Optical Resolution, Absolute Configuration and Empirical Force-field Calculations of (±)-5,8,15,18-Tetramethyl-2,11-diaza[3.3]paracyclophane

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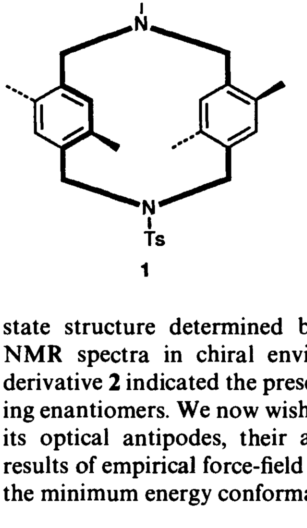
Partial resolution of the title compound **2** into its optical antipodes was achieved by enantioselective chromatography on triacetylcellulose. The absolute configuration of the enantiomers has been tentatively assigned on the basis of their CD spectra. Empirical force-field calculations were performed to characterize the minimum energy conformers of **2** and it was found that the two C_2 symmetrical isomers are *ca.* 3.7 kcal mol^{-1} (15.5 kJ mol^{-1}) more stable than those of C_i and C_1 symmetry. Calculated geometrical parameters of one C_2 symmetrical conformer of **2** are in good agreement with those found by single-crystal X-ray analysis of the *N,N'*-ditosylparacyclophane precursor **1**. The barrier to racemization has been estimated to be >35 kcal mol^{-1} (>146.5 kJ mol^{-1}).

In a previous paper[1] we reported the synthesis of the novel cyclophane *N,N'*-ditosyl-5,8,15,18-tetramethyl-2,11-diaza[3.3]-paracyclophane **1** and also described its C_2-symmetrical solid-state structure determined by single-crystal X-ray analysis; NMR spectra in chiral environments for the free diamino derivative **2** indicated the presence of the two non-interconverting enantiomers. We now wish to report the resolution of **2** into its optical antipodes, their absolute configurations and the results of empirical force-field calculations used to characterize the minimum energy conformations.



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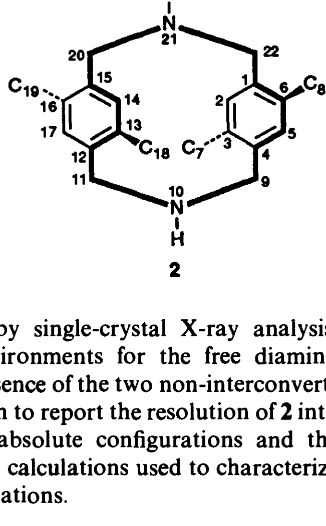

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Results and Discussion

Partial resolution of **2** into its optical antipodes was achieved by enantioselective chromatography on triacetylcellulose using a 'cycle-technique'[2] (eluant: ethanol, 96%; column: 30 × 2.5 cm, thermostatted at 40 °C; adsorbent particle size: 15–25 μm; sample size: *ca.* 20 mg). Because of excessive tailing, the partially resolved sample was eluted after passing the column twice. Several fractions of moderate optical activity (first fraction: $[\alpha]_D = -17.5°$, $[\alpha]_{578} = -16.5°$, $[\alpha]_{546} = -13.6°$, $[\alpha]_{436} = +27.2°$, $[\alpha]_{365} = +227°$) were collected. The CD spectra of the first eluted fractions, with a significant positive Cotton effect at 264 ± 1 nm, were exact mirror images to those of the last ones. Attempts to estimate the enantiomeric excesses by NMR methods failed.

Fig. 1 shows the CD spectra of both enantiomers. According to the work of Nakazaki *et al.* on optically active [8.8]paracyclophanes of known configuration, the sign of the transition at 264 nm is related to the conformation of the distorted benzene ring, which itself is related to the absolute configuration.[3] On the basis of a comparison of our CD spectra with those reported by Nakazaki *et al.*, and taking into account that a positive Cotton effect corresponds to an *S*-planar chirality,[3] the *S,S* absolute configuration was tentatively assigned to the first eluted enantiomer of **2**, as shown here.

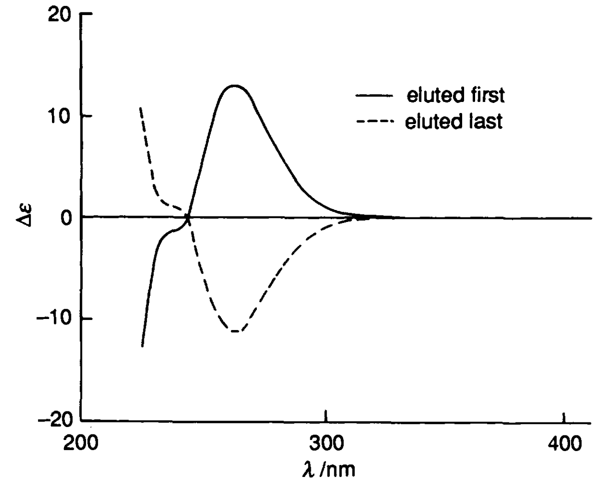

Fig. 1 CD spectra of **2** in ethanol

Interconversion of the enantiomers of **2** can take place *via* a two-step process: (i) starting from a molecule with *S,S* configuration, a flip of one arene ring by *ca.* 180° will result in an achiral structure with *R,S* configuration; (ii) rotation of the second arene ring will then give the enantiomeric *R,R* structure. In order to determine the overall energy barrier for this process, we tried to racemize the optically-active cyclophane **2** by heating a solution of the compound in diethylene glycol dimethyl ether. Heating the solution for 2.5 h at 150 °C did not result in a significant change of the CD spectrum; however, heating at 150 °C for 10 h induced decomposition of the cyclophane into at least three different compounds, as indicated by TLC. By assuming an error of measurement of 5% and taking into account the fact that heating for 2.5 h at 150 °C did not change the intensities of the CD transitions, we can calculate a lower limit for the racemization barrier, namely $k = 5.7 \times 10^{-6}$ s^{-1} and $\Delta G^{\ddagger}_{423} \geqslant 35{\cdot}(2)$ kcal mol^{-1} (147 kJ mol^{-1}). This finding is consistent with that of Staab[4] for tetramethoxydithia[3.3]-

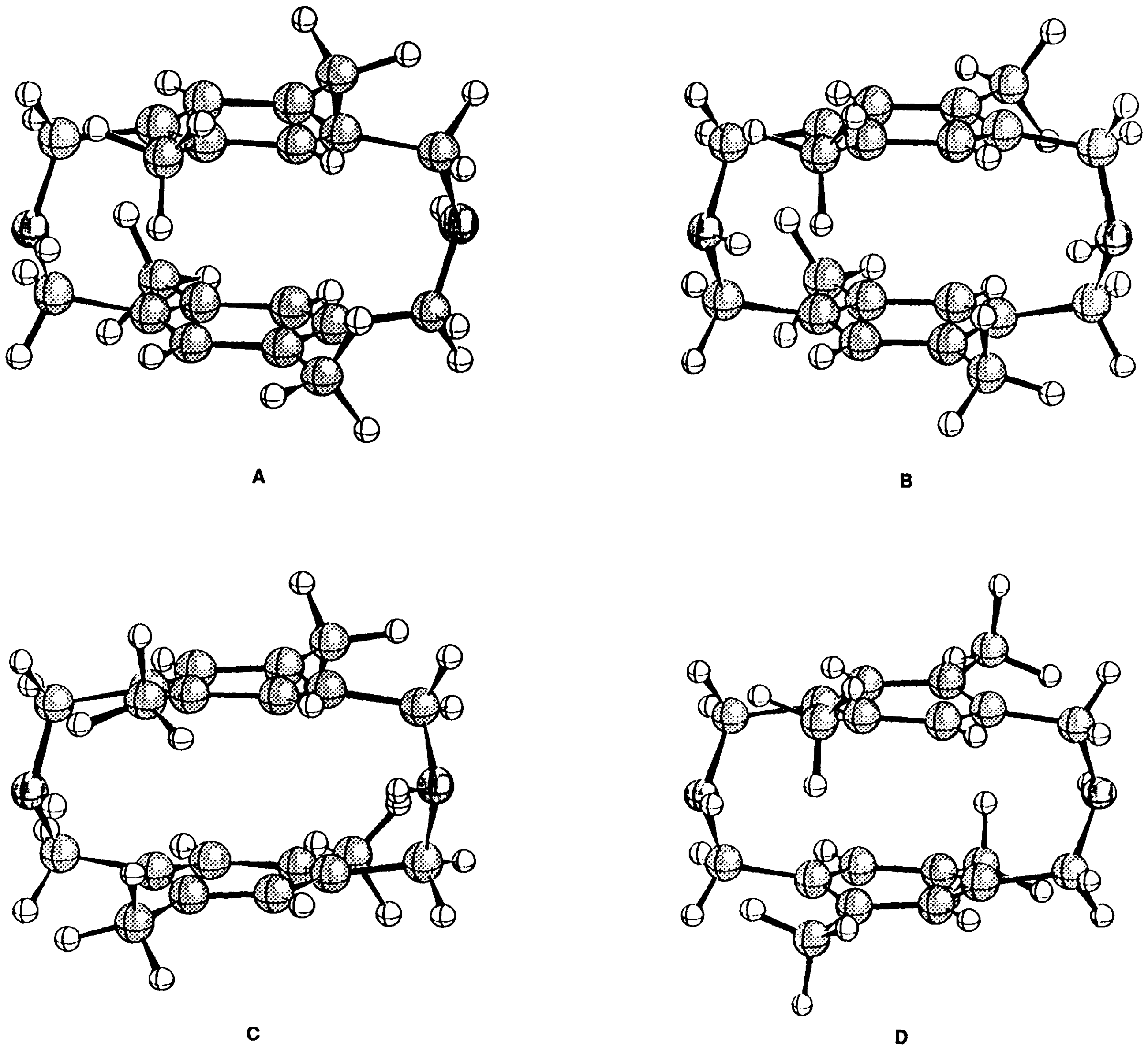

Fig. 2 Calculated minimum energy structures of **2**: **A**, C_2 symmetry (ground-state structure); **B**, C_2; **C**, C_1; **D**, C_i

paracyclophane, and is also in agreement with our results of the empirical force-field calculations.

Empirical Force-field Calculations.—All conformations of cyclophane **2** were minimized using Allinger's MM2(87) force-field program.[5] These calculations yielded four energy minima corresponding to two structures with C_2 symmetry and structures of C_i and C_1 (close to C_s) symmetry (Fig. 2). The ground-state structure **A** is of C_2 symmetry, with the C_2 axis passing through the arene centroids. The second C_2 symmetrical conformer **B**, with the C_2 axis bisecting the arene rings, is higher in energy by only 0.07 kcal mol^{-1} (0.3 kJ mol^{-1}), whereas the C_1 and C_i structures **C** and **D** are higher in energy by 3.59 and 3.68 kcal mol^{-1} (15.0 and 15.4 kJ mol^{-1}), respectively, indicating that the C_2 symmetrical conformers are the only ones present under thermodynamic control. This is in agreement with the finding that the synthesis of the ditosylcyclophane precursor **1** yielded just one diastereoisomer with C_2 symmetry in the solid state.[1]

In solution, all four conformers may interconvert by two different interconversion modes: (a) inversion of the configuration of one bridging nitrogen will interconvert the C_2 symmetrical conformers **A** and **B**, as well as the two conformers of higher energy (**C** and **D**), whereas (b) an arene flip by *ca.* 180° will interconvert both, **A** and **D** as well as **B** and **C**.

If only mode (a) is operating on the time scale of observation, molecular D_2 symmetry will result from the interconverting C_2 conformers **A** and **B** but C_{2h} symmetry from **C** and **D**. The experimental proton spectrum is in accordance with both D_2 and C_{2h} symmetry, but the optical activity is in agreement only with D_2.

The results of the calculations show that both C_2 conformations are under a considerable degree of strain, as judged by the puckering of the aromatic rings (by *ca.* 9°) and by the elongation of the N–CH$_2$ bonds, as well as by the enlargement of the C–N–C angles. In both conformers the *p*-xylyl rings lie in parallel planes, with the C_2 axis passing through the centroids of both rings in the ground-state conformer **A** but bisecting those planes in the second C_2 symmetrical structure **B**. It is interesting to note that the C_2 solid-state structure found for **1** is not identical with that of the calculated ground-state structure of **2**, but rather is very similar to that of **B**.

Table 1 lists geometrical parameters (bond lengths, bond angles and torsional angles) of **1** obtained by X-ray analysis and those calculated for the related conformer **B**. Comparison of

Table 1 Comparison of bond distances, bond angles and torsional angles calculated for **2** with those of the X-ray data of **1**

Bond distances/Å			Bond angles/°			Torsional angles/°		
	Calc.[a]	Found[b]		Calc.[a]	Found[b]		Calc.[a]	Found[b]
C(1)–C(2)	1.399	1.382	C(1)–C(2)–C(3)	122.4	122.8	C(1)–C(2)–C(3)–C(4)	0.6	1.4
C(1)–C(6)	1.404	1.400	C(1)–C(6)–C(8)	123.4	122.2	C(1)–C(6)–C(5)–C(4)	0.8	−0.3
C(1)–C(22)	1.514	1.509	C(2)–C(3)–C(7)	119.5	119.1	C(1)–C(2)–C(3)–C(7)	177.1	177.8
C(2)–C(3)	1.399	1.397	C(2)–C(1)–C(22)	119.1	119.4	C(1)–C(22)–N(21)–C(20)	−74.0	−63.8
C(3)–C(4)	1.401	1.382	C(4)–C(5)–C(6)	122.3	122.4	C(2)–C(1)–C(6)–C(5)	−9.2	−8.5
C(3)–C(7)	1.510	1.503	C(4)–C(3)–C(2)	118.5	117.3	C(2)–C(1)–C(6)–C(8)	173.1	174.1
C(4)–C(5)	1.399	1.389	C(4)–C(3)–C(7)	122.0	123.5	C(5)–C(4)–C(9)–N(10)	58.7	39.4
C(4)–C(9)	1.512	1.524	C(5)–C(4)–C(3)	118.7	119.7	C(2)–C(3)–C(4)–C(9)	169.3	167.5
C(5)–C(6)	1.398	1.386	C(5)–C(6)–C(1)	118.6	117.7	C(3)–C(2)–C(1)–C(6)	8.7	7.8
C(6)–C(8)	1.510	1.498	C(5)–C(6)–C(8)	118.0	120.1	C(3)–C(2)–C(1)–C(22)	−169.5	−168.2
C(9)–N(10)	1.467	1.488	C(6)–C(1)–C(2)	118.5	119.0	C(7)–C(3)–C(4)–C(9)	−7.1	−8.8
C(11)–N(10)	1.468	1.488	C(6)–C(1)–C(22)	122.4	121.3	C(8)–C(6)–C(1)–C(22)	−8.8	−11.7
			C(9)–N(10)–C(11)	115.2	116.0			
			N(10)–C(9)–C(4)	111.2	112.0			
			C(9)–C(4)–C(5)	118.4	119.1			
			C(9)–C(4)–C(3)	122.9	121.2			

[a] Only symmetry-independent values are reported. [b] In the original X-ray structure[1] the values of torsional angles refer to the enantiomeric structure (signs are inverted).

these data show that the overall agreement is quite satisfactory, the only remarkable difference being the torsional angles involving the nitrogen atoms. This is not very surprising, since the X-ray structure was solved for the ditosyl derivative **1** whereas the calculations were performed on the free diamine. Furthermore, the *N*-tosyl substitution could be the reason for the fact that the X-ray structure and the calculated ground-state structure are not identical, although on the other hand the calculated energy difference between the two C_2 conformers is so small that crystal packing forces will easily account for such a conformational change.

Unfortunately the calculations of the rotational barrier of an aryl flip [rotation of one aryl ring by *ca.* 180°; interconversion by mode (b)] were not successful. All attempts to calculate the barrier resulted in uncontrolled elongation of at least one C–C single bond; on the other hand, use of the bond stretching potential without the cubic term gave extremely high and unrealistic barriers. Nevertheless, this fact further supports the experimental finding that the racemization barrier of **1** should be >35 kcal mol^{-1} (146.5 kJ mol^{-1}) and very close to that of bond rupture processes.

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