cationic head may be important for an interaction with an aromatic binding site. The crystalline conformation of aprophen and the other four antimuscarinic agents share these features. The space-filling drawings of azaprophen and aprophen in Fig. 7 demonstrate the high similarity of the overall geometric shape of these two compounds. Even the exposed surface area of approximately 488 Å^2 for azaprophen and 482 Å^2 for aprophen as estimated by *MOGLI* (Evans & Sutherland, Salt Lake City, UT) is nearly identical. However, the direction and spatial location of the N^+—H bond in comparison to the C=O bond differs in the crystal structures of azaprophen and aprophen as well as between azaprophen and atropine and quinuclidinyl benzilate. Since even rotation of the C—O(ether) bond will not superimpose the nitrogen atoms of the antimuscarinic agents containing an azabicyclo ring system when the acyloxy ring system is superimposed, the muscarinic receptor must allow for the distribution of geometries found in the cationic sites of antimuscarinic agents.

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Molecular-Dynamics Simulation of Crystalline 18-Crown-6:* Thermal Shortening of Covalent Bonds

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Abstract

Molecular-dynamics simulations of crystalline 18-crown-6 have been performed in a study of the apparent thermal shortening of covalent bonds observed in crystal structures. At 100 K, a shortening of 0.006 ± 0.001 Å for C—C and C—O bonds was obtained. This result was found to be independent of details of the force field and the simulation. There was agreement between computational and experimental values for the thermal parameters, as well as for the molecular geometry (bond and dihedral angles) of 18-crown-6. Some differences are attributed to the inability of the force field to reproduce hydrogen-bonding geometries. Simulation at 295 K resulted in an estimated shortening of 0.019 ± 0.005 Å. Thus at room temperature for C—C bonds (apparent) thermal shortening and (real) chemical shortening, resulting from the electronegative oxygen substituents, are of the same order of magnitude. In the simulation at 295 K occasional dihedral transitions were observed, which may reflect the proximity of the melting point (312 K).

* IUPAC name: 1,4,7,10,13,16-hexaoxacyclooctadecane.

Introduction

Short C—C bonds in macrocyclic polyethers have been observed in numerous instances with single-crystal X-ray diffraction methods (Dalley, 1978; Goldberg, 1980). The normal aliphatic C—C bond length is 1·54 Å (Sutton, 1965), and an average value of 1·53 Å is reported for Csp^3—Csp^3 bond lengths derived from diffraction experiments (Allen, Kennard, Watson, Brammer, Orpen & Taylor, 1987). The shortening of the C—C bonds to values in the range 1·46–1·52 Å has been called the 'macrocyclic C—C shortening effect' (Shoham, Lipscomb & Olsher, 1983). The same effect is found, however, in linear polyethers (Weber, Hirayama, Saenger &

Sheldrick, 1984; Wei, Tinant, Declercq, van Meerssche & Dale, 1987). There has been some discussion of this shortening, which was explained as either an (apparent) effect resulting from inadequate representation of the thermal motion of atoms in the refinement of structural parameters (Dunitz, Maverick & Trueblood, 1988), or as a (real) chemical effect resulting from the attached ether O atoms. Thermal-motion analyses of structures determined at low temperature indicated that the shortening could not be completely attributed to rigid-body libration and rotation (Goldberg, 1976; Maverick, Seiler, Schweizer & Dunitz, 1980). This indicated that part of the shortening was due to intramolecular thermal motion in the flexible macrocyclic polyethers, or to a chemical effect. In a molecular-mechanics study of the effect of electronegativity on bond lengths (Allinger, Imam, Frierson, Yuh & Schäfer, 1986), a shortening of the C—C bond owing to electronegative substituents could reproduce experimentally observed bond lengths; for an ether O atom attached to a C—C bond, the shortening amounted to 0·009 Å, whereas for N and S substituents a value of only 0·001 Å was found. Thus for the polyoxa crown ethers, in which every C—C bond has two ether O atoms attached to it, there seemed to be a chemical effect, amounting to approximately 0·015 Å, which is not large enough, however, to explain the shortening completely. Moreover, the shortening was also observed for polyaza (Royer, Grant, van der Veer & Castillo, 1982) and polythia (Wolf, Hartman, Storey, Foxman & Cooper, 1987) crown ethers, which should not exhibit a chemical effect, according to the molecular-mechanics calculations. To clarify the situation we decided to carry out molecular-dynamics simulations on crystalline 18-crown-6, the results of which are presented in this paper.

X-ray diffraction experiments yield time-averaged atomic positions (centroids of distributions) and their fluctuations. Bond lengths are calculated as distances between the average positions. They are generally not equal to the 'real' bond lengths (Busing & Levy, 1964), i.e. the time averages of the instantaneous bond lengths. Molecular-dynamics simulations yield time series of atomic positions, from which average positions and subsequently bond lengths can be estimated. On the other hand, the time series of atomic positions can be converted to a time series of bond lengths, from which time-averaged bond lengths can be estimated. Molecular-dynamics simulation of a crystal thus allows a comparison of 'real' and 'X-ray' bond lengths, from which can be deduced the amount of apparent shortening of bond lengths, as observed in X-ray diffraction studies. Molecular-dynamics simulations of the crystalline state have been performed on compounds ranging from alkali halides (Shukla &

Heiser, 1986) to proteins (van Gunsteren, Berendsen, Hermans, Hol & Postma, 1983; Åqvist, van Gunsteren, Leijonmarck & Tapia, 1985; Brünger, Clore, Gronenborn & Karplus, 1986), with the focus ranging from lattice dynamics to hydration and average backbone structure. Crystal simulations of molecules of intermediate size have been performed on e.g. cyclodextrins (Koehler, Saenger & van Gunsteren, 1987), with detailed comparison of the molecular geometries from computational and experimental results.

18-Crown-6 seemed an appropriate case for an investigation because it is the prototypical member of the class of crown ethers, which exhibit the shortening effect, and because it has been studied extensively with experimental and computational methods. The crystal structure of 18-crown-6 has been determined at 100 K (Maverick et al., 1980) and at 295 K (Dunitz & Seiler, 1974). The compound crystallizes in the orthorhombic space group Pbca (Z = 4), with cell constants 8·066, 20·120 and 8·437 Å at 100 K, and 8·295, 20·230 and 8·490 Å at 295 K. Its melting point is 312 K. In Fig. 1 the crystal structure of 18-crown-6 is shown; noteworthy are the short intramolecular contacts of C(9')—H with O(4) and O(7). 18-Crown-6 has been the subject of a number of molecular-mechanics studies (Maverick et al., 1980; Bovill, Chadwick, Sutherland & Watkin, 1980; Wipff, Weiner & Kollman, 1982; Perrin, Decoret, Bertholon & Lamartine, 1983; Dobler, 1984; Uiterwijk, Harkema & Feil, 1987), in which various local steric energy minima of the rather flexible molecule were calculated. Recently, a molecular-dynamics study of an isolated 18-crown-6 molecule was reported (Billeter, Howard, Kuntz & Kollman, 1988). The hydration of 18-crown-6 has been studied with the Monte-Carlo method (Ranghino, Romano, Lehn & Wipff, 1985). The present work is the first computational study of crystalline 18-crown-6.
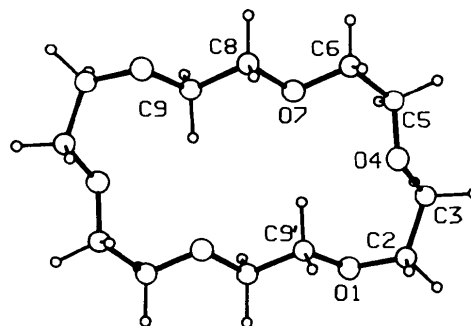

Fig. 1. Crystal structure of 18-crown-6 [redrawn from Maverick et al. (1980)] with spheres of arbitrary size. The atom numbering is shown; the prime indicates atoms related to each other by a crystallographic centre of symmetry, as shown for C(9)/C(9').

Computational method

Molecular-dynamics simulations were performed with the *GROMOS* package (van Gunsteren & Berendsen, 1987). Its potential-energy function contains harmonic potentials for stretching and bending interactions, a series expansion for the torsional energy, and Lennard–Jones and Coulomb potentials for the nonbonded interactions:

$$E_{pot} = \Sigma k_s/2(l - l_0)^2 + \Sigma k_b/2(\theta - \theta_0)^2$$
$$+ \Sigma\Sigma V_n/2[1 + \cos(n\omega - \delta)] + \Sigma C_{12}/r^{12}$$
$$- \Sigma C_6/r^6 + \Sigma q_i q_j/4\pi\varepsilon_0 r.$$

Summations (with the indices omitted for clarity) run over all bond lengths l and angles θ, all torsion angles ω, the terms in the series expansion for the torsional energy, and all atom pairs (i,j) with interatomic distances r, respectively; n is the order of a term with coefficient $V_n/2$ and δ is a phase angle in the torsional contribution, for which the number of terms can be chosen arbitrarily. The subscripts '0' denote the 'natural' values for the bond lengths and angles, and k_s and k_b are the corresponding force constants. C_6 and C_{12} are the Lennard–Jones coefficients, calculated as the geometric mean of the values for the two atoms involved in the interaction; q is the atomic charge and ε_0 is the dielectric constant in a vacuum. In the calculation of the nonbonded interactions, bonded and 1,3-bonded atom pairs are excluded; for 1,4-bonded atom pairs special parameters can be used. The parameters for the nonbonded interactions are assumed to define effective pair potentials that include an average effect of polarizability.

The computational box for the simulation of crystalline 18-crown-6 consisted of a number of crystallographic unit cells. The initial configuration was generated by application of the space-group symmetry operations plus unit-cell translations on the contents of the crystallographic asymmetrical unit, which contains half an 18-crown-6 molecule, the other half being generated by an inversion centre. The smallest box was composed of $2 \times 1 \times 2$ unit cells, with a minimum box dimension of approximately 16 Å, an acceptable value for truncation of the nonbonded interactions at a cutoff distance of 7·5 Å. The molecules in the four unit cells of the box were all treated independently, so the computational asymmetrical unit contained 16 molecules. Symmetry was imposed only by the periodic boundary conditions applied to the box as a whole. After generation of the box, energy minimization was applied, to remove spurious strain. Random velocities were assigned to the atoms, and the system was extensively equilibrated, which removed the artificial symmetry of the initial crystalline configuration.

Several simulation runs were performed to determine the effect of various changes in the computational model and in the parameters of the simulation. The characteristics of the runs are summarized in Table 1. The force-field parameters, listed in Table 2, were taken mainly from *AMBER* (Weiner, Kollman, Case, Singh, Ghio, Alagona, Profeta & Weiner, 1984; Weiner, Kollman, Nguyen & Case, 1986), with which calculations on 18-crown-6 have been performed before (Wipff *et al.*, 1982). Lennard–Jones interaction parameters from another source were also tried (Jorgensen & Ibrahim, 1981). The nonbonded 1,4-interactions were scaled to 50%. The atomic charges were taken from a previous study (Wipff *et al.*, 1982): $-0·3$ and $0·15$ e for the O and C atoms, respectively. For the methylene group both a united-atom model (one 'CH$_2$' atom) and an all-atom model were used. The united-atom model is less sophisticated but computationally preferable, as it reduces the number of atoms in the model, and hence (quadratically) the number of atom pairs in the calculation of nonbonded interactions, the time-consuming part of a simulation. Usually in molecular-dynamics calculations computing time is also saved by constraining the covalent bonds with *SHAKE* (Ryckaert, Ciccotti & Berendsen, 1977), which removes the fastest vibrations in the system, allowing the use of a timestep of typically 0·002 ps. The constraints have been shown not to influence the overall dynamics of a system (van Gunsteren & Karplus, 1980). As in the present case small effects in the bond lengths are studied, which might be affected by *SHAKE*, calculations without this constraint were performed as well; in that case the timestep was 0·0005 ps. During simulation the temperature, calculated from the mean kinetic energy, was maintained at a required value of 100 or 295 K, by scaling of the atomic velocities with a time constant of 0·1 ps, and the pressure, calculated with the virial, was kept at 1 atm (1·013 × 10^5 Pa) by volume (and position) scaling with a time constant of 0·5 ps and an isothermal compressibility of 9·9 × 10^{-11} Pa^{-1} (Berendsen, Postma, van Gunsteren, DiNola & Haak, 1984).

Quantities such as volume, pressure, temperature and energy of the system, as well as the atomic coordinates were stored during simulation every 0·02 or 0·05 ps, depending on the length of a run. From the time series of the coordinates, average and root-mean-square (r.m.s.) fluctuations were calculated for the bond lengths and angles, the dihedral angles, and the coordinates. The average coordinates yielded bond lengths and angles, and dihedral angles, corresponding to the values calculated from X-ray coordinates. The shortening of a bond was obtained as the difference between the average bond length and the bond length calculated from the average coordinates.

Table 1. Characteristics of the molecular-dynamics runs

CPU times on a VAX 8650 ranged from 5 h (run A) to 35 h (run F). Notes: (a) For runs B–G, only the differences from the standard run A are given. (b) Weiner et al. (1986). (c) Jorgensen & Ibrahim (1981). (d) Weiner et al. (1984).

Run	Time (ps)	Characteristics (see text)[a]
A	25	Standard run: temperature 100 K, 50% scaling of 1,4-interactions, 2 × 1 × 2 unit-cell box, cut-off distance 7·5 Å, Kollman's AMBER parameters,[b] united CH₂ atom, bonds constrained with SHAKE, $\Delta t = 0.002$ ps
B	25	100% scaling of 1,4-interactions
C	4	4 × 2 × 4 unit-cell box, cut-off distance 10 Å
D	25	Jorgensen's Lennard–Jones parameters[c]
E	20	All-atom model with modified Lennard–Jones parameters for H atoms,[d] cut-off distance 8 Å
F	10	All-atom model with modified Lennard–Jones parameters for H atoms,[d] cut-off distance 8 Å, unconstrained bonds, $\Delta t = 0.0005$ ps
G	25	Temperature 295 K

Table 2. GROMOS force-field parameters

The source of the parameters, unless otherwise indicated, is Weiner et al. (1986). The units nm and rad used here are required for GROMOS input; in the text the more appropriate units Å and ° are used. 1 Å = 0·1 nm, 1° = 0·017453 rad.

Lennard–Jones parameters and atomic charges

Atom type	$C_6 (10^{-6} \text{kJ mol}^{-1} \text{nm}^6)$	$C_{12} (10^{-9} \text{kJ mol}^{-1} \text{nm}^{12})$	q (e)
C2, united CH₂	3270	5326	0·15
C2, united CH₂[a]	7636	30501	0·15
CT, all-atom C	1093	1190	0·15
HC, H (CH₂)	71·44	30·49	0·0
HC, H (CH₂)[b]	137·5	29·74	0·0
OS, ether O	1621	1047	−0·3
OS, ether O[a]	2615	2092	−0·3

Stretching parameters

	$k_s (10^3 \text{kJ mol}^{-1} \text{nm}^{-2})$	l_0 (nm)
C2—C2	217·6	0·1526
C2—OS	267·8	0·1425
CT—CT	259·4	0·1526
CT—OS	267·8	0·1410
CT—HC	277·0	0·1090

Bending parameters

	$k_b (\text{kJ mol}^{-1} \text{rad}^{-2})$	θ_0 (°)
C2—C2—OS	669·4	109·5
C2—OS—C2	836·8	111·8
CT—CT—OS	418·4	109·5
CT—OS—CT	502·1	109·5
CT—CT—HC	292·9	109·5
OS—CT—HC	292·9	109·5
HC—CT—HC	292·9	109·5

Torsional parameters

	n	$V_n/2$ (kJ mol⁻¹)	δ (°)
OS—C2—C2—OS	2	2·092	0·0
	3	8·368	0·0
C2—C2—OS—C2	2	0·418	0·0
	3	6·067	0·0
OS—CT—CT—OS	2	2·092	0·0
	3	0·604	0·0
CT—CT—OS—CT	2	0·837	180·0
	3	1·604	0·0
OS—CT—CT—HC	3	0·604	0·0
HC—CT—CT—HC	3	0·604	0·0
HC—CT—OS—CT	3	1·604	0·0

References: (a) Jorgensen & Ibrahim (1981), (b) Weiner et al. (1984).

The fluctuations of the coordinates were taken to represent the X-ray thermal parameters of the atoms (atomic displacement parameters). In the analysis, averaging was performed over all configurations in the time series, and over all molecules; for this purpose the coordinates were transformed back to an asymmetrical unit, by applying the inverse of the symmetry operations used to generate the box. This involved 16 operations for the 16 different molecules in the 2 × 1 × 2 box. Owing to limitations of the program used (maximum of 16 symmetry operations), the last symmetry operation, the inversion within a molecule, was not applied, so one unique 18-crown-6 molecule was obtained in the analysis, whereas the crystallographic asymmetric unit contains only half a molecule. An approximate centre of symmetry, however, was observed in the results, so additional averaging over all pairs of 'symmetry-related' quantities within the unique molecule was performed. Statistical errors were estimated from the differences within the pairs of 'symmetry-related' quantities.

Results and discussion

A number of molecular-dynamics simulations of crystalline 18-crown-6 have been performed, the results of which are summarized in Table 3. As a first exploration of the problem, a run with a relatively simple model was performed (run A). A simulation with a small (2 × 1 × 2 unit-cell) box, a cut-off distance of 7·5 Å, parameters from Kollman's AMBER force-field (Weiner et al., 1986), united CH₂ atoms, 50% scaling of the 1,4-interactions, a timestep of 0·002 ps, and constrained bond lengths, was carried out for 25 ps at 100 K. From the coordinates stored during the run, a bond-length shortening of 0·0058 Å was calculated, a value somewhat less than the assumed chemical effect, but still appreciable in view of the low temperature. A striking result was the 16·1% reduction in volume of the system, with respect to the experimental volume. The shrinkage takes place almost completely along the b axis, which more or less coincides with the longest axis of the 18-crown-6 molecule in the crystal. It is probably due to the use of the united-atom model, which may give an adequate description of the CH₂ group in solution, where there is orientational disorder, but not in the crystal, where the interactions are more directionally specific. The 'van der Waals' (packing) radius of the CH₂ united atom is smaller than the sum of the radius of the H atom and the C—H bond length in the all-atom model; this can result in a shorter distance of approach for united atoms, and hence in a reduction of the volume.

Several aspects of the computational model of 18-crown-6 were considered with regard to their effect on the simulation result. The scaling of the 1,4-interactions was found to have no effect. In a simulation with 100% scaling of these interactions (run B), the same values for bond shortening and volume reduction were found as with 50% scaling

Table 3. *Results of the molecular-dynamics simulations*

For each run (see Table 1) the following quantities are presented: total energy, E_{tot}; potential energy, E_{pot}; temperature, T; pressure, p; box dimensions, a, b and c; volume, V; the expansion/reduction of the volume (ΔV) relative to the experimental volume of the crystal box, V_{cr}; and the average shortening (Δl) of the macrocyclic covalent bonds. The r.m.s. fluctuations are given in parentheses. The statistical error in Δl is estimated as less than 10×10^{-4} Å, except for run G.

	A	B	C	D
E_{tot} (kJ mol^{-1})	-423(3)	2348(4)	-4579(14)	2493(4)
E_{pot} (kJ mol^{-1})	-661(9)	2109(10)	-6498(31)	2255(9)
T (K)	100·7(38)	100·8(38)	100·3(14)	100·4(37)
p (10^5 Pa)	-3(231)	4(251)	-38(128)	3(159)
a (Å)	16·09(1)	16·07(1)	31·21(2)	17·08(1)
b (Å)	17·77(1)	17·91(1)	37·85(3)	20·53(1)
c (Å)	16·07(1)	16·01(1)	30·74(1)	16·88(1)
V (Å^3)	4594(4)	4608(5)	36308(21)	5916(4)
$\Delta V/V_{cr}$ (%)	-16·1	-15·9	-17·1	8·0
Δl (10^{-4} Å)	58	56	53[a]	62

	E	F	G
E_{tot} (kJ mol^{-1})	367(3)	918(3)	573(12)
E_{pot} (kJ mol^{-1})	-175(16)	85(19)	-127(33)
T (K)	97·2(27)	99·6(22)	295(13)
p (10^5 Pa)	-5(370)	9(412)	25(509)
a (Å)	17·13(1)	17·13(1)	16·47(2)
b (Å)	19·35(1)	19·43(1)	17·95(2)
c (Å)	16·94(2)	16·94(2)	16·32(3)
V (Å^3)	5615(6)	5638(5)	4824(16)
$\Delta V/V_{cr}$ (%)	2·5	2·9	-15·3
Δl (10^{-4} Å)	57	60	197[b]

Notes: (a) calculated for the first 16 (of the total 128) molecules in the box; (b) average calculated after omission of the outlier; see text.

(run A). The average r.m.s. fluctuations of the dihedral angles were also equal (5·2°) for both runs, which suggested that the scaling did not have a significant effect on the intramolecular dynamics of 18-crown-6.

The influence of the size of the box was also investigated. The box in run A was small, and consequently a rather short cut-off distance (7·5 Å) had to be applied. Therefore a larger box, containing 128 molecules, was created, with all three dimensions doubled, which allowed a longer cut-off distance (10 Å). A short 4 ps simulation was then performed (run C), and a slightly larger volume reduction was observed, as compared with runs A and B. Here the longer cut-off distance gives a larger number of nonbonded attractive interactions, and hence an increased contraction of the system. The shrinkage is more evenly distributed over the three directions. The bond-length shortening could be calculated only for the first 16 molecules in the box, because of the symmetry-operator limitations noted earlier. A value of 0·0053 Å was found, equal to the previous results within estimated statistical error. Analysis showed that this value was not affected by the inclusion of only a limited number of molecules in the calculation, given the short time-span of the run. For an equilibrated system averaging over 16 molecules in a 4 ps time series the shortening was obtained with reasonable statistical error.

Jorgensen's Lennard–Jones united-atom parameters, which had yielded good agreement between simulated and experimental density in a Monte-Carlo study of liquid dimethyl ether (Jorgensen & Ibrahim, 1981), were used in run D. These parameters should have an effect on the contraction of the system and, as expected, a larger volume was found, corresponding to an 8·0% increase with respect to the crystal cell. This indicated that the molecular volume of 18-crown-6 is very sensitive to the Lennard–Jones parameters of the united atoms, as the molecule contains a relatively large number of CH_2 groups. The shortening was calculated as 0·0062 Å and we conclude that details of the united-atom model do not influence the observed amount of shortening significantly.

The united CH_2 groups were replaced by an all-atom model, in which the H atoms were included explicitly. The current *AMBER* force field contains a large, 'soft' H atom (van der Waals radius 1·54 Å, well depth 0·04 kJ mol^{-1}; Weiner *et al.*, 1986). During equilibration of the system a strong expansion was observed, with continuous and correlated drift in the dimensions of the box; convergence was not obtained. Instabilities in the system were attributed to weak intermolecular interactions between H atoms. The H-atom parameters, which had been modified to reproduce base-stacking energies in nucleic acids (Weiner *et al.*, 1986), were obviously not satisfactory in the present case. Therefore the earlier *AMBER* values were used (radius 1·38 Å, well depth 1·59 kJ mol^{-1}; Weiner *et al.*, 1984), which should yield a stronger intermolecular attraction. Reasonable results were, indeed, obtained in a 20 ps run (E) with a system that remained stable and showed a moderate expansion of 2·5%. The volume of the system allowed a cut-off distance of 8 Å in the simulation. The shortening calculated for the macrocyclic C—C and C—O bonds was 0·0057 Å, the same as with the united-atom models. The C—H bonds showed a shortening in the range 0·005–0·015 Å. Use of the all-atom model therefore reproduced the observed volume well, and did not affect the shortening, compared with the united-atom approach. As a last step, the influence of the *SHAKE* constraints on the shortening of bond lengths was studied. The constraints were removed, and a smaller timestep of 0·005 ps was used in a 10 ps run (F). The shortening was found to be approximately the same.

In Table 4 the shortening is given for the separate bonds, for some of the runs. Comparing the runs E and F (all-atom model, with and without bond-length constraints) we see that bonds in the latter show an additional shortening of about 0·0003 Å. Comparison with the standard run (A) shows little agreement for the individual bonds, but full agreement for the average. No significant differences between C—C and C—O bonds are observed. From the collected results a value of 0·006 ± 0·001 Å is

Table 4. Shortening of the covalent bonds

The shortening (in 10^{-4} Å) of the individual bonds; the statistical errors are estimated as less than 10×10^{-4} Å, except for run G.

	A	E	F	G^a
O(1)—C(2)	52	38	41	144/199
C(2)—C(3)	52	55	61	165/196
C(3)—O(4)	60	42	46	196/210
O(4)—C(5)	67	58	63	207/212
C(5)—C(6)	46	36	39	146/134
C(6)—O(7)	64	53	56	216/198
O(7)—C(8)	54	67	71	236/194
C(8)—C(9)	63	77	78	251/203
C(9)—O(1')	65	89	90	247/1061
Average	58	57	60	197^b

Notes: (a) values for the two related bonds in the unique molecule are given separately; (b) calculated after omission of the outlier, bond C(9')—O(1), see text.

deduced for the apparent thermal shortening of covalent bonds in 18-crown-6 at 100 K.

Attention was then given to simulation at 295 K, the temperature at which most crystal structures are determined, and at which a crystal-structure determination of 18-crown-6 has been performed. First the simple standard model, which had yielded the same amount of shortening at 100 K as the more sophisticated models, was used in a 25 ps run (*G*). A volume reduction of 15·3% was observed, almost the same as in run *A* at 100 K, indicating that the thermal expansion is well reproduced (4·0% from 100 to 295 K for the X-ray unit cell, 5·0% for the molecular-dynamics box). During the run, however, a few dihedral transitions occurred in one of the molecules. The resulting positional disorder had a dramatic effect on the calculated shortening for the bond C(9)—O(1') involved in the transitions. Since there is no evidence for major positional disorder in the crystal structure at 295 K, the outlier associated with the dihedral transitions was omitted from the calculation of the average shortening to yield a value of 0·0197 Å. The bonds adjacent to C(9)—O(1') also showed an effect of the disorder, as indicated (Table 4) by relatively large differences between supposedly symmetry-related values of the shortening. When the shortening was calculated only for the half of the molecule [atoms C(5') to O(4)] opposite to the disordered region, a value of 0·0188 Å was obtained. Thus a value of 0·019 Å, with an error possibly as large as 0·005 Å, was estimated for the apparent bond-length shortening at 295 K. A simulation with the all-atom model at 295 K was attempted but instability of the system was observed, although the Lennard–Jones parameters were used for the H atom which, at 100 K, had yielded a stable system. The occurrence of the instability and the dihedral transitions was attributed to the proximity of the melting point at 312 K, 17 K above the temperature of the simulation, and simulations at 295 K were discontinued.

Table 5. Comparison of the molecular geometries of 18-crown-6 at 100 K, from molecular-dynamics and experimental results

Results of the molecular-dynamics simulation (MD, run *F*) and the crystal structure determination [Exp., Maverick *et al.* (1980)]: bond lengths *l*, bond angles θ and dihedral angles ω, calculated from the average coordinates. The statistical errors in *l*, θ and ω are estimated as less than 0·0005 Å, 0·05° and 0·2°, respectively, for the molecular-dynamics results. For the experiment estimated standard deviations were 0·001 Å in the bond lengths, and less than 0·1° in the angles.

				l (b—c) (Å)		θ (a—b—c) (°)		ω (a—b—c—d) (°)	
a	b	c	d	MD	Exp.	MD	Exp.	MD	Exp.
C(9')	O(1)	C(2)	C(3)	1·422	1·425	113·0	113·0	−76·0	−80·3
O(1)	C(2)	C(3)	O(4)	1·527	1·511	113·9	114·1	73·2	74·7
C(2)	C(3)	O(4)	C(5)	1·410	1·423	110·9	110·2	−170·5	−154·9
C(3)	O(4)	C(5)	C(6)	1·410	1·421	112·9	112·8	171·9	165·6
O(4)	C(5)	C(6)	O(7)	1·527	1·506	108·9	109·6	−59·2	−65·1
C(5)	C(6)	O(7)	C(8)	1·409	1·418	108·6	108·3	174·9	175·2
C(6)	O(7)	C(8)	C(9)	1·408	1·422	113·0	112·7	176·8	172·4
O(7)	C(8)	C(9)	O(1')	1·521	1·512	107·6	105·5	175·4	173·7
C(8)	C(9)	O(1')	C(2')	1·411	1·430	113·1	108·3	173·9	169·2

A comparison was made between the molecular-dynamics and experimental results, in respect of properties that can be derived by both methods. The simulation with the most elaborate model (run *F*) was used for this purpose. In Table 5 the molecular geometry of 18-crown-6 is considered, calculated from the atomic coordinates obtained as an average over the time series of the simulation, or from the X-ray diffraction experiment. All macrocyclic bond lengths, bond angles and dihedral angles were considered. For the bond lengths no particlar agreement is observed; all molecular-dynamics bond lengths are close to their natural values (see Table 2), except for the elongated O(1)—C(2) bond. Bond-angle agreement is better, except for O(7)—C(8)—C(9) and C(8)—C(9)—O(1'); the larger value of these angles in the simulation is possibly related to the inability of the model to reproduce hydrogen-bonding geometries without inclusion of a special function, as demonstrated in molecular-mechanics calculations on 18-crown-6 (Uiterwijk *et al.*, 1987). Values of the C···O and H···O distances, and the C—H···O angle found in the molecular-dynamics simulation were 2·98, 2·34 Å and 116° (experimental values 3·04, 2·46 Å and 112°) for the C(9')—H···O(4) contact and 3·98, 2·93 Å and 167° (experimental values 3·71, 2·64 Å and 169°) for the C(9')—H···O(7) contact. The C(9')···O(7) distance shows a discrepancy of 0·27 Å, the molecular-dynamics value being too large, which could explain the larger value of the C(8)—C(9)—O(1') angle. Average values for bond angles (not shown in Table 5) can be compared with those calculated from the average coordinates (shown in Table 5). An expansion of the angles is then observed (0·1–0·6°, mean 0·26°) where the angles calculated from average coordinates are larger than average angles. The degree of angular expansion is correlated with the shortening of the bond

lengths; the largest expansion is observed for C(8)—C(9)—O(1′), which involves the two bonds C(8)—C(9) and C(9)—O(1′) with the largest shortening. The dihedral angles show reasonable agreement between the molecular-dynamics and experimental values, with one outlier, C(2)—C(3)—O(4)—C(5), showing a deviation of 15·6°. In molecular-mechanics calculations this angle also gave problems (Maverick *et al.*, 1980; Bovill *et al.*, 1980; Uiterwijk *et al.*, 1987), probably because (*a*) it is far removed from a local minimum, *i.e.* 180°, and (*b*) because one of its central atoms, O(4), is engaged in a short nonbonded contact. The r.m.s. deviation between the dihedral angles from the molecular-dynamics and the experimental coordinates amounted to 6·5°, whereas energy minimization of a single molecule yielded an r.m.s. deviation from experiment of 10·0°. Thus thermal motion and crystal packing can account for part of the discrepancies between experimental and energy-minimized geometries.

The coordinates resulting from simulation and experiment were also compared. A least-squares fit yielded an r.m.s. difference of 0·14 Å, after a rotation of 5° about an axis approximately parallel to *a*. A comparison of thermal parameters (Willis & Pryor, 1975) is reported in Table 6. The mean-square fluctuations of the (non-H) atoms were found to be nearly equal for the molecular-dynamics simulation and the crystal structure, with average values for the equivalent isotropic mean-square fluctuation U_{eq} of 168 and 175 × 10^{-4} Å^2, respectively. This agreement suggests that the absence of lattice modes, owing to the small size of the computational box, is of no consequence. The values of U_{eq} for the individual atoms showed little correlation between simulation and experiment, but the anisotropy of the thermal motion, as represented by the values of the Cartesian components U_{11}, U_{22} and U_{33} of the mean-square fluctuations relative to U_{eq}, was qualitatively reproduced for most atoms.

Finally, the distributions of the parameters were considered. From the third and fourth moments the skewness (asymmetry) and kurtosis ('peakedness') were calculated (Kreyszig, 1970) as a measure of the deviation from Gaussian behaviour. Values of 0·05 and 1·20 were calculated for skewness and kurtosis for the atomic positions, comparing well with the expectation values 0 and 1 for a Gaussian distribution. For the bond lengths, bond angles and dihedral angles values were calculated in the ranges 0·02–0·06 and 3·0–3·3, for skewness and kurtosis, showing symmetric distributions with large tails compared to a Gaussian distribution.

We conclude that a reasonable overall agreement between simulation and experiment is found for the molecular geometry of 18-crown-6. Together with the observed insensitivity to the simulation details,

Table 6. *Comparison of the thermal parameters of 18-crown-6 at 100 K, from molecular-dynamics and experimental results*

Results of the molecular-dynamics simulation (MD, run *F*) and the crystal structure determination [Exp., Maverick *et al.* (1980)]: the Cartesian components U_{11}, U_{22} and U_{33} of the mean-square fluctuations of the atoms, are presented as relative values to indicate anisotropy; the equivalent isotropic mean-square fluctuation is defined by $U_{eq} = (U_{11} + U_{22} + U_{33})/3$. A statistical error of less than 4% in the molecular-dynamics results is estimated. The experimental values had e.s.d.'s of approximately 1%.

| | $U_{eq}(10^{-4}\,\text{Å}^2)$ | | U_{11}/U_{eq}, U_{22}/U_{eq}, U_{33}/U_{eq} | | | | | |
	MD	Exp.	MD			Exp.		
O(1)	189	172	1·50	0·87	0·63	1·29	0·89	0·82
C(2)	163	174	1·36	0·65	1·00	1·21	0·83	0·96
C(3)	140	188	0·90	0·81	1·29	1·13	0·99	0·88
O(4)	128	164	0·76	1·03	1·21	1·01	1·06	0·92
C(5)	179	177	0·73	0·96	1·31	0·99	0·98	1·04
C(6)	184	176	1·19	0·92	0·89	1·20	1·00	0·81
O(7)	164	182	1·35	0·88	0·77	1·46	0·84	0·70
C(8)	183	175	1·49	0·93	0·58	1·31	0·96	0·73
C(9)	178	167	1·58	0·82	0·59	1·27	0·93	0·80

this gives some confidence in the values obtained for the thermal shortening of the covalent bonds.

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Crystallographic Characterization of Reaction Intermediates with Bridgehead Double Bonds: Structures of Diels–Alder Adducts of (*E*)- and (*Z*)-9-Thiabicyclo[3.3.1]non-1-ene Derivatives with 1,3-Diphenylisobenzofuran

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Abstract

Adduct *B*, (1*R**,2*R**,9*S**,10*S**,13*S**)-2,9-diphenyl-18-oxa-17-thiapentacyclo[11.3.1.1^{2,9}.0^{1,10}.0^{3,8}]octa-deca-3(8),4,6-triene 17,17-dioxide, $C_{28}H_{26}O_3S$, $M_r = 442\cdot58$, monoclinic, $P2_1/n$, $a = 16\cdot186$ (10), $b = 9\cdot452$ (4), $c = 15\cdot583$ (4) Å, $\beta = 111\cdot06$ (4)°, $V = 2225$ (2) Å^3, $Z = 4$, $D_x = 1\cdot319$ g cm^{-3}, $\lambda(Cu\ K\alpha) = 1\cdot5418$ Å, $\mu = 14\cdot8$ cm^{-1}, $F(000) = 936$, $T = 298$ K, $R = 0\cdot047$, $wR = 0\cdot044$ for 2317 unique observed reflections with $I > 2\sigma(I)$. Adduct *D*, (1*R**,2*R**,9*S**,10*R**,13*S**)-13-methyl-2,9-diphenyl-18-oxa-17-thiapentacyclo[11.3.1.1^{2,9}.0^{1,10}.0^{3,8}]octadeca-3(8),4,6-triene 17,17-dioxide, $C_{29}H_{28}O_3S$, $M_r = 456\cdot61$, monoclinic, $P2_1/n$, $a = 11\cdot343$ (3), $b = 19\cdot323$ (5), $c = 11\cdot006$ (2) Å, $\beta = 106\cdot70$ (2)°, $V = 2311$ (1) Å^3, $Z = 4$, $D_x = 1\cdot311$ g cm^{-3}, $\lambda(Cu\ K\alpha) = 1\cdot5418$ Å, $\mu = 14\cdot4$ cm^{-1}, $F(000) = 968$, $T = 298$ K, $R = 0\cdot041$, $wR = 0\cdot044$ for 2351 unique observed reflections with I

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$> 2\sigma(I)$. The Diels–Alder addition of a diene to 9-thiabicyclo[3.3.1]non-1-ene can take place in two ways, leaving the ring-junction hydrogen in the adduct in the *endo* or *exo* configuration. Also, the diene 1,3-diphenylisobenzofuran can add with its oxygen on the same (*syn*) side as the sulfur atom, or on the opposite (*anti*) side. Adduct *B* is shown to have the *exo, anti* configuration, while adduct *D*, a methyl derivative, has the *endo, anti* configuration. The crystals of adduct *B* contain a 15% admixture of adduct *C*, the *endo* isomer of *B*. Bond distances and angles reflect strain and overcrowding; short intra-molecular non-bonded contacts are O(sulfone)⋯ C(aromatic) = 2·869 (5) Å in adduct *D*, and H⋯ H = 1·88 (6) Å between hydrogens on the terminal carbons of the chair–chair bicyclononane moiety of adduct *B*.

Introduction

In a program (Wiseman and co-workers) aimed at exploring the stabilities of bicyclic molecules with a