculated and observed geometry of the urea complex seems to indicate that the bond dipole moments, incorporated in the MM2 program, are probably too small for this complex. This may be due to polarization effects and is in agreement with the findings of Kollman and Rothenberg,<sup>31</sup> that charge redistribution effects play an important role. However, no such pronounced effect was observed for the formamide complex.

The excellent agreement between the observed and calculated (using MM2HB) geometries of the complexes of 18-crown-6 with urea and with formamide indicate that the MM2HB method may also fruitfully be used to predict the geometries and relative stabilities of complexes of crown ethers with neutral guest molecules, for which no experimental data are available. In this way it may aid the search for promising crown ether complexes.

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