Molecular Mechanics and ab Initio Conformational Analysis of 12-Membered and 14-Membered Tetrathia-Crown Ethers

Patrick Bultinck,*,† Annelies Huyghebaert,† Christian Van Alsenoy,‡ and Andre Goeminne†

Department of Inorganic and Physical Chemistry, Ghent University, Krijgslaan 281 (S-3), B-9000 Gent, Belgium, and Department of Chemistry, Universiteit Antwerpen, Universiteitsplein 1, B-2610 Antwerpen, Belgium

Received: June 18, 2001; In Final Form: October 12, 2001

Results of the theoretical conformational analysis using molecular mechanics and ab initio techniques for the tetrathia-crown ethers 1,4,7,10-tetrathiacyclododecane ([12]aneS$_4$) and 1,4,8,11-tetrathiacyclotetradecane ([14]aneS$_4$) are presented. MM3 was used for conformational searching using two schemes, and ab initio calculations with the 6-31G** basis set were carried out for the lowest energy minima. Importance of the quality of conformational searching is illustrated. 1,2-dithiomethoxyethane and 1,3-dithiomethoxypropane are studied to better understand conformational properties of the macrocyclic ligands.

Introduction

It is a well-known fact that macrocyclic ligands may exhibit remarkable selectivity toward complexation of metal ions. Since the discovery of crown ethers by Pedersen et al.,[1] macrocyclic chemistry and selective metal ion complexation have evolved into a major field of chemical research.[2] Large lists of kinetic and thermochemical data have been compiled for a large range of metal ions and ligands.[3] Another aspect of this research is the grounds for this selectivity. Hancock et al.[4] have summarized different factors which influence the complexation characteristics of different ligands toward different metal ions. Among these factors we find the role of the type of donor atom, the closure of a macrocyclic ring as compared to complexation with an acyclic polydentate ligand, the chelate ring-size effect, etc.

Hancock et al. succeeded in providing an explanation for many of these effects, mainly based on the calculation of changes of steric energy upon complexation. Such molecular mechanics calculations are however parameter-dependent and do not yield a wave function or electron density, thereby possibly leaving out a lot of chemistry. This paper is a further extension of our work on the conformational properties of macrocycles, differing in the type of donor atom and sizes of the chelate rings. We previously discussed 12-crown-4,[5] 14-crown-4,[6] [12]aneN$_4$,[7] and [14]aneN$_4$[7] and extend these studies with present results for [12]aneS$_4$ and [14]aneS$_4$. These conformational analyses are not solely important in our quantum chemical investigations of different stability determining effects in chelate complexes[8] but are also interesting by themselves, because these molecules tend to exhibit many types of intramolecular interactions, governing the energetic order of conformations.

Recently, and independently from our work, Hill et al.[9] published interesting results of a theoretical conformational analysis on 1,2-dithiomethoxyethane (DTME) and [12]aneS$_4$. We chose not to repeat their discussions but rather confront our findings with theirs and extend our knowledge by combining and confronting results. By comparison between their work and our work we can also investigate the sensitivity of ab initio findings on the quality of the molecular mechanics conformational searching. We further extend the study to include ligands with more separated sulfur atoms, most notably 1,3-dithiomethoxypropane (DTMP) and [14]aneS$_4$, and we discuss differences in conformational properties between oxygen bearing 12- and 14-membered macrocycles 12- and 14-membered azamacrocycles and the present molecules.

Computational Methods

The method used here is similar to that used in our previous studies on macrocycles[5−7] and is a combination of Monte Carlo (stochastic) analysis and a systematic search, both using molecular mechanics and a later ab initio study of all conformations with relative MM3 energies under 8 kcal/mol for [12]aneS$_4$ and the 36 lowest energy structures for [14]aneS$_4$.

Macrocycles 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. Ab initio calculations using only minimal basis sets are not a good choice, as we have shown earlier[7] and will again show in the results below. Another approach which allows us to explore the potential energy hypersurface efficiently, yielding qualitatively good geometries, is molecular mechanics. In this work, the MM3 force field[10] is used in the MM3(94) and MM3(96) implementations.[11] 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

---

* To whom correspondence should be addressed. Fax: 32/9/264.49.83. E-mail: Patrick.Bultinck@rug.ac.be.

† Ghent University.

‡ Universiteit Antwerpen.

10.1021/jp0122934 CCC: $20.00

that type. If this distance is smaller than the criterion mentioned, we consider the geometry to correspond to a cyclic structure. This ring geometry is then saturated with hydrogen atoms and 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−S 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 efficiently 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 (meaning minima with MM3 relative energy below 10 kcal/mol) there are minima which were found only once, this indicates that the search may not have converged. The necessity of convergence will be made clear in the results. Because the systematic search did not converge and because 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.[12] 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 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 each energy minimum with a relative energy under 5 kcal/mol found using the systematic method, we carried out stochastic searches. The MM3 program is hereby used only for the actual MM3 optimizations and stochastic runs. Generating structures in the systematic search approach; distributing previously located minima to stochastic searches; and processing, combining, and sorting of the data resulting from the several separate searches are handled outside the MM3 program using self-written programs and scripts. After each stage in conformational searching, a list of minima is generated from the combined systematic search and the completed 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 a user specified number of times (see below for details). A second requirement is that a new stochastic search should not yield any new minima with relative energy below 10 kcal/mol. Stochastic searches were applied previously by Hay et al.[13] and by the present authors for different macrocyclic molecules.[5−7] The reason we applied a combination of stochastic and systematic searching was to avoid the fact that our results and conclusions would depend on the starting structures used for conformational searching.

Ab initio calculations were performed using the GAMESS[14] and BRABO[15] ab initio programs. These were compiled on a set of three IBM RS/6000 machines working in parallel using TCGMSG[16] for GAMESS and PVM[17] 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[18] linked to it. Gaussian 94[19] 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, because it includes the MIA approach. This approach is a combination of direct SCF[20] and the multiplicative integral approximation.[21] 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.

All MP2 level calculations were performed as full MP2 calculations, rather than using the frozen core (FC) approximation.

Results and Discussion

1. 1,2-Dithiomethoxyethane and 1,3-Dithiomethoxypropane. Understanding the conformational properties of macrocycles, and differences between them, is greatly improved by a study of the smaller building blocks of macrocycles. To that end, we previously investigated 1,2-ethanedithiol[22] and 1,3-propanedithiol,[23] where we found that the gauche effect plays a (much) smaller role than in the oxygen-bearing analogues 1,2-ethanediol and 1,3-propanediol.[24] We did find that the gauche conformers in the sulfur bearing molecules exhibit a more negative one-electron energy than the trans rotamers, but this lower (negative) term is more than compensated for by the higher (positive) two-electron and nuclear repulsion energies in the gauche conformers compared to the trans conformers. These findings are directly relevant for the macrocycles, because they let us expect to find more trans XCCX and XCCC dihedral angles in the sulfur macrocycles (X = S) compared to 12-crown-4[5] and 14-crown-4[6] (X = O) and [12]aneN$_4$ and [14]aneN$_4$[7] (X = N). In order not to bias our results on the basis of our earlier studies, a study of 1,2-dithiomethoxyethane (DTME) and 1,3-dithiomethoxypropane (DTMP) was carried out. For both molecules, the SCCS, CSCC, and SCCC dihedral angles were developed systematically in a 30° grid, and the resulting structures were optimized on the HF/6-31G** level. For all stationary points identified at that level, Hessian eigenvalues are calculated to ensure that the structures correspond to minima. All structures were further optimized at the MP2(full)/6-31G** level. Results are given in Tables 1 and 2 for 1,2-dithiomethoxyethane and 1,3-dithiomethoxypropane, respectively. Results of single-point calculations on the MP2 level, using the Hartree−Fock geometries (MP2(full)/6-31G**//HF/6-31G**), are also presented.

In the case of 1,2-dimethoxyethane,[5] we previously found that the gauche effect plays a role in causing a low relative energy of the tGt structure. Another important finding was the possibility of an intramolecular 1,5 C−H···O interaction. Such an interaction has been shown to stabilize certain conformations in crown ethers.[5,6,25] On the basis of interatomic distances between the sulfur and hydrogen atom in a similar C−H···S interaction, we find that similar interactions in DTME are

TABLE 1: Minimum Energy Structures Located Using HF/6-31G and MP2/6-31G** Calculations for 1,2-Dithiomethoxyethane**[a]

conformation	HF RE	MP2//HF RE	MP2 RE
g′Tg	**0.00**	**0.00**	**0.00**
gTg	0.22	0.22	0.24
tTg	0.16	0.59	0.67
tTt	0.17	1.05	1.21
g′Gg	2.21	1.66	1.46
tGg	2.19	1.79	1.61
gGg	2.38	1.91	1.47
tGg′	2.08	1.93	1.88
g′Gg′	2.68	1.98	1.83
tGt	2.02	2.14	2.16

[a] HF RE, MP2//HF RE, and MP2 RE are relative energies in kcal/mol on the HF/6-31G**, MP2/6-31G**//HF/6-31G**, and MP2/6-31G**//MP2/6-31G** levels, respectively.

unlikely. C−H···S interaction distances are larger than the sum of van der Waals radii. Contrary to C−H···O interactions in crown ethers, we do not find an indication of C−H···S interactions in the hydrogen NPA charges either. From Table 1, we also see that there is a preference for trans SCCS arrangements, both on the Hartree−Fock and the MP2(full)/6-31G**//MP2(full)/6-31G** levels of theory. The two levels of theory indicate a different global minimum, but both indicate lower energies for the xTy geometries. No outspoken trend is found for conformational preferences in CSCC dihedral angles.

DTME was also studied by Hill et al.[9] They generated a potential energy curve for rotation about the SCCS dihedral angle, both for gauche CSCC and CCSC dihedral angles and one for trans CSCC and CCSC dihedral angles. The SCCS dihedral angle was developed in a grid, and for every value of this angle, the entire geometry (except the SCCS dihedral angle) is optimized. This way they obtained a potential energy curve for the gXg′ and tXt structures, where X denotes the SCCS dihedral angle. When going from HF/6-31+G* to the MP2(FC)/6-31+G*//MP2(FC)/6-31+G* level, the energy difference tTt−gTg′ increases from nearly zero to 1.1, stating a lower energy for gTg′. This is in fine agreement with our results obtained using HF/6-31G** and MP2(full)/6-31G**//MP2(full)/6-31G** calculations. From the curves they give, we also deduce that there is fine agreement between their HF/6-31+G* results and our HF/6-31G** results for the relative energies of the minima present in these curves (g′Xg and tXt structures, where X stands for G or T). We believe that gXg and tXg structures should be considered as well, because we find the gTg and tTg structures to have a low relative energy as well, even below that of tTt, both on the HF/6-31G** and MP2(full)/6-31G**//MP2(full)/6-31G** levels of theory.

For molecules such as macrocycles, MP2 level geometry optimizations are currently not yet routinely feasible. MP2 single-point calculations, on the other hand, are well within reach of modern workstations. It is therefore interesting to investigate for small model molecules to what extent results of MP2 calculations including geometry optimization at that level agree with the results obtained using MP2 single-point calculations on Hartree−Fock optimized geometries (in this case MP2(full)/6-31G**//MP2(full)/6-31G** versus MP2(full)/6-31G**//HF/6-31G**). The results given in Table 1 show that lack of geometry optimization, in this case, does not influence the energetic order and relative energies of the different minima. Especially for the lower energy minima, we see that the MP2(full)/6-31G**//HF/6-31G** results do not differ significantly from the MP2(full)/6-31G**//MP2(full)/6-31G** results.

Turning to 1,3-dithiomethoxypropane (DTMP), we find 19 different minimum energy geometries. Relative energies at the Hartree−Fock and MP2 levels of theory are given in Table 2. This reveals a Hartree−Fock level preference for structures with trans SCCC orientations. All four possible (symmetry-unique) minima with two trans SCCC dihedral angles are within the five lowest energy structures, with tTTt as the global minimum. Note the very compact grouping of 13 minima; these all have a relative energy below 1 kcal/mol. This compact grouping is maintained on the MP2 level of theory, but the preference for xTTy structures is no longer present. The global minimum is the gGGg structure.

We have previously studied 1,3-dimethoxypropane[6] and found that there is evidence for an intramolecular 1,4 C−H···O interaction, which stabilizes gauche OCCC conformations. The importance of this interaction was examined through study of geometrical features in different conformations of the molecule, through calculation of NPA atomic charges and their changes, and by study of the effect of substitution of the methoxy group by other functional groups such as $-CH_2CH_3$, $OCCl_3$, OCF_3, OF, and OCl. We found that the effect of these substitutions on the strength of the intramolecular interactions, and as such on the relative energies of different conformations, agrees with what is expected on the basis of chemical intuition. The Hartree−Fock energy ordering of minima, especially for the tXYt structures, suggests a minor role for 1,4 C−H···S interactions. The lowest energy (i.e., most negative total energy) is found for tTTt, followed by tTGt and tGGt. In tTTt, there are no possible C−H···S interactions, whereas one or two are possible in tTGt and tGGt, respectively. On the MP2(full)/6-31G**//MP2(full)/6-31G**level of calculation, we note an important change: the tGGt structure now has the most negative energy, followed by tTGt, and with least negative energy, tTTt. The MP2 treatment of electron correlation seems to induce a more important role for C−H···S interactions, but still, there are no large energetic separations between minima which may or may not exhibit C−H···S interactions.

TABLE 2: Minimum Energy Structures Located Using HF/6-31G and MP2/6-31G** Calculations for 1,3-Dithiomethoxypropane**[a]

conformer	HF RE	MP2//HF RE	MP2 RE	conformer	HF RE	MP2//HF RE	MP2 RE
gGGg	0.89	**0.00**	**0.00**	g′TGt	0.78	0.72	0.90
gTTg	0.18	0.05	0.22	tGGt	0.82	0.80	0.91
gTGg′	0.61	0.13	0.22	tGGg′	1.79	1.04	0.94
gTGg	0.69	0.21	0.29	tTGt	0.44	0.79	1.04
gGGt	0.84	0.38	0.42	tTTt	**0.00**	0.73	1.06
tTGg	0.31	0.26	0.42	g′TGg′	1.98	1.37	1.43
gTTg′	0.43	0.28	0.45	gTGt	2.11	1.35	1.56
gGGg′	1.83	0.72	0.60	tTGg′	1.76	1.54	1.67
gTTt	0.07	0.36	0.62	tGG′g′	4.42	3.47	3.40
gTGt	0.54	0.51	0.68				

[a] HF RE, MP2//HF RE, and MP2 RE are relative energies in kcal/mol on the HF/6-31G**, MP2/6-31G**//HF/6-31G** and MP2/6-31G**//MP2/6-31G** levels, respectively.

From these results, we conclude that 1,5 C−H···S interactions do not play a very important role in DTME and, therefore, will probably play only a minor role in the ethylene bridges of [12]aneS_4 and [14]aneS_4 (of course this hypothesis will be checked below). 1,4 C−H···S interactions become clear on the MP2 level for DTMP. A more important conclusion than C−H···S interactions is the observation that both molecules exhibit many minima within a small range of relative energies. We can therefore not even qualitatively predict any preferences for the conformations of the macrocycles (as we could for crown ethers), because the small preference for some minima compared to others may well be more than compensated by the higher suitability of somewhat higher energy minima for closing the macrocyclic ring. The cyclic nature of the macrocycles itself induces preferences for some dihedral angle combinations and may even prohibit occurrence of some combinations of skeletal dihedral angles.

We also performed MP2 single-point calculations, to see if the conclusions drawn for DTME are valid for DTMP as well. Table 2 shows that this is indeed the case. The relative energies do not differ very much. We do find that the influence on the energetic order is somewhat bigger, which is due to the compact grouping of the minima in DTMP. Minor differences in relative energies can cause a different ordering of the minima.

2. [12]aneS_4. As stated in the Introduction, the focus of the present discussion will be based on the comparison of our findings with those of Hill et al.[9] They recently studied several thiacrown ethers, also using a combination of molecular mechanics and ab initio calculations. We did, however, find a number of instances where our findings differ from theirs and will discuss possible grounds for these differences. The computational strategy used by Hill et al. is described in detail in their work and can be summarized as a stepwise methodology consisting of (1) high temperature molecular dynamics to maximally explore the potential energy hyperspace, (2) CVFF force field minimization of the structures obtained through the high-temperature sampling in step 1, (3) the submitting of the optimized structures to small to medium basis set RHF calculations, and (4) larger basis set Hartree−Fock calculations and MP2 single-point energy calculations (in some cases supplemented with geometry optimization at the MP2 level). This strategy resembles our approach, but there are a number of differences. In our experience, the CVFF force field is rather far from an optimal choice for a molecular mechanics study of macrocyclic compounds.[8] We found that the spread in relative energy can be quite different depending on the force field used and even of a different order of magnitude than that obtained from ab initio calculations. We found that this may bias the choice of structures to be submitted for further ab initio calculations. Hill et al. do also observe that relative energies are underestimated using CVFF but continue using this force field. In our approach, we have chosen MM3 and found it to yield structures which agree well with ab initio geometric parameters for crown ethers and tetra-aza-macrocycles.[5−8] Despite the fact that MM3 energetic orders are also different from ab initio energetic orders, we have found that when all geometries with a relative steric energy under 6−8 kcal/mol are submitted to larger basis set calculations we usually find that no higher steric energy structures enter the lower end of the ab initio energetic order when we randomly select some higher steric energy structures for further ab initio level geometry optimization. In some instances, the energetic order even remains quite similar between MM3 and ab initio levels of calculation. Concerning the convergence of the conformational analysis used by Hill et al. for the thiacrown ethers, we did not find the exact criteria used to consider their conformational searches converged. The computational procedure used by us was described in detail in the section on computational methods, described above. Specifically, for [12]aneS_4, we have chosen that each minimum with relative energy under 10 kcal/mol should be found at least five times, before concluding sufficient convergence of the conformational search. It is not possible to show that the conformational search was truly complete, but when submitting four extra searches starting from simply sketched structures in a chemical structure drawing program and randomly choosing a kick size in the range of [1,4] Å, no new minima were discovered. This leads us to believe we should have at least a fairly good idea of the lower steric energy end of the energetic order of minima. All five CVFF structures reported by Hill et al. were also found using our MM3 calculations. As expected, CVFF gives relevantly different relative energies. Not only is the scale different but also the energetic order of minima is different. In Table 3, both the MM3 and CVFF relative energies are given. Comparing both sets of data, we note that, for example, structures 4 and 6 reported by Hill et al. correspond to the 22nd and 20th lowest energy structures found using our approach (correspondence between their structures and ours was established on the basis of the skeletal dihedral angles reported by them, and found by us. For the eighth and the ninth structure, for which no structural data were given, we assessed correspondence on the basis of the molecular symmetry). This may indicate that their conformational search procedure has not converged to the same extent as ours or that, for these structures, CVFF gave a relative energy above 2.2 kcal/mol (the largest value for a minimum reported by Hill et al.), causing them to exclude these structures from further calculations. Table 3 also gives the conformer descriptions using the nomenclature by Hay et al.[13] and the symmetry of the structure. Each symbol in the Hay code refers to the value of a certain dihedral angle. The first symbol describes the dihedral angle 12−1−2−3, the second describes 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°. Atom numbering is shown in Figure 1.

Table 3 shows that the lowest energy structure corresponds to a D_4 symmetry, in agreement with the experiment. The Cambridge Structural Database[26] holds two experimental structures for free [12]aneS_4, both resembling the MM3 global minimum. The D_4 global minimum agrees with that located by Hill et al. Raithby et al.[27] performed MM2 calculations, but their use of the Dale nomenclature for the localized minima hampers the comparison with our findings. The Dale nomenclature is often the same for different conformers, but their [3333] structure is probably also the D_4 symmetrical structure (note: in the Dale geometry description, the MM3(11) structure is also [3333]; for a description of the Dale nomenclature, see Raithby et al.). [12]aneS_4 clearly exhibits a preference for trans oriented SCCS dihedral angles, in good agreement with previous results for ethane-1,2-dithiol[22] and 1,2-dithiomethoxyethane. We further find that the lowest energy minima exhibit many gauche CSCC dihedral angles. Gauche C_aSCC_b angles suffer a smaller steric energy penalty from H···H repulsion between hydrogen atoms on C_a and C_b because of the larger SC bond lengths compared to the close H···H contact in gauche COCC atom sequences in crown ethers.

All minima with relative MM3 energy below 8 kcal/mol were then submitted for further optimization on the HF/6-31G** level,

TABLE 3: Conformation (Based On HF/6-31G Structures), Symmetry, MM3 Relative Energy (MM3 RE in kcal/mol), and HF/6-31G** Relative Energy (HF RE in kcal/mol) for [12]aneS_4**[a]

conformation				symmetry	MM3 RE	HF RE	MM3 pos.	CVFF RE	HF/3-21G
+0+	+0+	+0+	+0+	D_4	**0.00**	**0.00**	1	**0.0**	**0.0**
+0+	−0−	+0+	+0+	C_1	3.16	2.38	3	1.0	2.2
−0−	−0−	−0−	+0+	C_2	2.94	2.38	2		
+0+	+0+	−0−	−0−	C_{2h}	3.52	2.70	4	2.2	2.6
−00	++−	−0−	−0−	C_1	4.05	3.86	5		
+−+	00−	−0−	−00	C_2	5.29	4.67	7		
+−−	−0−	−++	0+0	C_1	7.44	4.85	22	1.8	4.7
+0+	+0+	−++	0+−	C_1	7.42	5.36	21		
−0−	−0−	+−−	0−+	C_1	7.14	5.36	20	2.2	5.6
−−+	+0+	−0−	−++	C_s	7.58	5.43	23		5.3
00+	+0+	+−−	0−−	C_1	6.05	5.64	8		
+0+	−0−	+0+	−0−	S_4	5.28	5.64	6		8.7
−0−	−++	00−	+0+	C_1	6.08	5.79	9		
+−−	0−+	00−	+0+	C_1	6.26	6.15	12		
++0	+−+	00−	−0−	C_1	6.91	6.16	18		
++0	+−0	−−+	00−	C_1	6.71	6.44	15		
+0+	−−0	−−0	−−+	C_1	6.86	6.65	16		
−−0	−−0	−+−	00+	C_1	6.64	6.81	14		
−0−	+00	−++	00−	C_1	7.00	6.86	19		
−−0	−−0	−−+	+0+	C_1	6.53	6.92	13		
+0+	00−	0−−	00+	C_1	6.10	6.97	10		
++−	00+	−00	++0	C_1	7.64	7.41	24		
+00	−+0	++0	++0	C_1	6.86	8.33	17		
−−0	0+−	+00	−−0	C_1	7.65	9.29	25		
0++	0++	0++	0++	C_4	6.20	11.13	11		13.8

[a] Structures are sorted on HF/6-31G** energy, and MM3 position refers to the rank of each minimum in the MM3 energetic order. CVFF RE and HF/3-21G denote the relative energies for different minima reported by Hill et al. using molecular mechanics and HF/3-21G calculations, respectively.

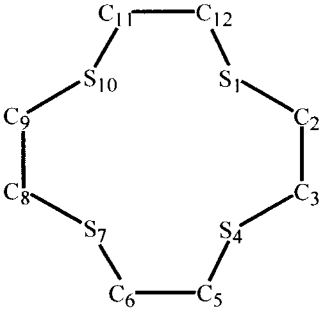


Figure 1. Atom numbering in [12]aneS_4.

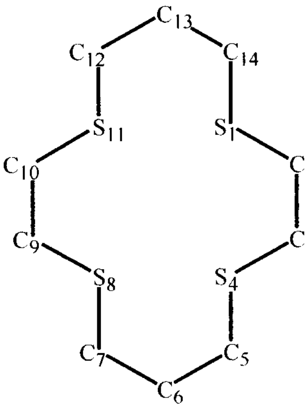


Figure 2. Atom numbering in [14]aneS_4.

previously used for different types of macrocycles.[5−8] Such computations are quite demanding, because of the often very large number of optimization cycles to be performed before the structures are optimized, the number of minima to be further optimized, and the size of the molecular structure. One approach would be to smooth the gap between the MM3 level and HF/6-31G** level by applying a small basis set. Hill et al. have used the 3-21G basis set as a relatively cheap method to reduce computing time in the lengthy geometry optimizations with larger basis sets. We have however found that, for example, in the case of tetra-aza-macrocycles,[7] such an approach is error prone. Starting from the MM3 structures, we did not find some minima on the HF/3-21G level, whereas we did find them when going immediately to the HF/6-31G** level. To avoid such an unwanted bias, we have used another method to reduce the computational cost, namely, by using the BRABO program.[15] This program includes the MIA approach[21] for the calculation of two-electron integrals, which results in an important gain in speed for calculations on systems with many basis functions. Though using an integral approach, the results of the calculations are of equal quality to those obtained using more conventional integral evaluation methods because cases where MIA fails can be identified and those integrals are calculated in the usual way.

Table 3 also gives the relative energies for all minima located on the HF/6-31G** level. In two cases, two different MM3 minima converge to the same HF/6-31G** minimum (structures 2 and 3, and structures 20 and 21). The lowest minima in the MM3 energetic order largely remained in the lower relative energy spectrum on the HF/6-31G** level, but the energetic separation is reduced somewhat. We note a couple of noteworthy cases where minima are shifted quite strongly upward or downward in the energetic order when going from the MM3 to HF/6-31G** level. The energetic order for the lowest energy minima remains very similar for the four lowest energy minima, accounting for an energetic range of 3.86 kcal/mol above the global minimum. From the Hay conformation descriptions, we see that there is a preference for trans SCCS dihedral angles. Table 3 also gives the ab initio results of Hill et al. Their HF/3-21G relative energies agree well with ours, except for the S_4 and C_4 structures, where larger differences are found. This is a noteworthy observation, because we previously found for different types of macrocycles that small basis sets (such as

TABLE 4: Results of MP2(full)/6-31G//HF/6-31G** Calculations on the Combination of MM3 Minima with Relative Energy below 6 kcal/mol and HF/6-31G** Minima with Relative Energy below 6 kcal/mol for [12]aneS_4[a]**

conformation				symm.	HF RE	MP2 RE	MP2/ 6-31+G*	MP2/ aVDZ
+0+	+0+	+0+	+0+	D_4	**0.00**	**0.00**	**0.0**	**0.0**
−0−	−0−	−0−	+0+	C_2	2.38	2.26	2.3	1.8
+0+	+0+	−0−	−0−	C_{2h}	2.70	2.77	2.7	2.9
−00	++−	−0−	−0−	C_1	3.86	3.46		
+−+	00−	−0−	−00	C_2	4.67	4.87		
+0+	−0−	+0+	−0−	S_4	5.64	5.09	10.5 (4.80)[b]	
+−−	−0−	−++	0+0	C_1	4.85	5.11	5.3	5.3
00+	+0+	+−−	0−−	C_1	5.64	5.18		
−−+	+0+	−0−	−++	C_s	5.43	5.39	5.6	5.8
−0−	−++	00−	+0+	C_1	5.79	5.41		
+0+	+0+	−++	0+−	C_1	5.36	6.04	6.0	

[a] HF RE and MP2 RE denote relative energies for both levels of calculation. Columns MP2/6-31+G* and MP2/AVDZ give the results obtained by Hill et al. on the MP2(FC)/6-31+G*//HF/6-31+G* and MP2(FC)/aug-cc-pVDZ//MP2(FC)/aug-cc-pVDZ levels of theory, respectively. [b] Value found by us for the S_4 structure on the MP2(FC)/6-31+G*//HF/6-31+G* level, with the structure optimized on the HF/6-31+G* level (optimization starting from our HF/6-31G** optimized geometry).

3-21G) may yield energetic orders that differ substantially from those found using larger basis sets. Also, we repeatedly found that when MM3 structures were used to initiate geometry optimizations using smaller basis sets several molecular mechanics minima collapse to the same structure, whereas they converge to different structures when optimized using larger basis sets. Turning to the number of minima located in the HF/3-21G relative energy span of the 10 minima reported by Hill et al., we found that there are 23 distinct minima. In our calculations, we find minima with gauche SCCS dihedral angles already at a relative energy of 3.86 kcal/mol, about 1 kcal/mol lower than the 4.7 kcal/mol reported by Hill et al. for the lowest energy structure with gauche SCCS dihedral angles. Both structures MM3(5) and MM3(7) have only one such gauche SCCS dihedral angle. The lowest energy structure with two gauche SCCS dihedral angles is MM3(22), which corresponds to structure number 4 reported by Hill et al. The C_i structure reported by Hill et al. was not included in our HF/6-31G** calculations. This is due to its high MM3 steric energy, which made us exclude this structure for ab initio level geometry optimization. To make a better comparison with the results of Hill et al. possible, we optimized the C_i structure at the HF/6-31G** level, to find that it has a relative energy of 6.60 kcal/mol, which places it among the higher energy structures in Table 3.

In 12-crown-4, we found that 1,5 C−H···O interactions help stabilize certain conformations of the macrocycle. In the case of [12]aneS_4, the existence of similar interactions could not conclusively be proven on the Hartree−Fock level. Contrary to crown ethers, where one can correlate short O···H distances in 1,5 C−H···O interactions with increased NPA charges on the hydrogen atom and increased $C^-{-}H^+$ polarization, no such effect was found in the possible C−H···S interactions in [12]aneS_4.

We further performed MP2 single-point calculations on all minima with HF/6-31G** relative energy under 6 kcal/mol, augmented with the MM3 minima with relative energy below 6 kcal/mol. Results of these calculations on 11 structures are shown in Table 4. This table reveals only a minor effect of the introduction of electron correlation. On the basis of our findings for the smaller dithio-compounds, we found that C−H···S interactions may play a more important role on the MP2 level than on the Hartree−Fock level, thereby possibly stabilizing certain minima in macrocycles as well. Our calculations however show that the energetic order remains largely the same. Two effects can play a role in this. First, the extra stabilization associated with C−H···S interactions may be too small to cause changes in energetic ordering. Second, MP2 geometry optimization might produce geometries that better accommodate C−H···S interactions. MP2 geometry optimization of the molecular structure of the macrocycles is currently not routinely possible. Hill et al. have calculated interaction energies for a dimer of dimethyl sulfide. From their study, a binding energy minimum was found near an S···H distance of 3.1 Å. The binding energy amounts to about 0.7 kcal/mol. Although they have shown that an intermolecular C−H···S interaction may exist, it is not possible to directly assess the importance of C−H···S interactions in the macrocyclic ring. They may very well be less important, bcause a good geometry for the C−H···S interaction may require a sterically unfavorable geometry. The effect of C−H···S interactions on relative energies of [12]aneS_4 can therefore not directly be assessed.

Concerning the agreement between our MP2 results and those reported by Hill et al., we find that there is good agreement between their MP2(FC)/6-31+G*//HF/6-31+G* results and our MP2(full)/6-31G**//HF/6-31G** calculations, except for the S_4 symmetrical structure, where both on the Hartree−Fock level and MP2 level the relative energy reported by them is relevantly higher than the one found by us. No reason for this observation could be found. We investigated what the effect is of reducing the electron correlation orbital space by doing MP2(FC)/6-31G**//HF/6-31G** calculations. We found that the relative energy is almost identical (the difference is less than 0.05 kcal/mol). We performed MP2(FC)/6-31+G*//HF/6-31+G* calculations starting from our HF/6-31G** structures for the global minimum and the S_4 structure and found a relative energy which is much lower than the value reported by Hill et al. (see Table 4).

Hill et al., using the aug-cc-pVDZ basis set, optimized five structures at the MP2 level. The results indicate only a minor effect of including geometry optimization on the relative energies compared to the ones obtained using the MP2 single-point calculations (MP2(FC)/6-31+G*//HF/6-31+G*). This agrees with what we expected on the basis of the comparison between the MP2(full)/6-31G**//HF/6-31G** and MP2(full)/6-31G**//MP2(full)/6-31G** results for the smaller dithio compounds (see above).

The Cambridge Structural Database[26] holds two entries for [12]aneS_4, namely, FOPCAO and FOPCAO01. Both structures resemble the global minimum found by us. There is good agreement between the dihedral angles in the FOPCAO structure and the HF/6-31G** global minimum. This is further support for Wolfs[28] conclusion that the solid state structures of thiamacrocycles are mainly governed by their intrinsic conformational properties.

Concerning the agreement between MM3 and HF/6-31G** geometries, qualitative geometries (as described by the Hay conformation) agree for most conformations optimized at both levels of theory. Tables 5 and 6 give both MM3 and HF/6-31G** geometrical parameters for the macrocyclic ring for the 5 HF/6-31G** lowest energy geometries. When comparing bond lengths between both levels of theory, one should take into account the different nature of bond lengths used in MM3 and ab initio calculations. Ab initio geometry optimizations are carried out in r_e space, whereas MM3 uses r_g. Ma et al.[29] have derived an empirical formula to obtain $r_{g,''ai''}$ bond lengths on

TABLE 5: MM3 Optimized Molecular Geometries for the Five Lowest Energy Minima of [12]aneS$_4$ (as Predicted by HF/6-31G Calculations)**

Nr.		S1	C2	C3	S4	C5	C6	S7	C8	C9	S10	C11	C12
1	r_e[a]	1.8145	1.5310	1.8145	1.8145	1.5310	1.8145	1.8145	1.5310	1.8145	1.8145	1.5310	1.8145
1	r_g	1.8252	1.5410	1.8252	1.8252	1.5410	1.8252	1.8252	1.5410	1.8252	1.8252	1.5410	1.8252
1	a	101.148	112.525	112.525	101.148	112.525	112.525	101.148	112.525	112.525	101.148	112.525	112.525
1	t	71.896	-173.956	71.896	71.896	-173.956	71.896	71.896	-173.956	71.896	71.896	-173.956	71.896
2	r_e	1.8235	1.5301	1.8148	1.8133	1.5333	1.8133	1.8148	1.5301	1.8174	1.8235	1.5297	1.8174
2	r_g	1.8349	1.5400	1.8256	1.8241	1.5434	1.8241	1.8256	1.5400	1.8285	1.8349	1.5397	1.8285
2	a	100.417	112.458	112.237	99.527	112.026	112.026	99.528	112.237	112.458	100.417	112.200	112.200
2	t	-83.358	172.166	-79.213	-76.928	166.578	-76.927	-79.213	172.165	-83.358	98.616	-172.163	98.616
3	r_e	1.8205	1.5304	1.815	1.815	1.5304	1.8205	1.8205	1.5304	1.8150	1.8150	1.5304	1.8205
3	r_g	1.8317	1.5403	1.8258	1.8258	1.5403	1.8317	1.8317	1.5403	1.8258	1.8258	1.5403	1.8317
3	a	100.037	112.462	111.432	98.964	111.432	112.462	100.038	112.462	111.432	98.964	111.432	112.462
3	t	93.386	-169.814	82.657	82.658	-169.814	93.385	-93.385	169.814	-82.657	-82.658	169.814	-93.386
4	r_e	1.8085	1.5298	1.8088	1.8048	1.5302	1.7970	1.8023	1.5252	1.8086	1.8106	1.5202	1.8149
4	r_g	1.8278	1.5421	1.8204	1.8206	1.5434	1.8339	1.8258	1.5413	1.828	1.8239	1.5416	1.8262
4	a	102.109	113.126	110.828	100.502	115.880	114.417	102.569	112.772	113.250	102.204	112.800	113.318
4	t	-61.113	161.501	-167.466	63.287	66.276	-94.016	-70.508	-176.442	-63.017	-69.108	168.539	-60.783
5	r_e	1.8196	1.5385	1.8195	1.8115	1.5325	1.8148	1.8152	1.5320	1.8152	1.8148	1.5325	1.8115
5	r_g	1.8302	1.5487	1.8302	1.8212	1.5423	1.8247	1.8250	1.5418	1.8250	1.8247	1.5423	1.8212
5	a	100.942	113.794	113.794	100.943	110.014	113.927	102.197	113.446	113.446	102.197	113.927	110.013
5	t	97.376	-90.930	97.375	-168.427	167.255	-60.409	-58.559	172.475	-58.558	-60.409	167.254	-168.428

[a] r_e and r_g are bond distances in Å. "a" refers to valence angles (in degrees), and "t" refers to dihedral angles (in degrees). r_e values are calculated from r_g values through weighing of the molecular vibrations in the MM3 force field.

the basis of ab initio $r_{e,ai}$ values. r_g is calculated as follows:

$$r_{g,\text{"}ai\text{"}} = r_{e,ai} + (r_{g,MM3} - r_{e,MM3}) + C \qquad (1)$$

Details of the method may be found in Ma et al. The value for C was recalibrated by us, using the same molecules as Ma et al., to account for differences in treatment of electron correlation and basis set size between the level of theory used by Ma et al. for the calibration and the present level of calculations. The agreement between MM3 and HF/6-31G** results is quite good. Bond lengths r_e in the first five minimum energy structures usually differ less than 0.01 Å. Agreement in r_g bond lengths is similar. Valence angles show good agreement between both levels of theory, but dihedral angles show larger differences, with average deviations of 11.5 and 8.5 degrees for SCCS and CSCC dihedral angles, respectively. A noteworthy case is the MM3(3) structure, where a difference is noted of over 50° in a CSCC dihedral angle, causing a difference in Hay conformation description between the MM3 and the HF/6-31G** geometry.

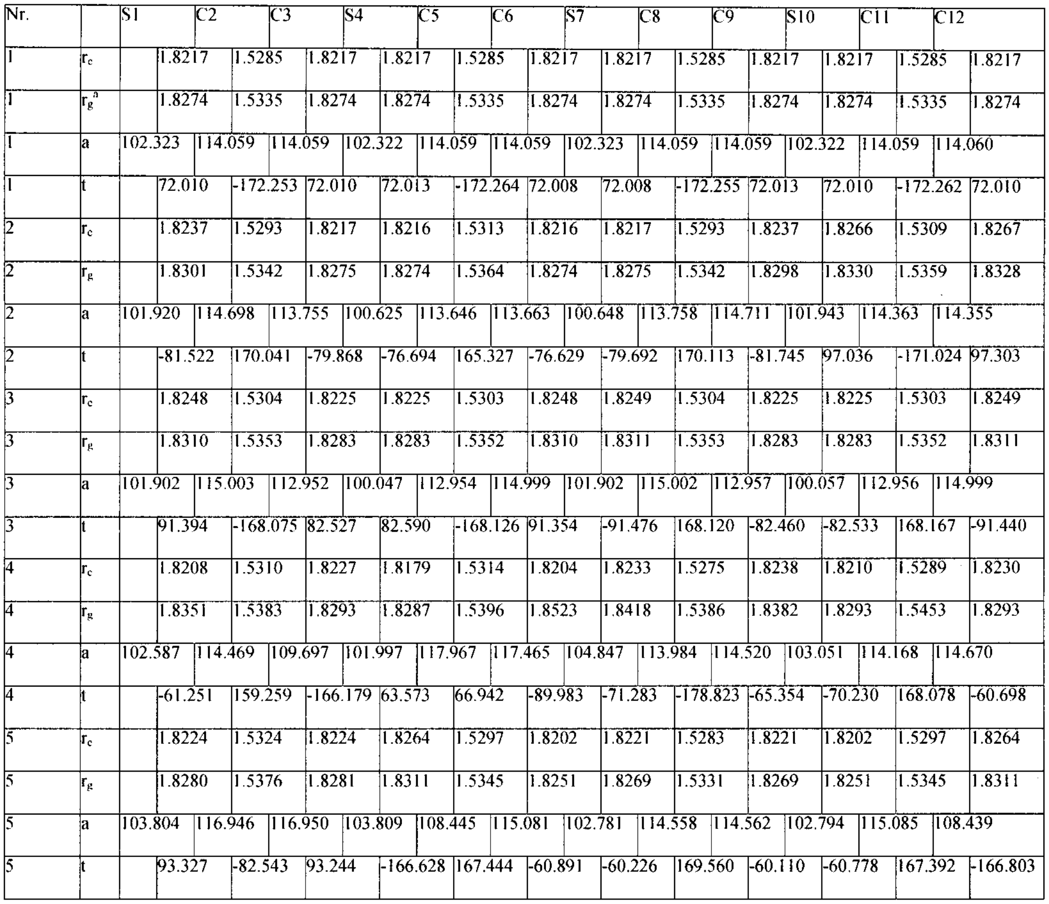
3. [14]aneS$_4$. Conformational searching was performed in a similar way as for [12]aneS$_4$, with a total of 1 systematic scan for possible cyclic structures and 88 following stochastic searches of 200 kicks each. In total, some 7000 minima were found. The MM3 program is not always as efficient in checking for redundancies, and using interatomic distance matrixes we found that there are about 2500 distinct minima. Table 7 shows the results of these MM3 calculations. This table shows that there is a preference for trans SCCS dihedral angles. Gauche SCCS dihedral angles occur only in the higher energy conformations. We further note a somewhat less outspoken preference for gauche CSCC dihedral angles. These preferences are similar to those in [12]aneS$_4$.

Results for HF/6-31G** geometry optimizations for the 36 lowest energy structures of [14]aneS$_4$ are also shown in Table 7. Computational limitations prohibited inclusion of even more minima for ab initio geometry optimizations. These calculations confirm the above-mentioned conformational preferences in the ethylene type bridges of the macrocycles. Considering the propylene type bridges, we find a preference for gGTg (++0+) and gTTg′ (+00-) structures. The presence of TT heavy atom dihedral angle combinations (here SCCC−CCCS) in low energy minima is a unique feature in the three classes of macrocycles studies thus far (crown ethers, aza-macrocycles, and thiacrown ethers). The gGTg and gTTg′ structures are also among the low energy minima of 1,3-propanedithiol. In 1,3-dithiomethoxyethane, both structures are also within less than 1 kcal above the global minimum.

Concerning the agreement between MM3 and ab initio structures, we find that the agreement is less than in case of [12]aneS$_4$. In several instances, the qualitative conformer description differs between the MM3 minimum and the HF/6-31G** minimum obtained after optimization starting from the MM3 structure.

The agreement between our results and the RUKKEN01 and TTHCTD structures in the Cambridge Structural Database is good. The TTHCTD01 structure does not shown any agreement with one of our low energy conformations. Even when

TABLE 6: HF/6-31G Optimized Geometries for the Five Lowest Energy Minima of [12]aneS$_4$**



Nr.		S1	C2	C3	S4	C5	C6	S7	C8	C9	S10	C11	C12
1	r_e	1.8217	1.5285	1.8217	1.8217	1.5285	1.8217	1.8217	1.5285	1.8217	1.8217	1.5285	1.8217
1	r_g[a]	1.8274	1.5335	1.8274	1.8274	1.5335	1.8274	1.8274	1.5335	1.8274	1.8274	1.5335	1.8274
1	a	102.323	114.059	114.059	102.322	114.059	114.059	102.323	114.059	114.059	102.322	114.059	114.060
1	t	72.010	-172.253	72.010	72.013	-172.264	72.008	72.008	-172.255	72.013	72.010	-172.262	72.010
2	r_e	1.8237	1.5293	1.8217	1.8216	1.5313	1.8216	1.8217	1.5293	1.8237	1.8266	1.5309	1.8267
2	r_g	1.8301	1.5342	1.8275	1.8274	1.5364	1.8274	1.8275	1.5342	1.8298	1.8330	1.5359	1.8328
2	a	101.920	114.698	113.755	100.625	113.646	113.663	100.648	113.758	114.711	101.943	114.363	114.355
2	t	-81.522	170.041	-79.868	-76.694	165.327	-76.629	-79.692	170.113	-81.745	97.036	-171.024	97.303
3	r_e	1.8248	1.5304	1.8225	1.8225	1.5303	1.8248	1.8249	1.5304	1.8225	1.8225	1.5303	1.8249
3	r_g	1.8310	1.5353	1.8283	1.8283	1.5352	1.8310	1.8311	1.5353	1.8283	1.8283	1.5352	1.8311
3	a	101.902	115.003	112.952	100.047	112.954	114.999	101.902	115.002	112.957	100.057	112.956	114.999
3	t	91.394	-168.075	82.527	82.590	-168.126	91.354	-91.476	168.120	-82.460	-82.533	168.167	-91.440
4	r_e	1.8208	1.5310	1.8227	1.8179	1.5314	1.8204	1.8233	1.5275	1.8238	1.8210	1.5289	1.8230
4	r_g	1.8351	1.5383	1.8293	1.8287	1.5396	1.8523	1.8418	1.5386	1.8382	1.8293	1.5453	1.8293
4	a	102.587	114.469	109.697	101.997	117.967	117.465	104.847	113.984	114.520	103.051	114.168	114.670
4	t	-61.251	159.259	-166.179	63.573	66.942	-89.983	-71.283	-178.823	-65.354	-70.230	168.078	-60.698
5	r_e	1.8224	1.5324	1.8224	1.8264	1.5297	1.8202	1.8221	1.5283	1.8221	1.8202	1.5297	1.8264
5	r_g	1.8280	1.5376	1.8281	1.8311	1.5345	1.8251	1.8269	1.5331	1.8269	1.8251	1.5345	1.8311
5	a	103.804	116.946	116.950	103.809	108.445	115.081	102.781	114.558	114.562	102.794	115.085	108.439
5	t	93.327	-82.543	93.244	-166.628	167.444	-60.891	-60.226	169.560	-60.110	-60.778	167.392	-166.803

[a] r_e and r_g are bond distances in Å. "a" refers to valence angles (in degrees), and "t" refers to dihedral angles (in degrees). r_g values are calculated from r_e values as described in the text.

TABLE 7: Relative Energies for Different Conformations of [14]aneS$_4$, Calculated at the MM3 and HF/6-31G Levels of Theory (Denoted MM3 RE and HF RE, Respectively, in kcal/mol)**

conformation				symm.	MM3 RE	HF RE	conformation				symm.	MM3 RE	HF RE
+0+	+00−	−0−	−00+	C_{2h}	**0.00**	**0.00**	−0−	−−0−	+00	−−0−	C_1	2.42	2.37
−00	++0+	+0+	+00−	C_1	0.87	0.75	000	−+00	−0−	−0−−	C_1	3.09	2.39
00−	−0−−	00+	+0++	C_i	0.46	0.77	+0+	−0−	−00+	−−0−	C_1	3.63	2.39
−0−	+00−	+0+	+00−	C_s	2.06	0.86	+0+	+0++	+0+	−00+	C_1	2.74	2.39
00−	++0+	+0+	+0++	C_1	1.59	1.01	00−	+00−	−0−	−00+	C_1	2.60	2.46
−0−	−00+	−0−	−00+	C_2	2.04	1.02	−0−	−00+	−00	++0+	C_1	3.17	2.50
−0−	−0−−	00+	−00+	C_1	2.34	1.30	−00	+0++	−00	++0+	C_1	3.02	2.53
−0−	+00−	−0−	−00+	C_2	2.39	1.57	−00	+00	−+0	0−00+	C_i	3.49	2.57
−00	++0+	−00	++0+	C_2	2.31	1.83	00+	−0−−	00+	+00−	C_1	2.95	2.66
0−−	+00−	−0−	−0−−	C_1	2.59	1.89	−0−	−0−−	−0−	++0+	C_1	3.25	2.67
−0−	−00+	+00	−+00	C_1	2.56	2.09	00+	+0++	0++	00−−	C_1	2.73	2.77
−00	+0++	00−	−00+	C_1	2.08	2.14	00−	−−0−	+0+	+0++	C_1	3.33	2.80
00+	+0++	0++	0++0	C_1	3.09	2.14	−0−	−−0−	−00	++0+	C_1	3.15	2.83
+0+	+00−	+00	−−0−	C_1	3.18	2.15	00+	−00+	+0+	00+−	C_1	3.63	2.96
+0+	−0−−	++0	++0+	C_1	3.48	2.15	+0+	+0++	+0+	+0++	C_2	2.89	3.29
+0+	−00+	+00	−0−	C_1	3.34	2.25	00+	+0++	−00	−0−−	C_1	3.65	3.39
+0+	+00−	−0−	+0++	C_1	2.52	2.29	+00	+0++	00−	+00−	C_1	3.22	3.47
+0+	−00+	−0−	−−0−	C_1	3.33	2.31	+00	−−00	++0	+00−	C_1	3.52	4.00

considering the lowest 250 MM3 minima, no structure is found which shows some agreement with this experimental structure. This is due to the fact that the experiment is conducted for a close dimer of [14]aneS$_4$, which apparently has an important effect on monomer geometries. We have submitted the experimental structure directly to HF/6-31G** optimization. After a very lengthy optimization, the geometry converges to the C_i structure with relative energy of 2.57 kcal/mol (see Table 7). The RUKKEN01 and TTHCTD structures have dihedral angles in the macrocyclic ring which differ less than 8° with the ab initio determined values for the global minimum.

4. Comparison between N, O, and S Donor Macrocycles. Our findings for [12]aneS$_4$ and [14]aneS$_4$ may be compared to earlier results for 12-crown-4[5] and 14-crown-4[6] and [12]aneN$_4$ and [14]aneN$_4$.[7] Thiacrown macrocycles such as [12]aneS$_4$ and [14]aneS$_4$ exhibit conformational preferences for trans SCCS angles and to a somewhat smaller extent for trans SCCC dihedral angles, with a further preference for gauche CSCC dihedral

TABLE 8: XCCX and XCCC Dihedral Angle Preferences in Different Types of Macrocycles, Together with the Nature of Intramolecular Interactions Governing the Conformational Properties of the Molecules[a]

macrocycle	XCCX pref.	XCCC pref.	no. 2	no. 5	intramolecular interactions
12-crown-4 (X = O)	gauche		2	14	gauche effect
14-crown-4 (X = O)	gauche	gauche	2	7	C−H···O interactions
[12]aneN$_4$ (X = N)	gauche		2	11	gauche effect
[14]aneN$_4$ (X = N)	gauche	gauche	2	14	electrostatic attraction between amine hydrogens and amine lone pairs
[12]aneS$_4$ (X = S)	trans		1	7	gauche effect largely absent
[14]aneS$_4$ (X = S)	trans	trans	10	> 30	C−H···S interactions unlikely or weak

[a] Nos. 2 and 5 give the number of minima with a relative energy below 2 and 5 kcal/mole, respectively. All data are based on HF/6-31G** results from the present study and previous studies.[5−8]

angles. The lowest energy geometries of both macrocycles correspond to exodentate structures, whereas the energetically most favorable metal−ligand interaction occurs in an endodentate geometry. Crown ethers such as 12-crown-4 and 14-crown-4 show a preference for gauche OCCO and OCCC dihedral angles. These are stabilized by the gauche effect, and by intramolecular CH···O interactions Similar CH···S interactions in the thiacrown ethers play a smaller role. The lower energy minima of aza-macrocycles are characterized by gauche NCCN dihedral angles.[7] In aza-macrocycles, we found that intramolecular electrostatic interactions between amine hydrogen atoms and lone electron pairs play an important role. The thiacrown ethers show important different characteristics in their conformational properties, because of the preference for trans heavy atom dihedral angles, and the weaker role played by intramolecular interactions.

A short summary of the observations mentioned above is given in Table 8, where XCCX and XCCC dihedral angle preferences are given, together with the nature of the intramolecular interactions, which govern the conformational properties of the different macrocycles. The table also gives the number of minima with a relative energy below 2 and 5 kcal/mol. Such a comparison is feasible, because for all macrocycles a very similar way of conformational analysis was used.[5−8] From the table, we learn that there are no substantial differences in the low energy structure density, except for the [14]aneS$_4$ structure, where a very large number of low energy minima exists. The [12]aneS$_4$ macrocycle on the other hand has somewhat fewer low energy minima compared to the other 12-membered macrocycles.

Conclusion

Conformational analysis of 1,2-dithiomethoxyethane and 1,3-dithiomethoxypropane was performed to investigate conformational preferences in the building blocks of thiacrown macrocycles. The main result was that many different minimum energy conformations have a low relative energy. C−H···S interactions play a smaller role than in the case of the C−H···O interactions in crown ethers.

Findings for [12]aneS$_4$ are similar as those obtained by Hill et al., but we find that the method of conformational searching plays an important role in finding low energy minima. Conformational preferences for trans SCCS and gauche CSCC dihedral angles in [12]aneS$_4$ were found, together with a preference for TT or TG arrangements of the SCCC dihedral angles in the propylene bridges of [14]aneS$_4$.

We found relatively good agreement between MM3 and HF/6-31G** structural data, except for dihedral angles where differences of over 10 degrees occasionally occur. MM3 energetic orders also agree qualitatively with the ab initio energetic ordering of minima, except for some cases.

Fine agreement between theoretical structures and experimental structures was found. For both macrocycles the global minimum corresponds to the experimentally observed structures, indicating that the solid state conformations are mostly dictated by intrinsic conformational properties rather than by environment, except in one case of a [14]aneS$_4$ dimer.

Acknowledgment. This research was financed in part by a specialization bursary of the Flemish Institute for the Advancement of Scientific-Technological Research in the Industry (IWT). We thank the Fund for Scientific Research (FWO) for their grant for the RS/6000 computer hardware. C.V.A. acknowledges the FWO for an appointment as ‘Onderzoeksdirecteur’. Dr. Schmidt is gratefully acknowledged for providing the GAMESS program.

References and Notes

(1) Pedersen, C. J. *J. Am. Chem. Soc.* **1967**, *89*, 2495.
(2) Cooper, S. R., Ed.; *Crown Compounds: Toward Future Applications*; VCH: New York, 1992.
(3) Martell, A. E.; Smith, R. M. *Critical Stability Constants*; Plenum Press: New York, 1974; Vol. 1−6.
(4) Hancock, R. D.; Martell, A. E. *Chem. Rev.* **1989**, *89*, 1875.
(5) Bultinck, P.; Goeminne, A.; Van de Vondel, D. *J. Mol. Struct. (THEOCHEM)* **1999**, *467*, 211.
(6) Bultinck, P.; Van Alsenoy, C.; Goeminne, A. *J. Phys. Chem. A* **2001**, *105*, 9203.
(7) Bultinck, P.; Van Alsenoy, C.; Goeminne, A.; Van de Vondel, D. *J. Phys. Chem. A* **2000**, *104*, 11801.
(8) Bultinck, P. Ab initio study of complexes between alkaline (-earth) metal ions and C2 and C3 bidentate ligands and macrocycles. Ph.D. Thesis (unpublished), Ghent University, Gent, Belgium, 1999.
(9) Hill, S. E.; Feller, D. *J. Phys. Chem. A* **2000**, *104*, 652.
(10) Allinger, N. L.; Yuh, Y. H.; Lii, J.-H. *J. Am. Chem. Soc.* **1989**, *111*, 8551.
(11) *MM3*, versions 1994, 1996; obtained from QCPE.
(12) Saunders, M. *J. Am. Chem. Soc.* **1987**, *109*, 3150.
(13) Hay, B. P.; Rustad, J. R.; Zipperer, J. P.; Wester, D. W. *J. Mol. Struct. (THEOCHEM)* **1995**, *337*, 39.
(14) Schmidt, M. W.; Balridge, K. K.; Boatz, J. A.; Elbert, S. T.; Gordon, M. S.; Jensen, J. H.; Koseki, S.; Matsunaga, N.; Nguyen, K. A.; Su, S. J.; Windus, T. L.; Dupuis, M.; Montgomery, J. A. *J. Comput. Chem.* **1993**, *14*, 1347.
(15) Van Alsenoy, C.; Peeters, A. *J. Mol. Struct. (THEOCHEM)* **1993**, *286*, 19.
(16) Harrisson, R. J. *TCGMSG message passing toolkit*; Battelle Pacific Northwest Laboratory.
(17) Beguelin, A. L.; Dongarra, J. J.; Geist, G. A.; Jiang, W. C.; Manchek, R. J.; Moore, B. K.; Sunderam, V. S. *PVM*, version 3.3: *Parallel Virtual Machine System*; Oak Ridge National Laboratory: Oak Ridge, TN.
(18) Glendening, E. D.; Badenhoop, J. K.; Reed, A. E.; Carpenter, J. E.; Weinhold, F. *NBO 4.0*; Theoretical Chemistry Institute, University of Wisconsin: Madison, WI, 1994.
(19) Frisch, M. J.; Trucks, G. W.; Schlegel, H. B.; Gill, P. M. W.; Johnson, B. G.; Robb, M. A.; Cheeseman, J. R.; Keith, T.; Petersson, G. A.; Montgomery, J. A.; Raghavachari, K.; Al-Laham, M. A.; Zakrzewski, V. G.; Ortiz, J. V.; Foresman, J. B.; Cioslowski, J.; Stefanov, B. B.; Nanayakkara, A.; Challacombe, M.; 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 C.1; Gaussian, Inc.: Pittsburgh, PA, 1995.

(20) Almlöf, J.; Faegri, K.; Korsell, K. *J. Comput. Chem.* **1982**, *3*, 385.

(21) Van Alsenoy, C. *J. Comput. Chem.* **1988**, *9*, 620.

(22) Bultinck, P.; Goeminne, A.; Van de Vondel, D. *J. Mol. Struct. (THEOCHEM)* **1995**, *334*, 101.

(23) Bultinck, P.; Goeminne, A.; Van de Vondel, D. *J. Mol. Struct. (THEOCHEM)* **1996**, *360*, 119.

(24) Bultinck, P.; Goeminne, A.; Van de Vondel, D. *J. Mol. Struct. (THEOCHEM)* **1995**, *357*, 19.

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

(26) Allen, F. H.; Bellard, S. A.; Brice, M. D.; Cartwright, B. A.; Doubleday, A.; Higgs, H.; Hummelink, T.; Hummelink-Peters, B. G.; Kennard, O.; Motherwell, W. D. S.; Rodgers, J. R.; Watson, D. G. *Acta Crystallogr.* **1979**, *B35*, 2331. The authors wish to thank the CAOS/CAMM department of the University of Nijmegen for providing access to these database.

(27) Raithby, P. R.; Shield, G. P.; Allen, F. H. *Acta Crystallogr.* **1997**, *B53*, 241.

(28) Wolf, R. E., Jr.; Hartman, J. A. R.; Storey, J. M. E.; Foxman, B. M.; Cooper, S. R. *J. Am. Chem. Soc.* **1987**, *107*, 4328.

(29) Ma, B.; Lii, J.-H.; Schaefer, H. F., III; Allinger, N. L. *J. Phys. Chem.* **1996**, *100*, 8763.