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Theoretical Conformational Analysis of 1,3-Dimethoxypropane and 14-Crown-4: Importance of Stabilizing Intramolecular Interactions

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Results of the theoretical conformational analysis of 14-crown-4 are presented. Conformational analysis was performed using molecular mechanics (MM3) and using two conformational search techniques. The lowest energy minima obtained are submitted to HF/6-31G** calculations, and further optimized. Results are discussed with emphasis on the importance of intramolecular interactions, and the energetic order of conformations is explained on the basis of findings for 1,2-dimethoxyethane and 1,3-dimethoxypropane.

Introduction

Crown ethers are very well-known agents for selective complexation of metal ions. As a consequence, since their discovery by Pedersen et al.[1] macrocyclic chemistry has become a major topic in chemical research over the past decades.[2] A large number of applications has been reported, and large lists of equilibrium constants for the formation of complexes between macrocyclic ligands and metal ions have been compiled.[3]

Despite the large interest in the applications of crown ethers and in their complexes, less research has focused on the conformational properties of the free macrocycle. These properties are certainly of fundamental interest, since they are likely to influence the characteristics of the complexation (e.g., preorganization). They are also interesting by themselves because macrocycles tend to exhibit some striking features influencing the energetic order of different conformations, e.g., 1,5 C−H···O interactions[4,5] and intramolecular electrostatic interactions.[6]

This work aims at further investigating the properties of macrocyclic crown ethers by conducting conformational searches using molecular mechanics and by performing an ab initio study of the lowest energy minima using polarized basis sets. Emphasis is placed on understanding the phenomena explaining the energetic ordering of conformations of crown ethers. To that end, 1,3-dimethoxypropane (DMP) and related molecules are studied as well.

Computational Methods

Macrocycles are quite tempting molecules for molecular modeling, especially for ab initio studies. The molecules are not only fairly large, they also exhibit very large numbers of energetically low lying minima. Even using the most modern workstations, a convergent conformational search using ab initio calculations is computationally too demanding. A method which allows one to explore the potential energy hypersurface efficiently, yielding qualitatively good geometries is Molecular Mechanics. In this work the MM3 force field[7] is used in the MM3(94) and MM3(96) implementations.[8] MM3 is used to locate as many minimum energy conformations as possible, after which the lowest lying minima can be further optimized on the Hartree−Fock level.

Conformational searching of the potential energy hypersurface using MM3 was performed using two different schemes. The first method is a systematic method. A **Z**-matrix for all ring atoms is constructed, with the dihedral angles as variables. The variables are developed in steps of 120°, starting from −60°. For each combination of the dihedral angles, and using standard values for the bond lengths and bond angles, we checked if the distance between the first atom in the **Z**-matrix and the last atom is smaller than 1.5 times the standard value for a bond of that type. If this distance is smaller than the criterion mentioned, we consider the geometry to correspond to a cyclic structure. This geometry is then submitted to MM3 optimization of the molecular geometry. Structures for which the criterion for a cyclic structure is not met are discarded. The criterion of 1.5 times the standard value for a C−O bond length to check whether the molecule has a cyclic structure was found to be a good compromise between possibly overlooking too many structures which might yield a cyclic structure when they are optimized using MM3, and considering too many, which makes the problem computationally too demanding. If, after the cyclic structure has been optimized, a minimum energy geometry is found, the atomic coordinates and steric energy are stored in a structure library.

One of the more important drawbacks of such a systematic method is of course the explosion of the number of combinations that occurs when smaller step sizes are used. The systematic search by itself is not convergent. Convergence or the lack of it is judged by considering the number of times the lowest minima are found. If among the lowest energy minima there are minima which were found only once, this indicates that the search probably has not converged. Since the systematic search did not converge, and since the quality of a systematic scan depends quite heavily on the step size used, we supplemented our list of minima with the minima obtained using the stochastic method by Saunders.[9] This method as implemented in the MM3 program optimizes one geometry of the molecule, stores this structure, and then randomly kicks the atoms. This new structure is then again optimized, yielding a new or possibly previously

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located stationary point, after which this new stationary point is kicked. The MM3 program automatically stores all stationary points found, together with the steric energy and atomic coordinates for each point, and the number of times it was found. The number of kick-optimization steps used in this work was limited to 200, with a maximum displacement of the atoms of 2 Å. Starting from the lowest energy minimum found using the systematic method, a first stochastic procedure was carried out. At each stage in the conformational searching a list of minima is generated from the combined systematic search and the stochastic searches. We then checked the number of times every minimum with relative energy below 10 kcal/mol above the global minimum was found. The lowest such minimum which was found only once is then used to initiate a new stochastic search. Conformational searching was considered converged if all minima with relative energy below 10 kcal/mol were found at least twice, and a new stochastic search did not yield any new minima with relative energy below 10 kcal/mol. Stochastic searches were applied previously by Hay et al.,[10] and by the present authors for different macrocyclic molecules.[4,6] The reason we applied a combination of stochastic and the systematic search is to cover as much as possible of the molecular PES by furnishing the stochastic searches with different starting minimum energy geometries.

Ab initio calculations were performed using the GAMESS[11] and BRABO[12] ab initio programs. These were compiled on a set of three IBM RS/6000 machines working in parallel using TCGMSG[13] for GAMESS and PVM[14] for BRABO. Hartree−Fock level calculations were carried out using different basis sets, each on geometries fully optimized using that same basis set. Basis set primitive exponents and coefficients were taken directly from the built-in values of GAMESS.

The BRABO program was used for the geometry optimizations. GAMESS was used for calculations of natural population charges with the NBO 4.0 package[15] linked to it. Gaussian94[16] was used for the calculation of normal modes and tighter optimizations of molecular geometry.

The BRABO program is especially useful for calculations involving a high number of basis functions, since it includes the MIA approach. This approach is a combination of Direct SCF[17] and the multiplicative integral approximation.[18] The result of an SCF calculation using the MIA approach is systematically of equal quality as a classic SCF calculation, whereas the speed of a MIA-SCF calculation is much higher than that of a classic calculation.

Results and Discussion

1. 1,3-dimethoxypropane and Intramolecular C−H···O Interactions. First 1,3-dimethoxypropane (DMP) will be studied, since findings for this molecule help us understand the conformational properties of 14-crown-4. The conformational properties of the ethylene bridges in crown ethers may be understood on the basis 1,2-dimethoxyethane (DME). DME and 12-crown-4 were studied previously using the same methods as the ones used here.[4] We found that the ethylene bridges exhibit tGt structures in the COCCOC atom sequence, and that DME and 12-crown-4 both exhibit intramolecular C−H···O interactions.

Conformational analysis of DMP was performed previously by Smith et al.[19] at relatively high levels of theory. The need for a new conformational analysis in this work is due to the need for a deeper study of C−H···O interactions within the molecule, and the fact that Smith et al. have found a smaller number of minima compared to our work. Smith et al. have considered only a 1,6 C−H···O interaction in one conformation, identifying the interaction on the basis of interatomic distances between the H and O atoms.

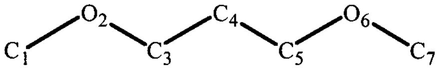

Figure 1. Atom numbering of 1,3-dimethoxypropane. Hydrogen atoms are not displayed, but are numbered consecutively from 8 to 19, starting with H8, H9, and H10 bound to C1.

TABLE 1: Relative Energies (in kcal/mol) for 1,3-Dimethoxypropane for All Minima Located at the HF/6-31G Level**

conformer	relative energy	conformer	relative energy
tGGt	0.00	gGG′t	3.96
tTGt	0.63	g′TGg	4.00
tTTt	1.63	gGGg	4.00
gGGt	1.90	gTGg	4.07
tTGg	2.17	tGG′t	4.20
gTGt	2.21	gTTg	4.74
g′TGt	2.50	gTTg′	5.01
gTTt	3.19	gGG′g′	7.01

It was found previously that 9-crown-3,[20] 12-crown-4,[4] and 18-crown-6[5] exhibit 1,5 C−H···O interactions within the molecule. These interactions may help stabilize certain conformations of these macrocycles. 1,5 C−H···O interactions may also help stabilize the structures of the ethylene bridges in 14-crown-4. In 14-crown-4 we find two ethylene type bridges and two propylene type bridges between two oxygen atoms in the macrocyclic ring. As will be discussed below, the propylene type bridges exhibit a preference for G or G′ OCCC arrangements. To understand the reason for this, we performed conformational analysis of DMP, using one systematic search, complemented with stochastic searching, both using the MM3 force field. The resulting minima were further optimized using HF/6-31G** calculations. Vibrational analysis was performed to ensure that all structures correspond to minima.

Table 1 shows that the lowest energy minimum is the tGGt structure, followed by the tGTt and tTTt structures (in the aBCd nomenclature of conformations, a refers to the dihedral angle C1−O2−C3−C4, B to O2−C3−C4−C5, C to C3−C4−C5−O6, and d to C4−C5−O6−C7, see Figure 1 for atom numbering. T and t indicate dihedral angles near 180°, g and G angles near 60°, and g′ and G′ indicate angles near −60°). The energetic order of the different minima is clearly influenced by a number of preferential orientations of the dihedral angles. For a given x and y, the xGGy structures are clearly the lowest in energy, followed by xTG(′)y orientations. Third, we find xTTy structures, followed by higher energy xGG′y structures. Concerning the COCC dihedral angles, we find that there is a clear preference for t orientations. The energetic order of all minima can largely be explained on the basis of these preferences with a higher weight for the preferences in OCCC dihedral angles.

The preference for trans COCC arrangements is reminiscent of that in DME,[4] and is due to unfavorable steric interactions in gauche COCC arrangements. In the case of 1,3-propanediol, the preference for gauche OCCC arrangements could be explained on the basis of the gauche effect, and intramolecular hydrogen bonds between the two alcohol groups.[21] These are "classical" hydrogen bonds of the type O−H···O. Such hydrogen bonds cannot occur in DMP. On the other hand, DMP may exhibit intramolecular C−H···O interactions. These interactions are sometimes considered hydrogen bonds as well, but do show some different features than the more classical hydrogen bonds. Gu et al.[22] have shown that they may be called hydrogen bonds, and have outlined some characteristic features of these interactions. In what follows, we will investigate the presence of the C−H···O hydrogen bonds in DMP and will investigate to what extent they govern the energetic order of minima.

In DME we found 1,5 C−H···O interactions.[4] Such interactions are absent in DMP. On the other hand, 1,6 C−H···O interactions may be present in DMP. The interatomic distances in such an interaction however are expected to be too large for most conformations. Only in the gGG′t structure such an interaction could occur. The H···O distance was found to be 2.71 Å, which is very similar to the value found by Smith et al.[19] This conformer has a quite high relative energy, and none of the other conformations exhibit such an interaction. 1,6 C−H···O interactions are expected to play only a very minor role. Beside 1,6 C−H···O interactions, no other C−H···O hydrogen bonds are expected for DMP. Shorter range C−H···O interactions are unlikely due to the very unfavorable C−H···O angles. This is, in the first instance, also the case for 1,4 C−H···O interactions.

The gauche effect as a stabilizing effect for gauche structures is often identified through observed differences in energy components for different conformations. This effect can usually be identified through the lower one-electron energies of gauche rotamers than those of trans rotamers, whereby the more negative one electron energy is not compensated by the accompanying increase of two electron energy and nuclear repulsion energy.[23] In the present molecule we find that, for the tXYt structures (which are the lowest energy structures), the one-electron energies are lowest for tGGt (nucleus−electron potential energy = −1475.23762 hartree), followed by the tTGt and tTTt structures, respectively (nucleus−electron potential energies respectively are −1460.86164 and −1449.02470 hartree). These differences are not fully compensated by the differences in two electron energy and nuclear repulsion energy: hence, the relative energies of the three conformers. It should be noted that in most occasions where the gauche effect is mentioned, one considers XCCY atom sequences, where X and Y are both electronegative atoms, carrying free electron pairs.[23] This is not the case in the present molecule. On the other hand the present observations for the one-electron energies and other components of the total energy are quite similar to what is found in the “classical” Gauche-effect, warranting further investigation. Given the fact that C−H···O hydrogen bonds are often mentioned as stabilizing in crown ethers, and given the fact that such interaction was not directly found for DMP (especially in the propylene bridge structures similar to those occurring in 14-crown-4), we investigated what effect may cause the energetic order of the tXYt structures.

We considered several molecular properties in the tXYt structures, as well as their variation as a function of the dihedral angles X and Y in these structures. We found that when the tTTt structure is converted to the tTGt structure by stepwise development of the dihedral angle, the energy grows more negative. When further varying dihedral angles in a stepwise fashion, we again find a lowering of the energy when moving from the tTGt structure to the tGGt minimum. At each step in these analyses, all geometry parameters are optimized, excluding the OCCC dihedral angles. Our calculations suggest that 1,4 C−H···O interactions may play an important role. It should be noted that we do not wish to categorize these interactions immediately as hydrogen bonds. Gu et al.[22] have shown that C−H···O hydrogen bonds do exhibit a greater tolerance of the C−H···O interaction angles as compared to classical hydrogen bonds, but still the angles in the C−H···O interactions in e.g. the tGGt structure are very far from ideal (100° vs 180°). As shown in Figure 2, a C−H bond is in fact a dipole, and an electrostatic interaction may occur between a relatively negatively charged oxygen atom, and this dipole. Ideally the C−H···O dihedral angle should be 180°. In the present situation, such a value cannot be obtained. We do find some features which indicate that this electrostatic interaction may be important in the stabilization of the gauche rotamers. We will first present purely geometrical indications of the existence of this kind of interaction, followed by observations for the NPA charges and eventually by studying the effect of atomic substitutions. The interaction such as that in Figure 2 cannot occur in the tTTt structure. When an OCCC dihedral angle in tTTt is varied to eventually obtain the tTGt structure, such an interaction grows. We examined how the energy varies with dihedral angle when all geometric parameters are optimized, except the stepwise-developed dihedral angle(s), and all other parameters in which the C, H, and O atoms from the possible C−H···O interaction are involved. We could not fully reproduce the observed difference in energy between the tTTt and tTGt structures. When allowing all parameters to relax during the stepwise developing of the dihedral angle, we found that the energy lowers more with the lowering of the OCCC dihedral angle from T to G. Another observation is that the C−H distance grows smaller when going from tTTt to tTGt. This in effect makes the C−H···O angle larger, strengthening the interaction. As shown in Figure 3, of all C−H bonds in similar chemical surrounding (C−H bonds contained in the C3 and C5 methylene groups, see Figure 1), those that could be involved in the C−H···O interaction, are (among) the shortest. The possibility of the C−H bond being involved in a C−H···O interaction is assessed by calculating the H···O interatomic distance. If this distance is lower than the sum of van der Waals radii, we consider it possible that the C−H bond is involved in a 1,4 C−H···O interaction. In the tTTt structure the four C−H bonds are equally long, namely, 1.0919 Å. In the tGGt structure, two of these are reduced to 1.0908 Å. The two C−H bonds that may be involved in the C−H···O interaction are 1.0877 Å long. In the tTGt structure, values of three such bond lengths are 1.0920, 1.0902, and 1.0923 Å. The C−H bond in the C−H···O interaction is 1.0873 Å. These effects are rather small, but we do find that C−H bonds which may be involved in a charge−dipole interaction, are almost always shorter than the other, similar C−H bonds in the structure. To show that these features are not a numerical coincidence due to the numerical convergence criteria used to consider a structure optimized, we reoptimized the structures to the minimum energy structure under more strict optimization limits (VeryTight optimization criteria in Gaussian94). The observed differences remained very similar to the ones described above.

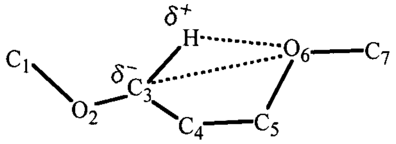

Figure 2. Qualitative representation of a 1,4 C−H···O interaction.

Following other observations were made: the charge on the hydrogen atom grows with lowering of the dihedral angle from tTTt to tGTt. The hydrogen NPA charge increases from 0.177 to 0.195, which is a relevant change. Charges on the carbon and oxygen atoms change only a few thousands. We believe this amount is too small to allow any decisive conclusion. On the other hand, changes of 0.001 NPA charge units have been considered significant in 18-crown-6.[5] Although changes are small in the present molecule, they do tend to point in the

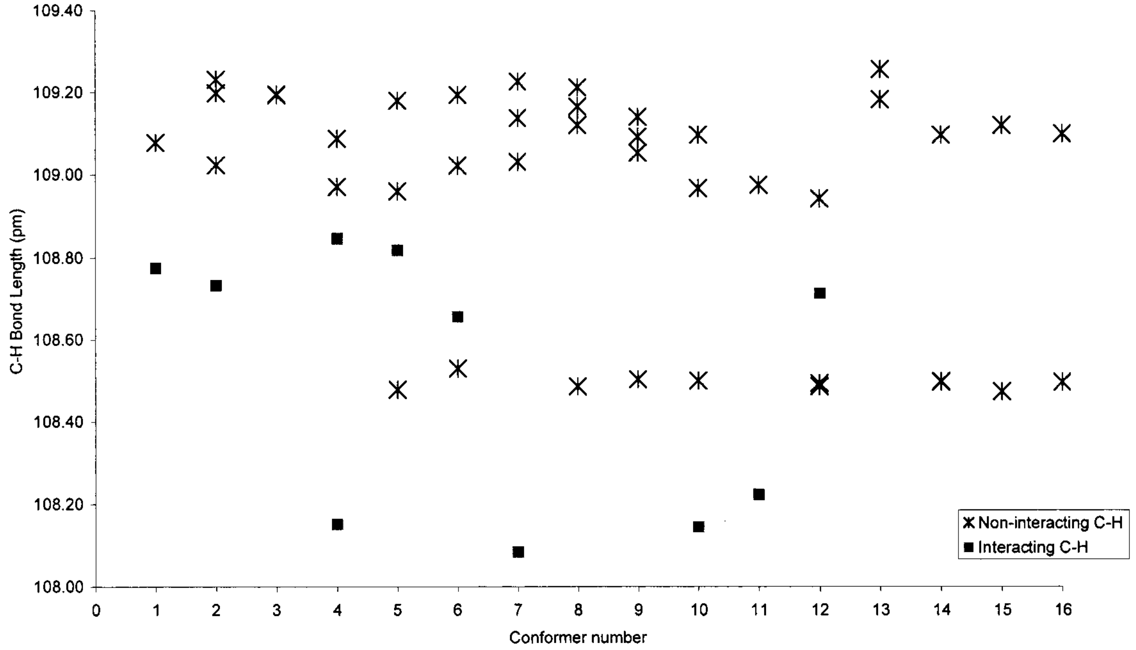

Figure 3. $C-H$ bond lengths for C3 and C5 methylene groups (see Figure 1). Illustration of the shorter bond lengths when H is possibly involved in a 1,4 $C-H\cdots O$ interaction. Because of symmetry, some data points coincide and are not separately visible in the plot. The conformer number refers to Table 1.

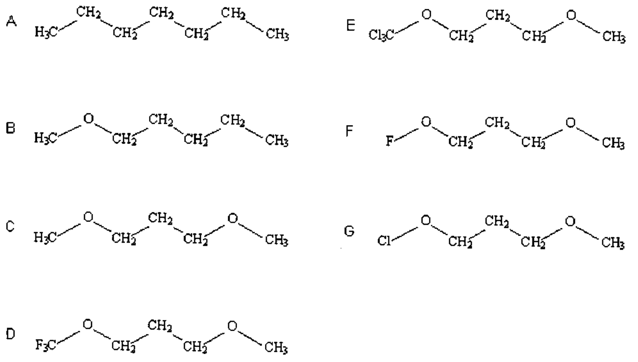

Figure 4. Molecules studied to investigate the effect of atomic substitution on the presence and strength of 1,4 $C-H\cdots O$ interactions.

expected direction, with C growing more negative by 0.002 as well as the oxygen atom when the $C-H\cdots O$ interaction produces.

The observations described above point in the direction of effective 1,4 $C-H\cdots O$ interactions. Although the aim of this work is mainly to investigate the conformational properties of crown ethers, we have performed studies on a series of molecules related to DMP, but where some atoms have been substituted. We consider the molecules shown in Figure 4. When the hydrogen atom is involved in the $C-H\cdots O$ interaction, its NPA charge increases by 0.02. As we have shown, only smaller differences in NPA charges on C and O have been found. Some of the increase of positive charge is dissipated in the methoxy groups. Our hypothesis aimed at providing further indications for a $C-H\cdots O$ interaction, is that when the methoxy groups are being replaced by other groups, which can better or less well dissipate the charge excess, this should manifest itself in the strength of the $C-H\cdots O$ interaction, which in turn influences the relative energies of the conformers. For all molecules we have studied the influence of atom substitution on the energy difference between the tTTt, tTGt, tGTg and tGGt structures. If $C-H\cdots O$ interactions are important, we expect the following trends:

TABLE 2: Relative Energies (in kcal/mol) for Different Conformations of All Molecules Depicted in Figure 4: Energies Given Relative to the tTTt Structure Calculated at the HF/6-31G Level**

	tTTt	tTGt	tGTt	tGGt
A	0.00	1.04	1.04	1.99
B	0.00	1.07	−0.16	0.76
C	0.00	−1.00	−1.00	−1.64
D	0.00	−1.52	−0.89	−2.06
E	0.00	−1.55	−0.93	−2.10
F	0.00	−1.27	−0.74	−1.60
G	0.00	−1.33	−0.92	−1.83

•Structures for which the charge can be better dissipated in the groups bound to the acceptor CH_2 group should show more negative energy differences tTGt-tTTt compared to DMP. Less well dissipating groups should show the opposite trend.

•When the substituted group is bound to the donor O atom, the energy difference tGTt-tTTt should grow less negative.

The idea behind this is that when more electronegative atoms are near the accepting H atom, the charge can be better dissipated over the group attached to the accepting methylene group, and the tTGt-tTTt energy difference should grow more negative. N-heptane and DMP are used as references. Consistent with steric considerations, for *n*-heptane the tTTt structure is the global minimum, whereas the tGGt structure has the highest energy. The better the excess charge can be accommodated, the more negative the tTGt-tTTt energy difference should be. Table 2 shows that the order is (using the abbreviations from Figure 4):

$$E < D < G < F < C \ll A$$

This is consistent with the more diffuse nature of Cl vs F, and the fact that an OCX_3 group is better at catering the charge than a single atom. The observed order of tTGt−tTTt structures agrees with the hypothesis.

Considering the tGTt structures (where the substitution occurs near the donating O atom), we find that the trend also agrees with the hypothesis. The differences are less outspoken, because

TABLE 3: MM3 Steric Energy (in kcal/mol) and Relative Energies (MM3 RE, in kcal/mol) of the 15 Lowest Energy Minima Located Using MM3 Conformational Searching for 14-Crown-4, Together with Description of the Molecular Geometry and Symmetry Point Group.

conformation				steric energy	MM3 RE	symmetry
0− −0	0+−	0− −0	0+−	19.8137	0.00	C_2
0+−0	0+0	0−+0	0−0	20.0744	0.26	C_{2h}
0++0	++0	0− −0	− −0	20.5968	0.78	C_{I}
0− −0	0++	0++0	++0	20.8932	1.08	C_2
0+−0	0++	0++0	0−0	21.3492	1.54	C_1
00+0	++0	0− −0	0+−	22.0274	2.21	C_1
0− −0	−+0	++00	−+0	22.0448	2.23	C_1
0− −0	−+0	0−+0	++0	22.2292	2.42	C_1
0++0	0− −	0−+0	0−0	22.2292	2.42	C_1
0−+0	0−+	0++0	0− −	22.3108	2.50	C_1
0+−0	0+−	0− − −	0−0	22.3912	2.58	C_1
0− − −	0− −	0− −0	0+−	22.4572	2.64	C_1
0−+0	0−+	00− −	0−0	22.5792	2.77	C_1
00+0	0− −	0− −0	0+−	22.6834	2.87	C_1
− −+0	0−0	− −+0	0−0	22.7563	2.94	C_2

the negative charge build-up on the oxygen atom when going from tTTt to tGTt is much less than the increase in charge on the accepting hydrogen atom.

The energy difference for the tGGt structures vs the tTTt structures for each molecule also agrees with the hypothesis of the existence of the 1,4 C−H···O interaction in DMP.

We believe that the observations described above, and which are not solely based on geometrical features, indicate the importance of a stabilizing 1,4 C−H···O interaction. This interaction stabilizes Gauche OCCC arrangements in DMP, and explains the energetic order of the tXYt structures in DMP.

2. 14-Crown-4. The first step was locating different minima, especially those with a low relative energy. Contrary to the case of 12-crown-4 where we found relatively fast convergence as a function of the number of stochastic searches, conformational searching was found very time-consuming for 14-crown-4. Many stochastic searches yielded a lot of stationary points which were found only once. To obtain a sufficiently high level of convergence the number of stochastic searches had to be increased quite strongly. Starting from the lowest energy minimum found using the systematic search, a first stochastic search was performed. The list of minima obtained during the latter search was combined with the list obtained from the systematic search, and the lowest energy minimum found only once was used to initiate a new stochastic search. Indicative of the difficulty of conformational searching for 14-crown-4 is the fact that the eventual global minimum was found for the first time only in the sixth stochastic search, whereas for most other macrocycles studied (12-crown-4, 12-aneN4, and 14-aneN4[4,6]) the global minimum was found in the earliest stages of the stochastic searches. In total we conducted 1 systematic search and 99 stochastic searches. Another problem was that the MM3 program often distinguished between two structures which are almost identical, but whose energy differed more than the threshold for identity in the MM3 program. We therefore checked the list of minima of the combined searches after every search, and programmed a routine to investigate similarity between conformers on the basis of intramolecular interatomic distance matrices. In total the 100 molecular mechanics searches yielded approximately 2000 minima. One hundred fourteen minima have a relative energy below 6 kcal/mol. The 15 lowest energy minima obtained using these searches are given in Table 3. In Table 3 we find the steric energy of each minimum together with its relative energy toward the global minimum and the symmetry of the structure. Atom numbering is shown in Figure 5. Conformation description is based on the codes introduced by Hay et al.[10] Each symbol in the code refers to the value of a certain dihedral angle. The first symbol describes the dihedral angle 14−1−2−3, the second 1−2−3−4, etc. A "+" means the dihedral angle has a value between 0° and 120°, a "−" signifies a value between 0° and −120°, and a "0" means a value between 120° and 240°. The groups of four symbols refer to the propylene bridges, the groups of three symbols to the ethylene bridges.

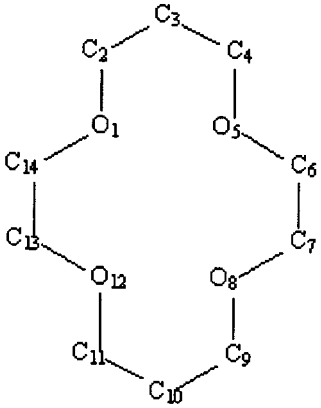

Figure 5. Atom numbering in 14-crown-4. Methylene hydrogen atoms are not shown.

TABLE 4: HF/6-31G Relative Energies (in kcal/mol), Together with Description of the Molecular Structure and Symmetry**

conformation				HF−RE	symmetry	MM3 position[a]
0− −0	0+−	0− −0	0+−	0.00	C_2	1
0++0	++0	0− −0	− −0	2.69	C_{i}	3
0− −0	0++	0++0	++0	3.07	C_2	4
0− −0	−+0	++00	−+0	3.16	C_1	7
00+0	++0	0− −0	0+−	4.14	C_1	6
0− − −	0− −	0− −0	0+−	4.17	C_1	12
00+0	0− −	0− −0	0+−	4.68	C_1	14
0+−0	0+−	0− − −	0−0	5.30	C_1	11
0+−0	0++	0++0	0−0	5.49	C_1	5
0− −0	−+0	0−+0	++0	5.90	C_1	8
0−+0	0−+	0++0	0− −	5.90	C_1	10
0++0	0− −	0−+0	0−0	5.93	C_1	9
0−+0	0−+	00− −	0−0	5.96	C_1	13
0+−0	0+0	0−+0	0−0	7.49	C_{2h}	2
− −+0	0−0	− −+0	0−0	8.97	C_2	15

[a] MM3 position refers to the rank of each minimum in the MM3-derived energetic order (see Table 3).

Table 3 shows that the global minimum of 14-crown-4 corresponds to a C_2 symmetrical structure. We clearly see that the OCCO dihedral angles adopt gauche values (see the 6th and 13th symbols). Concerning the OCCC dihedral angles we find that the two such angles in each propylene bridge are characterized by ++ or − − combinations. Trans:gauche combinations are rare. Trans:trans combinations are not present in the lowest energy minima. The lowest 15 MM3 minima were then fully optimized on the HF/6-31G** level. For the minima with HF/6-31G** energy under 5 kcal/mol, HF/6-31G** Hessian eigenvalues were calculated to ensure the located structures are minima. For the other optimizations, the MM3-optimized minima were used as starting structures for optimizations on the HF/6-31G** level, followed by evaluation of HF/3-21G geometry optimizations and calculation of the Hessian eigenvalues. The resulting structures were all found to be minima. The final step of Hessian evaluation on the HF/3-21G level was

TABLE 5: MM3 Optimized Molecular Geometries for the 5 Lowest Energy Minima of 14-crown-4

Nr.		O1	C2	C3	C4	O5	C6	C7	O8	C9	C10	C11	O12	C13	C14
1	r_e[a]	1.4132	1.5181	1.5183	1.4128	1.4121	1.5189	1.4163	1.4132	1.5181	1.5183	1.4128	1.4121	1.5189	1.4163
1	r_g	1.4212	1.5276	1.5278	1.4206	1.42	1.5284	1.4243	1.4212	1.5276	1.5278	1.4206	1.42	1.5284	1.4243
1	a	113.733	108.965	113.389	109.012	112.440	110.032	110.736	113.733	108.965	113.389	109.012	112.440	110.032	110.736
1	t	172.220	-63.217	-62.547	176.973	-177.156	72.222	-93.726	172.220	-63.217	-62.546	176.973	-177.156	72.222	-93.726
2	r_e	1.413	1.5182	1.5186	1.4131	1.4145	1.5183	1.4133	1.413	1.5182	1.5186	1.4131	1.4145	1.5183	1.4133
2	r_g	1.4209	1.5276	1.5281	1.4211	1.4224	1.5278	1.4212	1.4209	1.5276	1.5281	1.4211	1.4224	1.5278	1.4212
2	a	112.094	109.282	113.587	109.110	114.946	112.640	109.309	112.094	109.282	113.587	109.110	114.946	112.640	109.309
2	t	-175.719	57.228	56.896	176.982	66.682	60.309	-171.941	175.719	-57.228	-56.896	-176.982	-66.682	-60.309	171.941
3	r_e	1.4126	1.5188	1.5188	1.4126	1.4134	1.5181	1.4154	1.4138	1.5184	1.5184	1.4138	1.4154	1.5181	1.4134
3	r_g	1.4204	1.5283	1.5283	1.4204	1.4213	1.5275	1.4233	1.4217	1.5279	1.5279	1.4217	1.4233	1.5275	1.4213
3	a	112.252	109.267	113.544	109.267	112.252	108.996	112.106	114.560	109.154	113.788	109.154	114.561	112.106	108.996
3	t	176.472	-51.416	-51.416	176.472	-166.677	63.007	72.221	177.338	62.187	62.187	177.338	72.220	63.007	-166.678
4	r_e	1.4117	1.5183	1.5187	1.4161	1.4138	1.5195	1.415	1.413	1.5189	1.5195	1.4124	1.4154	1.5227	1.4161
4	r_g	1.4195	1.5277	1.5281	1.4241	1.4217	1.529	1.423	1.4208	1.5284	1.529	1.4203	1.4234	1.5323	1.4241
4	a	112.975	109.055	114.179	109.110	114.465	111.723	110.311	114.067	111.675	112.529	109.156	113.893	111.319	110.010
4	t	178.837	-61.517	-61.102	-179.168	-88.542	77.097	-178.941	76.678	56.390	-169.682	168.828	-81.931	76.526	-170.020
5	r_e	1.4118	1.5189	1.5197	1.4126	1.4164	1.5202	1.4131	1.4159	1.5202	1.5175	1.4129	1.4162	1.5217	1.4129
5	r_g	1.4196	1.5284	1.5292	1.4205	1.4244	1.5297	1.421	1.4239	1.5297	1.5269	1.4208	1.4242	1.5313	1.4208
5	a	114.327	109.818	111.500	108.294	114.926	110.572	109.180	112.111	109.786	114.468	109.473	112.770	109.552	112.633
5	t	-175.599	-174.732	62.735	-152.116	79.581	62.533	-168.872	178.309	-56.589	-52.605	-175.738	-160.893	82.309	-62.051

[a] r_e values are calculated from r_g values through weighing of the molecular vibrations in the MM3 force field.

introduced due to the large cpu-times necessary for evaluation of the Hessian on the HF/6-31G** level. One might wonder why this step was not taken as an intermediate step, between MM3 and HF/6-31G** levels of calculation. The reason is that we have previously shown that use of small basis sets such as 3-21G can lead to the loss of minima in the case of macrocyclic molecules.[6] For the present molecule we also found that some HF/3-21G optimizations starting from a specific MM3 minimum optimize to a previously located minimum, causing the loss of that minimum in the HF/6-31G** calculations. Straight submission of the MM3 minima to further optimization on the HF/6-31G** level did not cause any such effect. We feel that, in future research on macrocyclic compounds, one should take care in using intermediate smaller basis set calculations. The energetic ranking of the 15 minima on the HF/6-31G** level is given in Table 4.

Comparison of the MM3 and HF/6-31G** results shows that the global minimum remains the same on both levels of calculation. We do note that there are clear changes in the energetic order for the other minima. On the MM3 level there are several minima within 2 kcal/mol of the global minimum, whereas on the HF/6-31G** level the second lowest energy minimum has a relative energy of 2.69 kcal/mol. The rest of the energetic order is also clearly different between both levels of calculation. Especially the second lowest energy MM3 minimum is shifted upward in relative energy.

The agreement in structural features between the MM3 and HF/6-31G** levels of calculation was investigated for all 15 minima. Valence and dihedral angles were compared directly. Bond distances cannot be compared directly. The reason for this is that MM3 calculations are conducted in r_g bond lengths, whereas ab initio calculations are performed in r_e bond lengths. r_g bond lengths are longer than the r_e bond lengths since they include vibrational motion. Both types of bond lengths should not be compared directly. Since possible future experimental work will likely yield r_g distances, we will compare r_g bond lengths calculated on both levels of theory, where $r_{g,ai}$ values are deduced as described below. MM3 calculations give values of $r_{g,MM3}$ and $r_{e,MM3}$ (where $r_{e,MM3}$ values are easily calculated from $r_{g,MM3}$ values if optimizations are performed in a full matrix fashion; see the MM3 program manual.[8] A temperature of 298.15 K is used in the conversion). Ab initio calculations usually give $r_{e,ai}$ values (the subscript "ai" denotes "ab initio"). Ma et al.[24] have derived a simple, yet empirical formula to calculate $r_{e,ai}$-based values for $r_{g,ai}$, given $r_{g,MM3}$ and $r_{e,MM3}$ values. $r_{g,ai}$ values are calculated as follows:

$$r_{g,ai} = r_{e,ai} + (r_{g,MM3} - r_{e,MM3}) + C$$

The empirical nature of the formula lies in the use of an empirical constant C. This constant, which holds corrections for basis set truncation and insufficiently taking into account

TABLE 6: HF/6-31G* Optimized Geometries for the Five Lowest Energy Minima of 14-crown-4

Nr.		O1	C2	C3	C4	O5	C6	C7	O8	C9	C10	C11	O12	C13	C14
1	r_e	1.4051	1.5191	1.5190	1.4006	1.3947	1.5152	1.3972	1.4050	1.5191	1.5190	1.4006	1.3947	1.5152	1.3972
1	r_g[a]	1.4327	1.5227	1.5226	1.4280	1.4222	1.5188	1.4248	1.4326	1.5227	1.5226	1.4280	1.4222	1.5188	1.4248
1	a	116.343	108.469	113.630	109.163	114.593	110.105	112.766	116.341	108.472	113.635	109.167	114.591	110.115	112.778
1	t	171.939	-63.663	-63.504	177.312	-173.070	71.387	-94.149	171.998	-63.604	-63.455	177.303	-173.158	71.402	-94.057
2	r_e	1.3990	1.5191	1.5195	1.4001	1.3943	1.5186	1.3912	1.3990	1.5191	1.5195	1.4001	1.3943	1.5186	1.3912
2	r_g	1.4265	1.5226	1.5231	1.4277	1.4218	1.5222	1.4187	1.4265	1.5226	1.5231	1.4277	1.4218	1.5222	1.4187
2	a	115.024	108.889	113.153	108.747	116.612	114.848	109.526	115.030	108.885	113.152	108.744	116.612	114.845	109.526
2	t	-174.862	58.678	60.523	173.361	64.037	59.039	-164.710	174.914	-58.697	-60.604	-173.410	-64.068	-59.025	164.842
3	r_e	1.3987	1.5191	1.5191	1.3987	1.3928	1.5179	1.3952	1.4004	1.5193	1.5193	1.4004	1.3952	1.5179	1.3928
3	r_g	1.4261	1.5227	1.5227	1.4261	1.4203	1.5214	1.4227	1.4279	1.5229	1.5229	1.4279	1.4227	1.5214	1.4203
3	a	114.947	109.154	113.184	109.154	114.950	109.555	114.370	116.451	108.722	113.352	108.723	116.450	114.366	109.553
3	t	176.678	-56.064	-56.031	176.699	-157.925	63.385	71.869	176.206	61.750	61.704	176.256	71.927	63.398	-157.951
4	r_e	1.4002	1.5197	1.5199	1.4046	1.3974	1.5156	1.3982	1.4047	1.5254	1.5197	1.4054	1.3970	1.5180	1.3974
4	r_g	1.4276	1.5232	1.5234	1.4322	1.4249	1.5192	1.4258	1.4321	1.5290	1.5233	1.4329	1.4246	1.5217	1.4250
4	a	115.029	109.184	114.347	108.613	116.700	113.331	110.007	115.830	112.843	112.070	108.459	116.163	113.030	110.222
4	t	-177.421	-61.659	-62.280	-177.479	-93.615	73.877	-173.846	82.699	60.476	-169.299	162.011	-84.881	75.644	-166.630
5	r_e	1.4030	1.5192	1.5212	1.4032	1.3952	1.5180	1.3937	1.3992	1.5198	1.5202	1.4000	1.4010	1.5213	1.3969
5	r_g	1.4304	1.5228	1.5248	1.4307	1.4228	1.5216	1.4212	1.4268	1.5234	1.5237	1.4275	1.4286	1.5250	1.4244
5	a	116.084	108.947	111.157	108.498	117.489	112.974	109.375	114.635	109.542	113.988	109.274	115.224	110.407	114.060
5	t	177.600	-170.477	65.248	-149.068	81.766	63.367	-167.013	178.304	-57.985	-56.228	-178.138	-154.050	84.739	-68.800

[a] r_g values are calculated from $r_{e,ai}$ values as described in the text.

effects of electron correlation, is derived from the comparison of experimental $r_{g,exp}$ values and $[r_{e,ai} + (r_{g,MM3} - r_{e,MM3})]$ values for a relatively large set of small molecules (representing different types of bonds), where $r_{e,ai}$ values are obtained at the MP2/6-31G* level. In the present work, HF/6-31G** calculations are used. We have added to C a further correction accounting for deficiencies of Hartree−Fock calculations compared to MP2 calculations, and differences in basis set truncations. This correction for C was obtained from comparison of the $r_{e,ai}$ MP2/6-31G* values with our HF/6-31G** $r_{e,ai}$ values for the same set of molecules as used by Ma et al.[24] Tables 5 and 6 give r_e values for the five lowest ab initio minima, optimized on the MM3 and HF/6-31G** levels of calculation, respectively. They also give $r_{g,MM3}$ and calculated r_g values together with valence angles and dihedral angles. From these tables we see that for C−C bonds, the agreement in r_e is good, whereas it is much less for O−C bond lengths. By using the empirical formula, we see that there is a very good agreement for both bond lengths in r_g, with differences on average of less than 0.007 Å. We find a very good agreement for valence angles and dihedral angles between the MM3 and HF/6-31G** values, with differences of only 1.2° on average for valence angles, and 2.5° on average for dihedral angles.

A major point of interest is to examine if the energetic order of minima may be explained in terms of intramolecular interactions, or maybe other effects which govern it. Structural analysis of the propylene type bridges in 14-crown-4 reveals that there is a preference for 0xy0 conformations, indicating a preference for trans COCC dihedral angles. Concerning the OCCC angles, we find that the preferred conformation is a 0++0 or 0−−0 geometry, while 0+−0 and 00+0 similar conformations are less common in the lowest energy conformations. All this is in fine agreement with what is suggested on the basis of the conformational preferences of DMP. In DMP the global minimum was found to be tGGt (or in the Hay nomenclature 0++0, symmetry equivalent with 0− −0). Also in fine agreement is the fact that 00+0 combinations are energetically less favorable, and 0+−0 combinations are the least favorable. The conformational preference of the ethylene type bridges in 14-crown-4 (preference for 0+0 type combinations) is in good agreement with findings for 1,2-dimethoxyethane (DME).[4] It should be noted that the cyclic structure naturally prohibits the presence of some geometries for the ethylene and propylene bridges. Concerning the presence of the stabilizing C−H···O interactions, we find that NPA charges point to the existence of these stabilizing interactions as we described earlier for DME and 12-crown-4[4] and DMP (see above).

The geometry of free 14-crown-4 was studied experimentally by Groth et al.[25] Unfortunately, the published data contain errors, making a comparison with our calculated structure impossible. The Cambridge Structural Database[26] holds this same structure (TOXCTD file), but also mentions the presence of errors in the original coordinates, and does thus not hold useful geometrical information for 14-crown-4.

Conclusion

Using molecular mechanics and ab initio calculations, the lowest lying minima of 1,3-dimethoxypropane and 14-crown-4 have been located. Conformational searching using molecular mechanics was found to converge relatively slowly, indicating that care should be taken during conformational analysis for macrocycles, and maximum convergence sought. After thorough conformational searching, MM3 was found to give structures which agree well with the structures obtained after further optimization using HF/6-31G** calculations. Both the MM3 and ab initio calculations yield a C_2 symmetrical global minimum, but the ab initio calculations show a different energetic order for the rest of the minima.

The conformational analysis shows several clear conformational preferences in the macrocyclic structure. An in-depth study of the conformational properties of 1,3-dimethoxypropane revealed the existence and importance of stabilizing intramolecular interactions between an oxygen atom and a methylene hydrogen in a 1,4 C−H···O fashion in the propylene bridges. These bridges exhibit a geometry which agrees well with the structure of the global minimum of 1,3-dimethoxypropane.

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