Conformation of 6H,12H,18H-tribenzo[b,f,j][1,5,9]trithiacyclododecin revisited

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A theoretical study has been carried out on 6H,12H,18H-tribenzo[b,f,j][1,5,9]trithiacyclododecin (1) for the elucidation of its accessible molecular conformations, associated flexibility, and conformational transitions. For the description of the conformational space of 1 molecular dynamics and energy minimization techniques combined with semiempirical quantum chemical calculations have been applied. The calculated trajectories show 1 to be a highly flexible molecule undergoing several spontaneous conformational transitions during the simulation. The various conformational states accessible to 1 have been characterized and compared with previously reported experimental X-ray and NMR results.

Introduction

The conformational behaviour of medium-size molecules has long been of great interest in organic chemistry. Diffraction and spectroscopic methods permit the elucidation of conformations in the solid state and often also in solution. Theoretical calculations (molecular mechanics, semiempirical quantum chemical and *ab initio*) help us to shed light on conformational equilibria, to find the most stable conformations and in the knowledge of this information to evaluate time-averaged NMR spectra.

Among molecules accessible to such studies medium-sized rings are of special interest. Their intrinsic flexibility and ability to assume diverse conformations make the characterization of their conformational behaviour difficult. Hexahydrotribenzo-cyclododecin and its derivatives were the subject of a thorough structural analysis in the past, based on dynamic ^{13}C and ^{1}H NMR studies and strain energy calculations.[1-3] The structure of the 6H,12H,18H-tribenzo[b,f,j][1,5,9]trithiacyclododecin
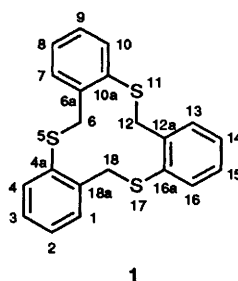
1

(1) has been described in the solid state[4] and in solution.[5,6] From the ^{1}H NMR spectrum (only one singlet for all CH_2 protons at room temperature splitting into six doublets on cooling to $-106\,°C$) 1 was concluded to have two inter-converting enantiomeric low-energy molecular conformations in solution. The presence of six non-equivalent methylene protons proved that the ground state conformation of the cyclic trisulfide 1 was of C_1 symmetry. Examination of molecular models suggested that 1 adopted a helical conformation in solution (Fig. 1, conformations I and II).

The dramatic development of computer technology in recent years has made it possible to apply efficient computational methods to molecules of medium size and this has prompted us to reinvestigate the conformational behaviour of 1. Our goal was to achieve a complete conformational analysis of 1, *i.e.* to find the significant local minima of the compound, to calculate their relative stabilities and compare the results with the earlier experimental studies.

Calculations

MD simulations were carried out with the DISCOVER 2.9 program (Biosym Technologies, 10065 Barnes Canyon Road, San Diego, CA 92121, USA) with time step 1 fs using the AMBER forcefield.[7] The input files for DISCOVER were prepared following the automatic parameter assignment procedure of INSIGHT II/DISCOVER 2.9. As an initial geometry the structure proposed by Ollis and co-workers[6] was generated and minimized to eliminate casual internal strains arising during the build-up process. This structure was then equilibrated by running dynamics at 300 and 600 K for 20 ps each. Data were collected from a subsequent 2000 ps run at 900 K. No additional forces or cutoffs were used. A total of 2000 configurations (one every 10^{-12} s) was sampled during the simulation. The generation of the various trajectories was done with the ANALYSIS option of INSIGHT II.

Molecular orbital calculations were performed on a SUN SPARCCENTER 2000 computer using PM3 and 1SCF options in MOPAC 7.0.[8] Comparisons of calculated conformations and X-ray geometry were done on an SGI workstation by PcModel.[9]

Results

The conformationsl space of 1 was explored by molecular dynamics calculations. One of the disadvantages of dynamics, is that several hundreds or even thousands of conformational states are sampled during a trajectory, thus complicating the analysis process. Furthermore, the transitions of interest may take place on a time scale of milliseconds to minutes or longer at 300 K and, at present, dynamics' simulations are limited to tens of nanoseconds. Thus, one has to apply high temperatures to impart enough kinetic energy to the molecule permitting it to visit the whole conformational space in a reasonable time.

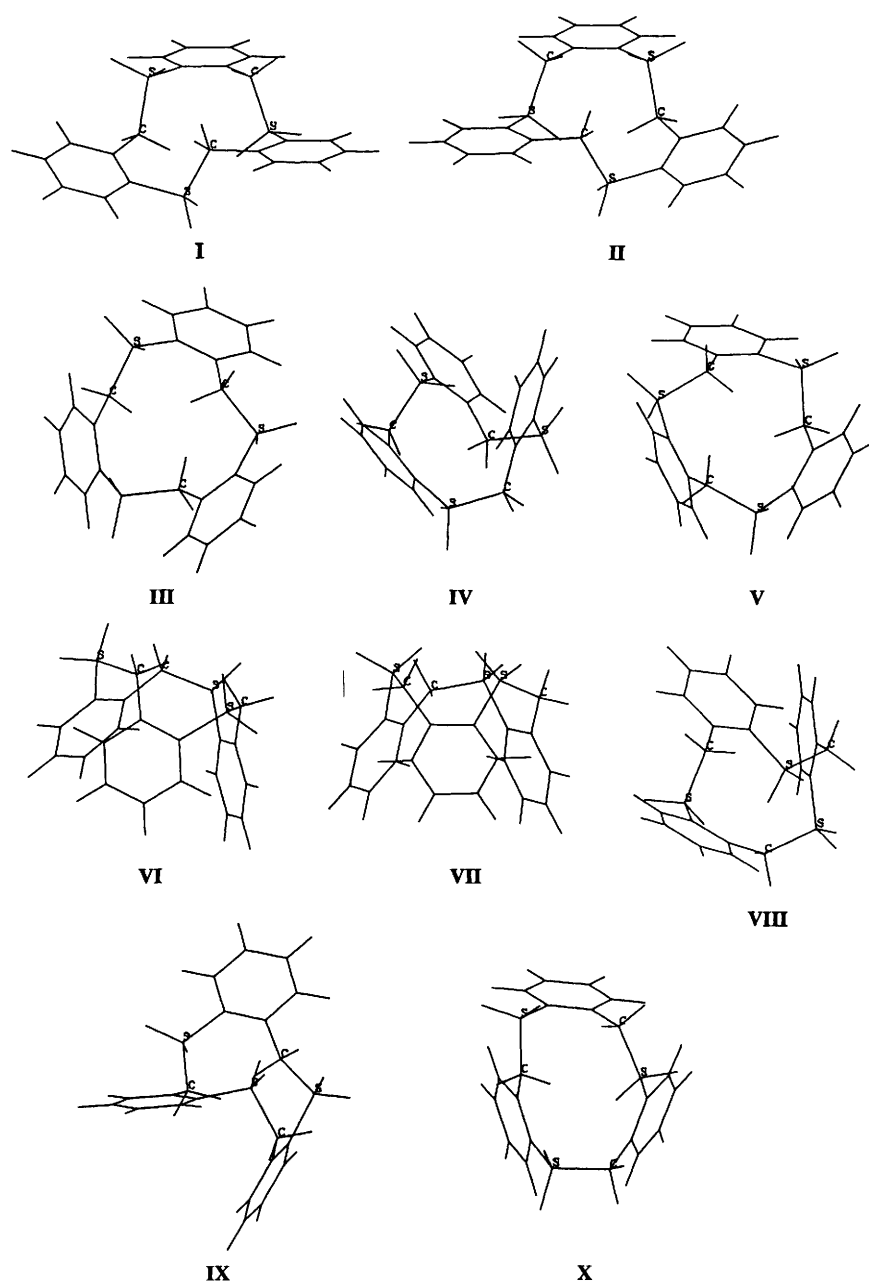Histories of some of the torsion angles are shown in Fig. 2. It

Fig. 1 Ten distinct structures (I–X) derived from the 25 conformational groups

can be seen that at 900 K fluctuations of 60° are typical. Because of the cyclic structure of the molecule a correlation between the dynamic behaviour of the dihedrals α, β, γ, δ, ε and φ (C4–C4a–S5–C6, S5–C6–C6a–C7, C1–C18a–C18–S17, C18–S17–C16a–C16, C13–C12a–C12–S11 and C12–S11–C10a–C10, respectively) is apparent. From the plots it can be seen that the shortest lifetime of a conformation is about 15 ps, thus for further investigation dynamic structures were taken at ten picosecond intervals reducing thereby the number of structures to be handled to 200.

Similarity of the structures along the trajectory was quantified by the rms deviation between backbone atoms. The similarity between structures was evaluated by comparing the rms deviations between each possible pair of structures. This procedure is summarized in Fig. 3 where the rms values are mapped in a grey scale and plotted in a 200 × 200 matrix.

Elements near the diagonal represent structures that are close in time having generally low rms values. Off-diagonal elements represent structures separated by long times, and had, in most cases, high rms deviations. A number of box-like areas appear along the diagonal, indicating that several distinct families of structures were encountered during the progress of the dynamics calculations. These areas could be divided into 25 conformational groups, represented by the 25 boxed regions in Fig. 3.

High temperatures greatly increase the frequency of producing conformational transitions as shown by a control run at 300 K which revealed no significant new conformational states over 1000 ps. Even at 600 K only one transition was found within 1000 ps, the dynamic trajectory and histories of dihedral angles α–φ were shown in Fig. 4.

Because the high-temperature dynamics may lead to higher-energy minima (starting from a higher point on the energy surface results in a higher energy local minimum) selected structures from each conformational groups (altogether 25) were subsequently subjected to lower-temperature dynamics at
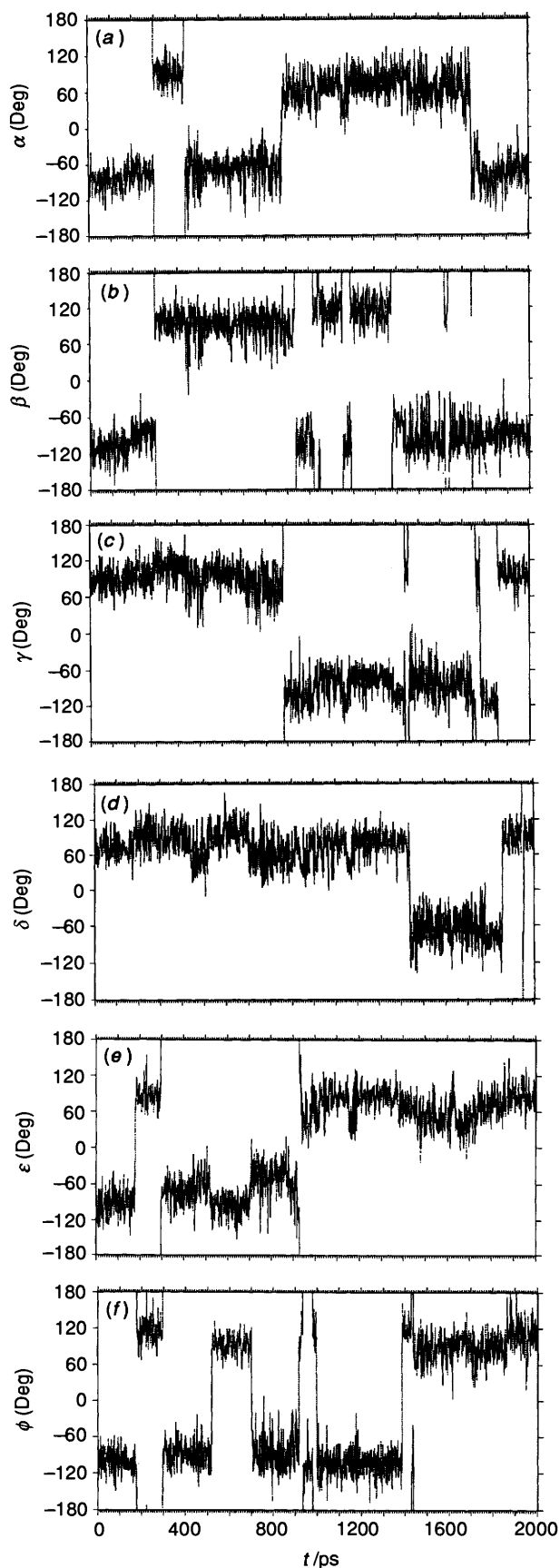
Fig. 2 Plots of the torsion angles α–φ as functions of the time elapsed in the dynamics simulation at 900 K
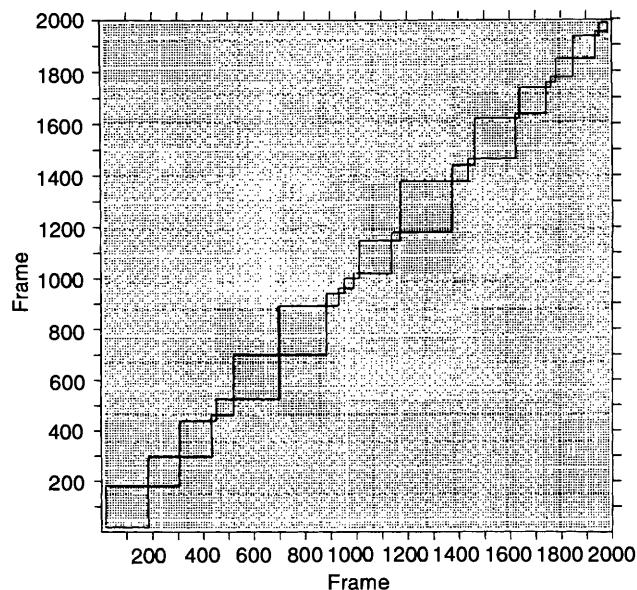

Fig. 3 Matrix of rms deviations between backbone atoms of 1 from the MD run at 900 K

Table 1 The relative abundance, total energy (E_T) and the heats of formation ($\Delta_f H$) of structures I–X from the 900 K run

Structure	Abundance	E_T/kcal mol^{-1}	$\Delta_f H$/kcal mol^{-1}
I	4	155.50	104.41
II	5	155.50	104.41
III	3	154.80	103.58
IV	1	159.90	106.50
V	3	154.80	103.58
VI	1	157.53	106.18
VII	2	161.76	110.05
VIII	4	158.52	109.08
IX	1	158.95	106.84
X	1	157.94	105.91

and compared with each other.† From the first 25 conformational groups ten distinct structures were found which are presented in Fig. 1.

From the ten structures two pairs (I–II and III–V) are enantiomers i.e. the number of diastereoisomeric conformations is eight. Inversion of the rest of the diastereoisomers to their enantiomers did not occur at the temperature of the present simulation. Similarities were observed between structures VI and VII, III and X, respectively. These pairs represent local minima in a conformational valley. The relative abundance and the total energy of each conformation from the 900 K run with the heats of formation gained from PM3 calculations indicating their relative stability are summarized in Table 1. Considering their main features, structures IV and VIII are similar, too, the only significant difference is that the chain carbon and sulfur atoms are interchanged.

The solid state conformation of 1 showed some similarity to conformers I and II, but had a higher heat of formation than the latter. The C_1 symmetry suggested by careful NMR experiments is compatible with several conformations, such as III and V, X, I and II. Ollis and co-workers postulated only one pair of enantiomeric conformations of C_1 symmetry (I and II) based on the multiplicity of the low temperature NMR spectrum (six AB doublets). The present analysis of the total conformational space suggests, in turn, III and V as the most stable enantiomeric conformations.
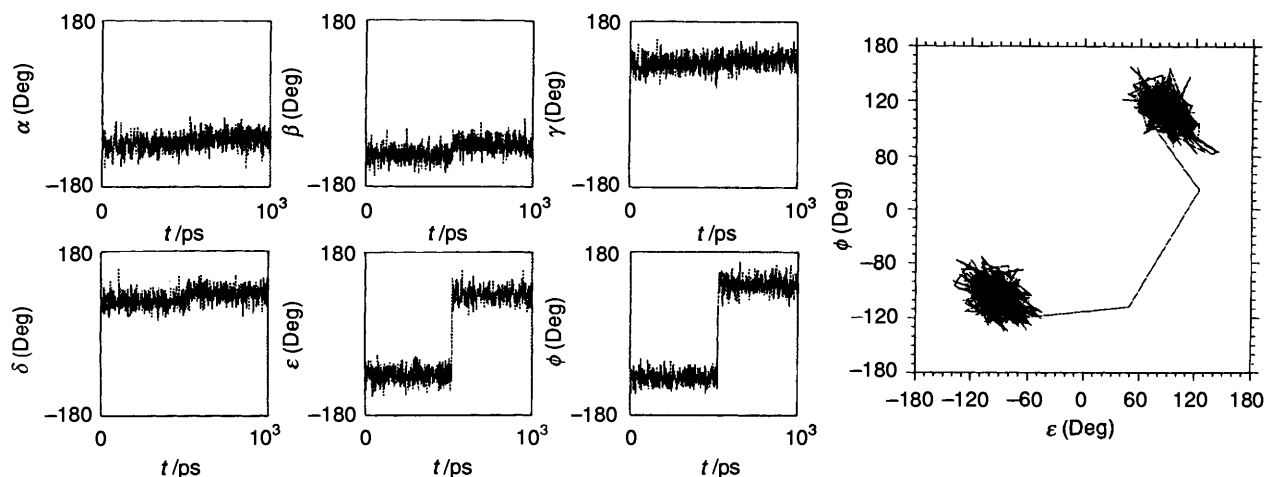
300 K for 10 ps. After that the structures were minimized until the maximum derivatives were less than 0.0005 kcal mol^{-1} Å

† 1 cal = 4.184 J.

Fig. 4 History of some of the α–φ torsion angles and the dynamic trajectory from the MD run at 600 K
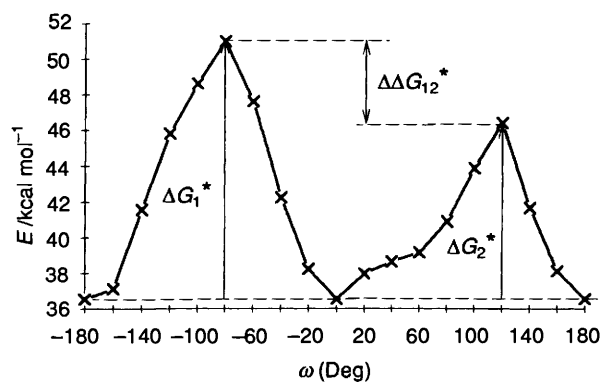

Fig. 5 Calculated inversion barriers for the pedalling motion of 1

In order to be able to decide between these alternatives a low temperature NOE analysis was undertaken, but unfortunately the speed of conformational interchange was not low enough even at 500 MHz and − 110 °C, and in the ROESY spectra the exchange effect dominated.

In the first paper on the conformation of 1 [5] for the inversion of the ring a pedalling motion of one of the CH$_2$ groups in which the hydrogen atoms penetrated through the centre of the ring was postulated. This hypothesis, based on inspection of a space filling model, is now supported by molecular mechanics calculations carried out by fixing the torsional angle involving

atoms C4a–S5–C6–C6a (ω) and relaxing the rest of the molecule. Angle ω was varied in steps of 10° in both directions starting from one enantiomer (ω = 0°) and arriving at its antipod (ω = 180°). In this process strain energy of the molecule passed two maxima.

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