Quantum Mechanics and Molecular Mechanics Studies of the Low-Energy Conformations of 9-Crown-3

Wayne P. Anderson,* Philip Behm, Jr., and Timothy M. Glennon

Department of Chemistry, Bloomsburg University, Bloomsburg, Pennsylvania 17815

Michael C. Zerner

Quantum Theory Project, University of Florida, Gainesville, Florida 32611

Received: July 18, 1996; In Final Form: December 30, 1996[⊗]

Quantum mechanics calculations and molecular mechanics calculations using the MMX force field have been performed on the low-energy conformations of 9-crown-3. A [144] conformation corresponds to the global minimum at the MP2/6-31G**//6-31G** level, with a [225] conformation only 0.72 kcal/mol higher in energy. The [333] conformation in which all three oxygen atoms are on the same side of the least squares plane passing through the ring, a structure particularly favorable as a tridentate ligand, is calculated to be 6.81 kcal/mol higher in energy. Electron correlation at the MP2 level and polarization functions on the hydrogen atoms have only minor effects on the relative conformational energies. However, polarization functions on the carbon and oxygen atoms are needed to obtain good results. MMX conformational energies are in good agreement with *ab initio* values if the electrostatic scale factor is set at 0.70. The role of transannular C−H···O hydrogen bonding in the low-energy conformations of 9-crown-3 is discussed. Results are compared with those obtained from AM1, PM3, and AMBER calculations.

I. Introduction

In contrast to the numerous experimental and computational studies that have been carried out on the crown ether 1,4,7,10,13,16-hexaoxacyclooctadecane (18-crown-6; [18]aneO_6),[1] few studies have been conducted on the prototype 1,4,7-trioxacyclononane (9-crown-3; [9]aneO_3).[2] Due to the difficult synthesis of 9-crown-3,[3,4] only its infrared spectrum,[3] its ^{13}C NMR spectrum,[3] and its interaction with Ba^{2+} ions[5] have been reported. Molecular mechanics calculations have been used to predict the low-energy conformations of 9-crown-3,[6] and semiempirical AM1 calculations of its proton affinity have been reported.[7] The only reported *ab initio* calculations on 9-crown-3 involve its complexes with the Li^+ ion[8,9] and with acetonitrile.[10] Although *ab initio* proton affinities of 12-crown-4, 15-crown-5, and 18-crown-6 were reported recently,[11] 9-crown-3 was not included in the study. We have calculated the structures and energies of the low-energy conformations of 9-crown-3 by *ab initio* and MMX molecular mechanics methods in order to assess the reliability of the MMX force field for determining conformational energies of crown ethers. Comparisons with other molecular mechanics and semiempirical quantum mechanics methods are also described.

II. Theoretical Models

A. Molecular Mechanics. The MMX force field[12] as implemented in PCModel[13] was used for the molecular mechanics calculations. MMX default parameters include partial charges derived from bond moments for electrostatic interactions, an electrostatic damping factor of 1.5, and lone pairs on oxygen atoms. A value of 0.70 for the electrostatic damping factor and use of dipole−dipole interactions for electrostatic effects were found to give better agreement between MMX and *ab initio* energies. The AMBER force field,[14−16] as implemented in version 3.0 of HyperChem,[17] was modified to include the parameters used for 18-crown-6 in previous investigations.[18,19]

B. Quantum Mechanics. Calculations were performed on an IBM RS6000 workstation. The programs GAMESS,[20] Gaussian 92,[21] and Gaussian 94[22] were used for the *ab initio* calculations. Standard STO-3G,[23] 3-21G,[24] 6-31G,[25] 6-31G*,[26] and 6-31G**[26] basis functions were employed. Single-point MP2[27,28] calculations using the Gaussian 92 frozen core option were performed on the 6-31G** optimized geometries. Frequencies were calculated on the 6-31G** optimized structures to confirm that they correspond to energy minima. MOPAC 6.0[29] was used for AM1[30] and PM3[31] calculations.

III. Results and Discussion

A. Molecular Mechanics: Comparison of 9-Crown-3 with Cyclononane. The conformational analysis of 9-crown-3 is best understood in the context of the conformations of cyclononane. Based on its ^{13}C NMR spectrum, the room-temperature composition of cyclononane is approximately 40% [333], 50% [225], and 10% [144],[32] where the numbers in brackets indicate the number of bonds between corner atoms.[33,34] These are the three lowest energy conformations found in molecular mechanics minimizations of cyclononane as well.[35−37] Molecular mechanics calculations indicate that a [9], a [234], and another [144] conformation lie within 10 kcal/mol of the global minimum. Two of these structures (the [9] and the [144]) are separated from the low-energy [144] conformation by very small energy barriers.[36] Replacement of three CH_2 groups in these cyclononane structures by oxygen atoms at various 1,4,7 positions and reminimization with the MMX force field using default parameters lead to 12 unique conformations of 9-crown-3 (Figure 1). To distinguish conformations that have the same Dale designation but different placements of the oxygen atoms in the ring, superscripts are added to the Dale designations to indicate the number of oxygen atoms at corner positions. In cases in which there is ambiguity concerning the positions of

---

* Author to whom correspondence should be addressed. Email: wpa@bloomu.edu

[⊗] Abstract published in *Advance ACS Abstracts,* February 1, 1997.

S1089-5639(96)02172-X CCC: $14.00

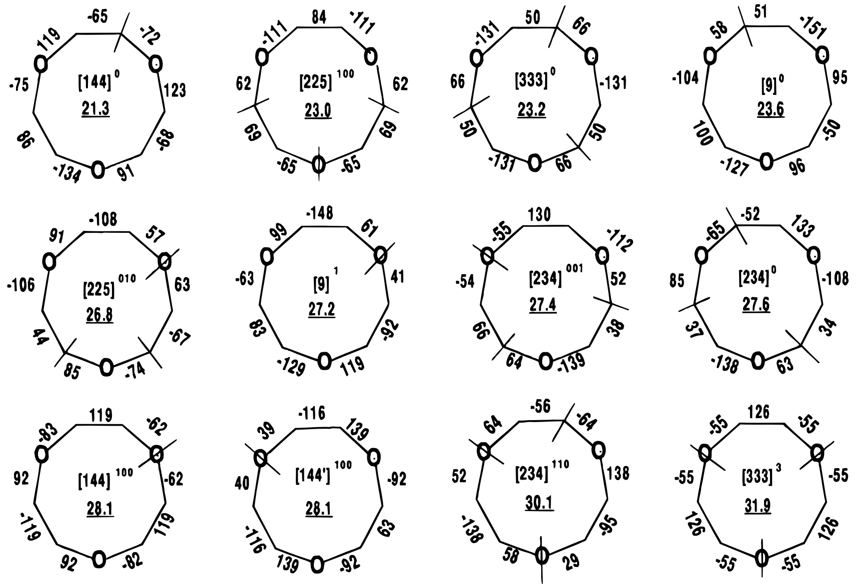


Figure 1. MMX strain energies (kcal/mol) using default parameters, torsional angles (deg), and modified Dale[33] designations of conformations of 9-crown-3 derived from the six lowest energy structures of cyclononane. Energies are underlined inside the structures. Lines on structures indicate corner positions, and superscripts on labels indicate the number of oxygen atoms at each corner.

TABLE 1: Comparison of Energies (kcal/mol) of Conformers of 12-Crown-4 Calculated with a Modified MMX Force Field (MMXϵ) in Which the Electrostatic Damping Factor Has Been Set at 0.70 and Those Obtained in *ab Initio* Calculations[a]

conformation	*ab initio*[a]	MMX, diple−dipole, $\epsilon = 0.70$
[333]; C_4	6.42	6.37
[48]; C_s	3.20	3.92
[66]; C_i	1.47	1.57
[12]; S_4	0.00	0.00

[a] Reference 44.

the corner oxygen atoms, multiple superscripts are used. The designation $[ABC]^{xyz}$ indicates that there are x oxygen atoms at corner AB, y oxygen atoms at corner BC, and z oxygen atoms at corner CA.[38] It is interesting that all structures that originated from the higher energy [144] form of cyclononane collapsed into 9-crown-3 conformations that originated from other cyclononane conformers either during the MMX minimization or later quantum mechanics minimization. An attempt was made to generate additional low-energy conformations of 9-crown-3 through use of the randomization algorithm of Saunders[39] contained in the DOS version 3.3 of PCModel starting with the $[144]^0$, $[225]^{100}$, and $[333]^0$ structures. No additional structures within 8 kcal/mol of the global minimum were found, although many higher energy conformations were obtained. The pattern of default MMX relative energies is similar to the one obtained in an early molecular mechanics study of crown ethers by Bovill *et al.*[6] for structures that are in common for the two studies. However, the global minimum $[144]^0$ was not included in the Bovill investigation.

Previous molecular mechanics calculations on 18-crown-6 indicated that default MM2[40,41] parameters give an incorrect ordering of the C_i and D_{3d} conformations. The order can be corrected either by increasing the C−O bond moments[42] or by lowering the value of ϵ, the "electrostatic damping factor".[43] Using the MMX force field with dipole−dipole electrostatic interactions and an electrostatic damping factor of 0.70, we obtained good agreement between the MMX conformational energies and *ab initio* values[44] for 12-crown-4 (Table 1). Using these parameters, the MMX energy difference between the C_i and D_{3d} structures of 18-crown-6 is 2.3 kcal/mol, which is somewhat lower than the *ab initio* values[1] of 4.4−5.4 kcal/mol depending upon the level of theory employed. Relative energies of seven low-energy conformations of 9-crown-3 based on this modified MMX force field (hereafter designated as MMXϵ) are shown in Figure 2 along with the corresponding cyclononane conformers. Five of the initial 12 structures obtained for 9-crown-3 ($[9]^0$, $[234]^0$, $[234]^{110}$, $[144]^{100}$, and $[144']^{100}$) converted to other structures during quantum mechanics optimizations and are excluded from the figure. Replacement of CH_2 groups by O atoms causes the range of energies to increase substantially. The MMXϵ energies are very sensitive to the position of the oxygen atoms in the ring. Structures in which the oxygen atoms occupy side positions in the ring are energetically more favorable than those in which the oxygen

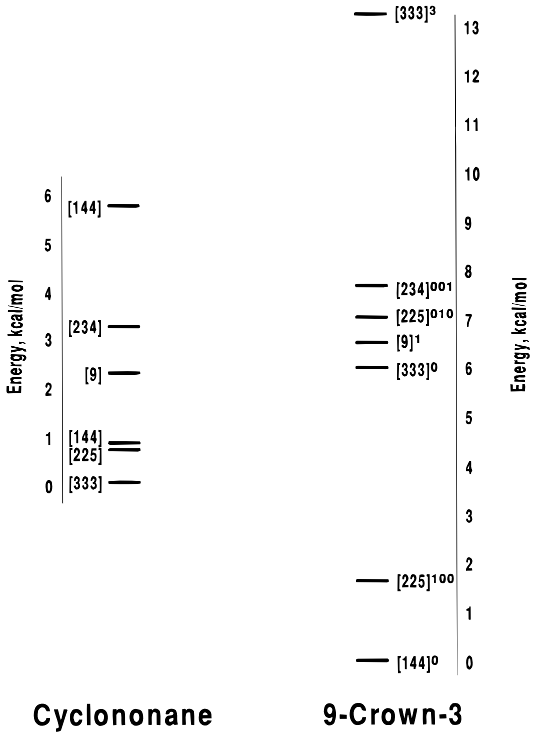


Figure 2. Comparison of conformational energies (kcal/mol) of cyclononane and 9-crown-3 based on the MMXϵ force field (see text).

TABLE 2: Strain Energy Contributions (kcal/mol) in Low-Energy Conformations of 9-Crown-3 Using a Modified MMX Force Field (MMXε) in Which the Electrostatic Damping Factor Has Been Set at 0.70

	stretch	bend	S–B[a]	torsional	VDW[b]	D–D[c]	MMX energy	relative energy
$[333]^3$	1.34	13.81	0.79	9.17	12.43	3.60	41.13	13.27
$[234]^{001}$	1.36	10.87	0.74	7.86	12.37	2.38	35.58	7.72
$[225]^{010}$	1.15	12.39	0.69	7.07	11.30	2.26	34.86	7.00
$[9]^1$	1.28	10.78	0.65	8.82	12.38	0.40	34.32	6.46
$[333]^0$	1.36	7.38	0.64	6.91	10.96	6.62	33.87	6.01
$[225]^{100}$	1.06	11.07	0.66	5.63	11.04	0.12	29.57	1.71
$[144]^0$	1.13	7.10	0.54	7.69	11.29	0.12	27.86	0.00

[a] Stretch–bend. [b] van der Waals. [c] Dipole–dipole.

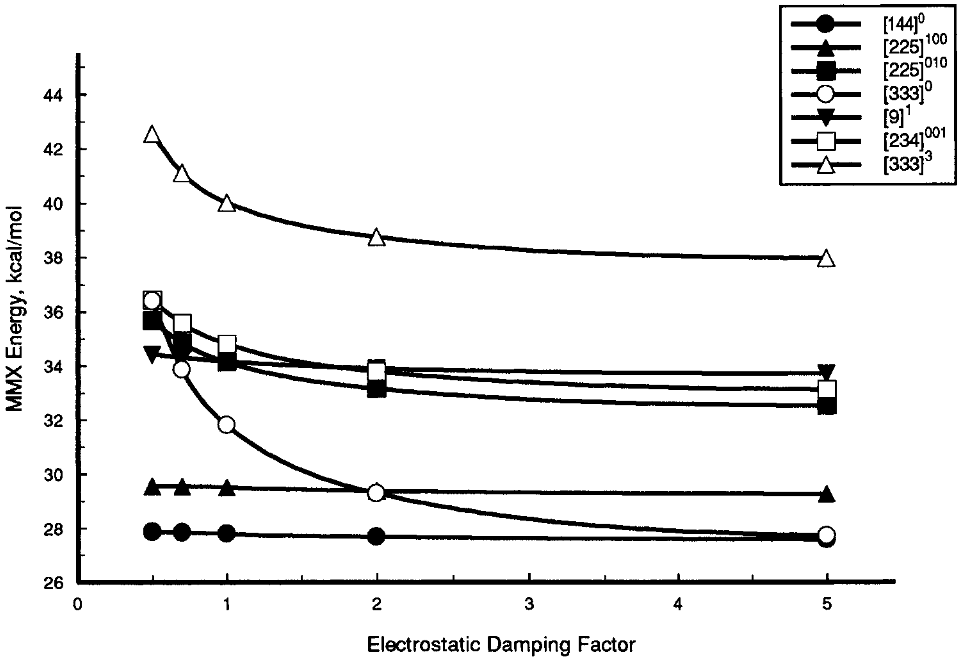
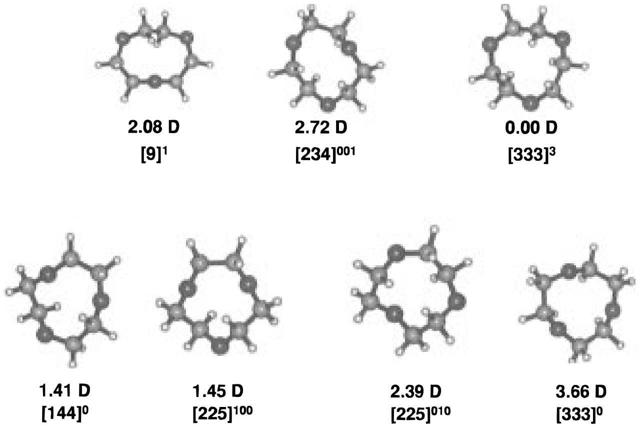


Figure 3. MMXε energy (kcal/mol) as a function of the electrostatic damping factor for low-energy conformations of 9-crown-3.

atoms are at corners. This is particularly apparent for the two [333] structures. The one in which all three oxygen atoms are at corners is the highest energy structure derived from the six cyclononane conformers, despite the fact that the [333] structure is the lowest energy one for cyclononane. This structure is also 7.3 kcal/mol higher than the [333] structure in which all three oxygen atoms are along sides. Contributions to the MMXε strain energy are given in Table 2. The bending strain energy is exceptionally large for $[333]^3$ because of the large C–O–C and C–C–O bond angles, whereas the bending strain energy is unusually low for $[144]^0$ and $[333]^0$. The bending strain energy is 6.4 kcal/mol larger in $[333]^3$ than in $[333]^0$. The torsional energy contribution is also unusually large for $[333]^3$ because of the large O–C–C–O dihedral angles. It has been pointed out previously that macrocyclic structures having gauche O–C–C–O torsional angles are favored, whereas structures having anti S–C–C–S torsional angles are preferred.[45] Our MMXε calculations suggest that the bending strain that accompanies structures having corner oxygen atoms is more significant than the torsional strain. Finally, electrostatic effects favor $[144]^0$, $[225]^{100}$, and $[9]^1$, whereas $[333]^0$ is disfavored by electrostatic effects because of repulsions between oxygen atoms.

The effect of the electrostatic damping factor on MMXε energies is shown in Figure 3. The energy of $[333]^0$ is affected most significantly by the change in the damping factor. Thus, the calculated relative energy of this conformation will be very dependent upon the extent to which a computational model successfully represents electrostatic effects. Since an increase in dielectric constant of the solvent buffers electrostatic interactions, the energy of this conformer should also be particularly sensitive to the nature of the solvent. In a high-dielectric medium, $[333]^0$ may be present to an extent similar to $[144]^0$ and $[225]^{100}$.


2.08 D $[9]^1$ 2.72 D $[234]^{001}$ 0.00 D $[333]^3$

1.41 D $[144]^0$ 1.45 D $[225]^{100}$ 2.39 D $[225]^{010}$ 3.66 D $[333]^0$

Figure 4. 6-31G** structures and dipole moments (debyes) of low-energy conformations of 9-crown-3.

B. *Ab Initio* Results. To assess the quality of the MMXε force field for 9-crown-3, *ab initio* calculations using a variety of basis sets were carried out. Optimized structures and calculated dipole moments are given in Figure 4. Total energies and relative energies are reported in Tables 3 and 4, respectively. The highest level of theory employed was a single-point MP2 calculation, excluding inner shells, at the 6-31G** optimized geometry. Comparison of relative energies at the correlated

TABLE 3: Total Energies (hartrees) of Conformations of 9-Crown-3 from *ab Initio* Calculations

	3-21G	6-31G	6-31G*	6-31G**	MP2/6-31G**//6-31G**
[333]^{3}	−456.168 523	−458.499 891	−458.702 819	−458.721 138	−460.102 971
[234]^{001}	−456.178 108	−458.508 580	−458.713 815	−458.732 350	−460.114 076
[9]^{1}	−456.184 410	−458.515 514	−458.718 536	−458.737 057	−460.118 594
[333]^{0}	−456.176 446	−458.510 473	−458.720 563	−458.739 159	−460.120 096
[225]^{010}	−456.183 349	−458.514 206	−458.719 676	−458.738 233	−460.120 226
[225]^{100}	−456.194 423	−458.523 838	−458.728 327	−458.747 018	−460.129 797
[144]^{0}	−456.193 918	−458.526 128	−458.731 201	−458.749 862	−460.130 943

TABLE 4: Relative Energies (kcal/mol) of Conformations of 9-Crown-3 from *ab Initio* Calculations

	STO-3G	3-21G	6-31G	6-31G*	6-31G**	MP2/6-31G**//6-31G**	zero-point energy[c]
[333]^{3}	17.80	15.94	16.46	17.81	18.02	17.55 (17.8)[b]	125.10
[234]^{001}	6.70	9.92	11.01	10.91	10.99	10.58 (9.9)	124.87
[9]^{1}	3.33	5.97	5.22	7.95	8.04	7.75 (7.4)	124.79
[333]^{0}	4.80	10.96	9.82	6.68	6.72	6.81 (5.3)	124.78
[225]^{010}	2.32	6.63	7.48	7.23	7.30	6.73 (6.2)	124.92
[225]^{100}	−1.20	−0.32	1.44	1.80	1.78	0.72 (0.7)	124.95
[144]^{0}	0.00	0.00	0.00	0.00	0.00	0.00 (0.0)	124.77
corr[a]	0.97	0.94	0.96	1.00	1.00		

[a] Correlation coefficients with MP2/6-31G**//6-31G** energies. [b] Includes estimated solvent shifts; see text. [c] Zero-point energies (kcal/mol).

TABLE 5: 6-31G//6-31G** Structural Parameters for Low-Energy Conformations of 9-Crown-3**

Conformation		O_1	C_2	C_3	O_4	C_5	C_6	O_7	C_8	C_9
[333]^{3}	r[a]	1.403	1.537	1.403	1.404	1.536	1.403	1.403	1.537	1.403
[333]^{3}	a[b]	121.1	115.5	115.5	121.0	115.5	115.4	121.1	115.4	115.4
[333]^{3}	t[c]	-53.8	120.7	-53.8	-53.8	120.6	-53.8	-53.9	120.6	-53.8
[234]^{001}	r	1.401	1.524	1.396	1.409	1.542	1.403	1.397	1.524	1.396
[234]^{001}	a	117.9	114.8	116.2	120.5	116.1	111.1	120.7	115.6	109.6
[234]^{001}	t	64.2	63.3	-51.5	-55.6	127.5	-105.1	42.4	45.1	-140.8
[9]^{1}	r	1.401	1.519	1.399	1.408	1.538	1.400	1.405	1.520	1.401
[9]^{1}	a	121.4	108.8	114.8	117.1	110.2	115.6	120.7	116.8	109.2
[9]^{1}	t	-132.6	72.6	-63.8	99.0	-143.5	68.6	27.6	-79.0	128.9
[333]^{0}	r	1.394	1.524	1.396	1.395	1.524	1.396	1.395	1.524	1.396
[333]^{0}	a	118.5	110.1	114.7	118.4	110.1	114.7	118.4	110.1	114.7
[333]^{0}	t	-128.0	52.6	62.4	-128.0	52.6	62.3	-128.0	52.7	62.3
[225]^{010}	r	1.397	1.521	1.394	1.410	1.532	1.405	1.394	1.526	1.396
[225]^{010}	a	119.5	114.9	115.1	121.0	116.6	115.5	119.5	112.1	115.0
[225]^{010}	t	-78.9	-59.9	62.8	53.9	-102.7	86.1	-102.5	49.1	80.4
[225]^{100}	r	1.403	1.521	1.403	1.400	1.519	1.399	1.403	1.521	1.403
[225]^{100}	a	119.6	114.9	115.5	118.6	112.0	112.0	118.6	115.5	114.8
[225]^{100}	t	-62.7	65.0	67.8	-108.3	71.4	-108.2	67.7	65.1	-62.6
[144]^{0}	r	1.406	1.517	1.398	1.400	1.519	1.399	1.399	1.515	1.398
[144]^{0}	a	118.1	110.6	114.0	118.2	110.7	114.1	117.6	110.2	111.0
[144]^{0}	t	132.8	-77.4	74.8	-117.0	62.2	74.3	-118.6	62.9	-96.2

[a] r is the distance in angstroms between the indicated atoms. [b] a is the bond angle in degrees about the indicated central atom. [c] t is the torsional angle in degrees with respect to the indicated central bond. Atom C_9 is connected to atom O_1 in the ring.

level with those at the 6-31G** SCF level indicates that electron correlation has a minor effect overall on the relative energies. The most important change brought about by inclusion of electron correlation is a decrease in the energy difference between the two low-energy conformations to 0.72 kcal/mol. Energies determined at the 6-31G*//6-31G* SCF level are similar to those at the 6-31G**//6-31G** level. Therefore, polarization functions on hydrogen atoms can be omitted. However, the calculated relative energies of the [9]^{1} and [333]^{0} conformations are altered significantly by inclusion of polarization functions on carbon and oxygen atoms. Based on our results, the 6-31G* basis set is sufficient to get meaningful results for crown ether conformational energies. Minimal basis sets and small split valence basis sets invert the ordering of [144]^{0} and [225]^{100}.

The MMXϵ relative energies are remarkably similar to the MP2/6-31G**//6-31G** values. The [144]^{0} and [225]^{100} structures are substantially lower in energy than any others, and the [333]^{3} structure is clearly the highest in energy. The average unsigned difference between the MP2/6-31G**//6-31G** results and the MMXϵ relative energies is 1.6 kcal/mol with a correlation coefficient of 0.985. This suggests that the MMXϵ force field is an adequate model for examining low-energy crown ether conformations.

Structural features of 9-crown-3 conformations are summarized in Table 5. The 6-31G** average C−O and C−C bond lengths are 1.400 and 1.526 Å, respectively. These are somewhat longer than the values of 1.395 and 1.512 Å obtained at the 6-31G* (6-31G+* on O) level for the C_i and D_{3d} structures of 18-crown-6.[1] Use of an unmodified 6-31G** basis set on the C_i conformation of 18-crown-6 gave differences of less than 0.01 Å for all calculated bond lengths.[1] The calculated C−O bond lengthening in 9-crown-3, therefore, may be a basis set effect. The O−O transannular distance in the [333]^{0} conformer is 2.828 Å with a 1.633 Å distance from O to the centroid of the O atoms. This emphasizes the small hole size in the 9-crown-3 conformer that has all three oxygen atoms on the same side of the least squares plane passing through the

TABLE 6: Calculated MMXϵ//MMXϵ Structural Parameters for Low-Energy Conformations of 9-Crown-3

Conformation		O_1	C_2	C_3	O_4	C_5	C_6	O_7	C_8	C_9
$[333]^3$	r[a]	1.428	1.540	1.428	1.428	1.540	1.428	1.428	1.540	1.428
$[333]^3$	a[b]	117.3	114.4	114.4	117.3	114.4	114.4	117.3	114.4	114.4
$[333]^3$	t[c]	-55.2	125.8	-55.1	-55.2	125.8	-55.1	-55.1	125.8	-55.1
$[234]^{001}$	r	1.422	1.544	1.429	1.426	1.548	1.428	1.431	1.543	1.422
$[234]^{001}$	a	114.9	113.4	115.9	117.5	115.0	110.6	115.7	115.1	109.6
$[234]^{001}$	t	66.8	64.6	-53.4	-54.9	131.6	-110.3	48.8	37.9	-141.1
$[9]^1$	r	1.423	1.543	1.428	1.428	1.543	1.424	1.429	1.544	1.425
$[9]^1$	a	117.2	108.4	113.6	115.3	109.9	114.9	117.2	115.8	108.5
$[9]^1$	t	-131.7	80.0	-62.3	98.7	-147.6	61.6	38.7	-89.1	122.5
$[333]^0$	r	1.427	1.545	1.426	1.428	1.545	1.426	1.426	1.545	1.426
$[333]^0$	a	114.5	110.4	113.7	114.5	110.3	113.7	114.5	110.3	113.7
$[333]^0$	t	-130.0	51.7	64.1	-130.0	51.7	64.1	-130.0	51.7	64.1
$[225]^{010}$	r	1.423	1.537	1.426	1.425	1.544	1.429	1.427	1.541	1.422
$[225]^{010}$	a	116.3	113.6	114.7	117.5	114.9	114.0	115.5	112.5	113.4
$[225]^{010}$	t	-76.9	-64.7	63.4	57.2	-108.2	89.4	-103.8	45.4	84.8
$[225]^{100}$	r	1.426	1.541	1.422	1.424	1.544	1.424	1.422	1.541	1.426
$[225]^{100}$	a	117.3	114.8	114.9	115.6	110.2	110.2	115.6	114.9	114.9
$[225]^{100}$	t	-64.5	67.6	64.2	-111.3	81.3	-111.4	64.4	67.5	-64.5
$[144]^0$	r	1.425	1.541	1.426	1.427	1.542	1.423	1.427	1.542	1.424
$[144]^0$	a	114.7	110.0	112.4	115.1	110.7	112.7	114.3	110.1	110.0
$[144]^0$	t	135.4	-85.2	73.3	-117.1	65.8	72.4	-121.9	66.6	-91.8

[a] r is the distance in angstroms between the indicated atoms. [b] a is the bond angle in degrees about the indicated central atom. [c] t is the torsional angle in degrees with respect to the indicated central bond. Atom C_9 is connected to atom O_1 in the ring.

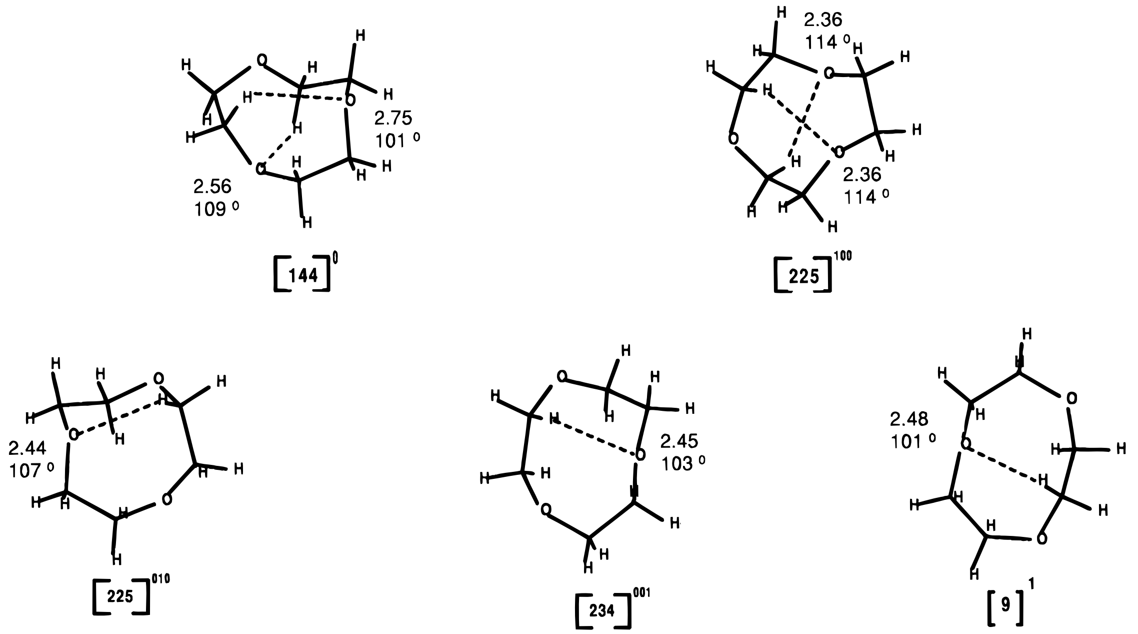


Figure 5. Possible C−H···O transannular interactions in conformers of 9-crown-3. H···O distances are in angstroms, and C−H···O angles are in degrees.

ring atoms. The average values of ∠COC range from 118.0° in $[144]^0$ to 121.1° in $[333]^3$, with an overall mean value of 119.4°, and the average values of ∠OCC range from 111.8° in $[144]^0$ to 115.5° in $[333]^3$, with an overall mean of 113.6°. These values are larger than those found for the C_i and D_{3d} conformations of 18-crown-6.[1] Thus, angle strain is greater in the smaller 9-crown-3 moiety. The 6-31G** results agree with the MMXϵ bending strain analysis in which $[144]^0$ had the smallest bending strain energy and $[333]^3$ the largest. MMXϵ structures (Table 6) are in reasonable agreement with the *ab initio* values. The average unsigned deviations of the MMXϵ bond lengths, bond angles, and torsional angles from the 6-31G** values are 0.023 Å, 1.7°, and 3.2°, respectively.

Recently it has been demonstrated that 1−5 CH···O nonbonded attractions help stabilize certain conformations of 1,2-dimethoxyethane.[46] Such interactions may also help stabilize the C_i conformation of 18-crown-6[1,30,47] and the [12] and [66] conformations of 12-crown-4.[44] The $[144]^0$ and $[225]^{100}$ conformations of 9-crown-3 contain two such interactions each in which the C−H···O distance is less than 3.00 Å and the C−H···O angle is greater than 100°. The $[225]^{010}$, $[234]^{001}$, and $[9]^1$ conformations contain one such interaction each. These are illustrated in Figure 5. Thus, as is the case for 12-crown-4, the two lowest energy conformations are the ones having the largest number of transannular 1−5 CH···O interactions. The extent to which these interactions help stabilize the conformations is uncertain. A previous investigation indicates that each such interaction is worth 1.2−1.4 kcal/mol.[46] Yet, the conformational energy differences in the MMXϵ calculations are similar to the *ab initio* differences. Similar 1−5 CH···O bond lengths and bond angles appear in the MMXϵ optimized structures as well, even though the C−H bond moments are 0.00 and no explicit hydrogen bonding is included in the force field. Mulliken charges on the CH···O hydrogen atoms do not reflect a specific CH···O interaction, as they are not the most positive hydrogen atoms in the molecules as might be expected if CH···O hydrogen bonding were occurring.[1] On the other hand, the 6-31G** vibrational spectra are consistent with such interactions. Although the frequency of O−H stretching vibrations decreases upon H-bond formation,[48] calculated C−H harmonic frequencies at the 6-31G** SCF level increase when C−H···O interactions occur.[49] In $[225]^{100}$, $[225]^{010}$, $[234]^{001}$, and $[9]^1$ the CH···O hydrogen atoms are primary contributors to highest energy vibrational modes that are 18−24 cm^{-1} above the next vibrational modes in the molecules. In $[144]^0$, one of the two high-energy modes is dominated by a CH···O hydrogen motion, but the other one is not. In $[333]^0$ and $[333]^3$, in which no 1−5 CH···O interactions are possible, the highest energy vibrational modes are within 2−6 cm^{-1} of the next highest modes. Thus, bond distances and vibrational frequencies suggest that 1−5 CH···O interactions are present, but they may be a *consequence* of the overall geometries of the molecules that are brought about by other factors and may not be an important *contributor* in determining the structures.

Our calculations pertain to gas phase molecules at 0 K. However, we can use the calculated dipole moments to estimate the differences in the heats of solution of the various 9-crown-3 conformers. The free energy of solution is given by

$$\Delta G_{\text{sol}} = \Delta G_{\text{elect/pol}} + \Delta G_{\text{cavitation}} + \Delta G_{\text{dispersion}}$$

Since the various geometric conformers might be expected to have very similar size and electronic spectroscopy, we can assume that the differences in solvent stabilization are given by $\Delta G_{\text{elect/pol}}$, the differences in the electrostatic/polarization term. Accordingly, the leading term in a moment expansion of the solvation energy is given by Onsager as[50,51]

$$-\frac{\epsilon - 1}{2\epsilon + 1}\frac{\mu^2}{{a_0}^3}$$

where a_0 is the radius of a spherical cavity separating the solute from the solvent, μ is the dipole moment, and ϵ is the dielectric constant. Taking a_0 from mass density as[52]

$$a_0(\text{Å}) = 0.734(\text{MM}/\rho)^{1/3}$$

where MM is the molar mass (132 amu) and ρ is the density of 9-crown-3 (taken as 1.0 g/cm^3), yields a_0 as 3.74 Å. For water ($\epsilon = 78.5$) this then gives

$$\Delta G(\text{elec})\ (\text{kcal/mol}) = -0.135\mu^2\ (\text{debye})$$

In the above we have neglected the polarization term as small. The next to last column of Table 4 includes this correction. The only change this makes is in the relative order of $[225]^{010}$ and $[333]^0$. Because the dipole moments of $[144]^0$ and $[225]^{100}$ are essentially the same, their energy difference remains the same.

The $[144]^0$ conformation is favored over the $[225]^{100}$ conformation by 0.72 kcal/mol at the MP2 level (1.78 kcal/mol at the SCF level). Zero-point energies and entropies are similar for the two conformations.[53] Therefore, the $[144]^0$ conformation is also favored by free energy. The calculated dipole moments of 1.41 D for $[144]^0$ and 1.45 D for $[225]^{100}$ agree well with the observed value of 1.55 D.[3]

TABLE 7: Relative Energies (kcal/mol) of Conformations of 9-Crown-3 from AM1, PM3, and AMBER Calculations

	AMBER[b]	AM1	PM3
$[333]^3$	9.19	4.61	1.17
$[234]^{001}$	13.00	*c*	3.12
$[9]^1$	4.49	*c*	−1.47
$[333]^0$	4.13	6.18	4.24
$[225]^{010}$	4.84	3.17	−0.02
$[225]^{100}$	−0.28	−0.82	−0.18
$[144]^0$	0.00	0.00	0.00
corr[a]	0.83	0.72	0.30

[a] Correlation coefficients with MP2/6-31G**//6-31G** energies. [b] Electrostatic 1-4 scale factor set at 1.0. [c] Did not converge.

C. Comparison of *Ab Initio* Results with Other Models

Since the AMBER force field has been used in numerous molecular mechanics and molecular dynamics studies of 18-crown-6,[54] and the AM1 model has been used in some hybrid quantum mechanics/molecular mechanics investigations,[55] we investigated the conformational energies of the structures in Figure 2 by these methods and by the related PM3 method as well. Results are shown in Table 7. AMBER conformational energies are in general agreement with the *ab initio* values, although the correlation coefficient with MP2/6-31G**//6-31G** results is only 0.83 and the relative positions of the two lowest energy conformations are reversed. It should be emphasized that no attempt was made to reparameterize AMBER in order to improve the results. It was necessary to set the 1−4 electrostatic scale factor in AMBER to 1.0 in order to get the correct ordering of the conformations of 12-crown-4 and to improve the 9-crown-3 results.[56] Use of RESP charges[57] might improve the AMBER calculated energies, since the conformational energies of some of the crown ether conformations (e.g. $[333]^0$) are very sensitive to electrostatic effects. AM1 and PM3 give unacceptable errors in conformational energies, with the PM3 method giving particularly poor results. Bond lengths, bond angles, and torsional angles (not included) from AM1 calculations are in much better agreement with the *ab initio* values for the various conformers than are the energies.

IV. Conclusions

Ab initio calculations at the MP2/6-31G**//6-31G** level on low-energy conformations of 9-crown-3 indicate that the $[144]^0$ and $[225]^{100}$ structures are substantially lower in energy than any others, with $[144]^0$ favored by 0.72 kcal/mol. The $[333]^0$ structure, in which the three oxygen atoms are oriented in a suitable fashion for the molecule to function as a tridentate ligand, lies 6.81 kcal/mol above the global minimum. The $[333]^3$ conformation, in which all three oxygen atoms lie at corner positions, is particularly unfavorable because of exceptionally large C−O−C and O−C−C angles. Calculations at the 6-31G*//6-31G* *ab initio* level agree well with the MP2/6-31G**//6-31G** results, suggesting that correlation is not important, but smaller basis sets give some notable errors. Bond distances and vibrational frequencies indicate that two 1−5 CH···O transannular interactions are present in the $[144]^0$ and $[225]^{100}$ structures, although the importance of these interactions in stabilizing these structures is unclear.

Molecular mechanics calculations using a modified version of the MMX force field in which the electrostatic damping factor is set at 0.70 and dipole−dipole interactions are used to represent electrostatic interactions give conformational energies and structures that agree well with the *ab initio* results. This force field is an attractive alternative to *ab initio* calculations for determining conformational preferences of crown ethers. In contrast, semiempirical AM1 and PM3 quantum mechanics calculations give poor agreement with *ab initio* energies and cannot be recommended for conformational studies on crown ether systems.

Acknowledgment. Acknowledgement is made to the donors of the Petroleum Research Fund, administered by the American Chemical Society, for partial support of this research. W.P.A. thanks Bloomsburg University for two Research and Disciplinary Projects grants and for a Sabbatical Leave during which time a portion of this research was carried out.

References and Notes

(1) Glendening, E. D.; Feller, D.; Thompson, M. A. *J. Am. Chem. Soc.* **1994**, *116*, 10657.

(2) Anet, F. A. L. In *Conformational Analysis of Medium-Sized Heterocycles*; Glass, R. S., Ed.; VCH Publishers, Inc.: New York, 1988; pp 35−95.

(3) Borgen, G.; Dale, J.; Anet, F. A. L.; Krane, J. *J. Chem. Soc., Chem. Commun.* **1974**, 243.

(4) Schwesinger, R.; Fritz, H.; Prinzbach, H. *Chem. Ber.* **1979**, *112*, 3318.

(5) Benken, R.; Buschmann, H.-J. *Inorg. Chim. Acta* **1987**, *134*, 49.

(6) Bovill, M. J.; Chadwick, D. J.; Sutherland, I. O. *J. Chem. Soc., Perkin Trans. 2* **1980**, 1529.

(7) Esseffar, M.; El Mouhtadi, M.; Abboud, J.-L. M.; Elguero, J.; Liotard, D. *Can. J. Chem.* **1991**, *69*, 1970.

(8) Hori, K.; Haruna, Y.; Kamimura, A.; Tsukube, H.; Inoue, T. *Tetrahedron* **1993**, *49*, 3959.

(9) Rencsok, R.; Kaplan, T. A.; Harrison, J. F. *J. Chem. Phys.* **1993**, *98*, 9758.

(10) Anderson, W. P.; Behm, P., Jr.; Glennon, T. M.; Graves, S. H.; Zerner, M. C. *Prepr.-Am. Chem. Soc., Div. Pet. Chem.* **1992**, *37* (2), 580.

(11) Wasada, H.; Tsutsui, Y.; Yamabe, S. *J. Phys. Chem.* **1996**, *100*, 7367.

(12) Gajewski, J. J.; Gilbert, K. E.; McKelvey, J. In *Advances in Molecular Modeling*; Liotta, D., Ed.; JAI Press, Inc.: Greenwich, CT, 1990; Vol. 2, pp 65−92.

(13) Serena Software, Bloomington, IN.

(14) Weiner, P. K.; Kollman, P. A. *J. Comput. Chem.* **1981**, *2*, 287.

(15) Weiner, S. J.; Kollman, P. A.; Case, D. A.; Singh, U. C.; Ghio, C.; Alagona, G.; Profeta, S. Jr.; Weiner, P. *J. Am. Chem. Soc.* **1984**, *106*, 765.

(16) Weiner, S. J.; Kollman, P. A.; Nguyen, D. T.; Case, D. A. *J. Comput. Chem.* **1986**, *7*, 230.

(17) HyperChem, R. 3; Autodesk, Inc.

(18) Howard, A. E.; Singh, U. C.; Billeter, M.; Kollman, P. A. *J. Am. Chem. Soc.* **1988**, *110*, 6984.

(19) Grootenhuis, P. D. J.; Kollman, P. A. *J. Am. Chem. Soc.* **1989**, *111*, 4046.

(20) Schmidt, M. W.; Boatz, J. A.; Baldridge, K. K.; Koseki, S.; Gordon, M. S.; Elbert, S. T.; Lam, B. *QCPE Bull.* **1987**, *7*, 115.

(21) Frisch, M. J.; Trucks, G. W.; Head-Gordon, M.; Gill, P. M. W.; Wong, M. W.; Foresman, J. B.; Johnson, B. G.; Schlegel, H. B.; Robb, M. A.; Replogle, E. S.; Gomperts, R.; Andres, J. L.; Raghavachari, K.; Binkley, J. S.; Gonzalez, C.; Martin, R. L.; Fox, D. J.; Defrees, D. J.; Baker, J.; Stewart, J. J. P.; Pople, J. A. *Gaussian 92* (Revision D.3); Gaussian, Inc.: Pittsburgh, PA, 1992.

(22) Frisch, M. J.; Trucks, G. W.; Schlegel, H. B.; Gill, P. M. W.; Johnson, B. G.; Robb, M. A.; Cheeseman, J. R.; Keith, T. A.; Petersson, G. A.; Montgomery, J. A.; Raghavachari, K.; Al-Laham, M. A.; Zakrzewski, V. G.; Ortiz, J. V.; Foresman, J. B.; Peng, C. Y.; Ayala, P. Y.; Chen, W.; Wong, M. W.; Andres, J. L.; Replogle, E. S.; Gomperts, R.; Martin, R. L.; Fox, D. J.; Binkley, J. S.; Defrees, D. J.; Baker, J.; Stewart, J. P.; Head-Gordon, M.; Gonzalez, C.; Pople, J. A. *Gaussian 94* (Revision B.3); Gaussian, Inc.: Pittsburgh, PA, 1995.

(23) Hehre, W. J.; Stewart, R. F.; Pople, J. A. *J. Chem. Phys.* **1969**, *51*, 2657.

(24) Binkley, J. S.; Pople, J. A.; Hehre, W. J. *J. Am. Chem. Soc.* **1980**, *102*, 939.

(25) (a) Ditchfield, R.; Hehre, W. J.; Pople, J. A. *J. Chem. Phys.* **1971**, *54*, 724. (b) Hehre, W. J.; Ditchfield, R.; Pople, J. A. *J. Chem. Phys.* **1972**, *56*, 2257.

(26) Hariharan, P. C.; Pople, J. A. *Theor. Chim. Acta* **1973**, *28*, 213.

(27) Moeller, C.; Plesset, M. S. *Phys. Rev.* **1934**, *46*, 618.

(28) Head-Gordon, M.; Pople, J. A.; Frisch, M. J. *Chem. Phys. Lett.* **1988**, *153*, 503.

(29) Stewart, J. J. P. MOPAC 6.0; Quantum Chemistry Program Exchange, QCPE #455.

(30) Dewar, M. J. S.; Zoebisch, E. G.; Healy, E. F.; Stewart, J. J. P. *J. Am. Chem. Soc.* **1985**, *107*, 3902.

(31) Stewart, J. J. P. *J. Comput. Chem.* **1989**, *10*, 209; 221.

(32) Anet, F. A. L.; Krane, J. *Isr. J. Chem.* **1980**, *20*, 72.

(33) Dale, J. *Acta Chem. Scand.* **1973**, *27*, 1115.

(34) A corner position is one in which adjacent dihedral angles are gauche ++ or gauche −−. Pseudocorners have gauche +− or gauche −+ dihedrals.

(35) Ferguson, D. M.; Glauser, W. A.; Raber, D. J. *J. Comput. Chem.* **1989**, *10*, 903.

(36) Anet, F. A. L. *J. Am. Chem. Soc.* **1990**, *112*, 7172.

(37) Saunders, M. *J. Comput. Chem.* **1991**, *12*, 645.

(38) The designation [144] is an alternative for some [9] structures. In this paper, the [144] designation will indicate approximate 144 symmetry in the magnitudes of the dihedral angles.

(39) Saunders, M. *J. Am. Chem. Soc.* **1987**, *109*, 3150.

(40) Allinger, N. L. *J. Am. Chem. Soc.* **1977**, *99*, 8127.

(41) Burkert, U.; Allinger, N. L. *Molecular Mechanics*; American Chemical Society: Washington, DC, 1982.

(42) Damewood, J. R., Jr.; Anderson, W. P.; Urban, J. J. *J. Comput. Chem.* **1988**, *9*, 111.

(43) Uiterwijk, J. W. H. M.; Harkema, S.; Feil, D. *J. Chem. Soc., Perkin Trans. 2* **1987**, 721.

(44) Seidl, E. T.; Schaefer, H. F., III. *J. Phys. Chem.* **1991**, *95*, 3589.

(45) Wolf, R. E., Jr.; Hartman, J. R.; Storey, J. M. E.; Foxman, B. M.; Cooper, S. R. *J. Am. Chem. Soc.* **1987**, *109*, 4328.

(46) Tsuzuki, S.; Uchimaru, T.; Tanabe, K.; Hirano, T. *J. Phys. Chem.* **1993**, *97*, 1346.

(47) Maverick, E.; Seiler, P.; Schweizer, W. B.; Dunitz, J. D. *Acta Crystallogr.* **1980**, *B36*, 615.

(48) Scheiner, S. In *Annual Review of Physical Chemistry*; Strauss, H. L., Ed.; Annual Reviews Inc.: Palo Alto, CA, 1994; Vol. 45, p 23.

(49) The frequency of the calculated C−H vibration in CHF_3 at the 6-31G** level increases by 49 cm^{-1} upon H-bond formation with dimethyl ether. It is unclear whether the calculated frequency elevation is a real effect or whether it is an artifact resulting from the use of 6-31G** wave functions, the lack of inclusion of electron correlation, and/or basis set superposition error.

(50) Bottcher, C. J. F. *Theory of Electronic Polarization*, 2nd ed.; Elsevier: Amsterdam, 1973; Vol. 1, p 1486.

(51) Onsager, L. J. *J. Am. Chem. Soc.* **1936**, *58*, 1486.

(52) Karelson, M. M.; Zerner, M. C. *J. Phys. Chem.* **1992**, *96*, 6949.

(53) Using the standard scaling factor of 0.89 for frequencies, the zero-point energies are 124.77 and 124.95 kcal/mol, respectively, for the $[144]^0$ and $[225]^{100}$ conformations (Table 4). The entropy is 87.41 cal/mol K for $[144]^0$ and 85.28 cal/mol K for $[225]^{100}$.

(54) Sun, Y.; Kollman, P. A. *J. Comput. Chem.* **1992**, *13*, 33.

(55) Thompson, M. A. *J. Phys. Chem.* **1995**, *99*, 4794.

(56) No cutoffs were used in the AMBER calculations. The van der Waals 1−4 interaction factor was set at 0.50.

(57) Bayly, C. I.; Cieplak, P.; Cornell, W. D.; Kollman, P. A. *J. Phys. Chem.* **1993**, *97*, 10269.