Conformational Analysis of 9,18-Difluoro-2,11-diaza[3.3]metacyclophane

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The conformational isomers (syn and anti) of 9,18-difluoro-2,11-diaza[3.3]metacyclophane, **1**, were isolated at ambient temperature and each was identified by ^{19}F NMR spectra. The anti isomer gradually converted to the syn isomer in solution, and kinetic measurements of this conversion afforded the Arrhenius activation energy, $E_a = 24.8 \pm 0.9$ kcal/mol, in acetonitrile. The difference in thermodynamic stability of the syn and anti isomers in DMSO was estimated to be ca. 2 kcal/mol (298 K) on the basis of the variable temperature NMR method. The three conformational isomers, boat−boat, chair−boat, and chair−chair, are present in the syn isomer in solution. The relative stability order of the three isomers, boat−boat, chair−boat, chair−chair, is estimated by the ^{1}H- and ^{19}F NMR spectra. The boat−boat isomer is predominant at low temperatures, but the ratio of the other two isomers, chair−boat and chair−chair, is gradually increased as the temperature is raised.

Introduction

Over the last 2 decades, the chemistry of cyclophanes has been extensively studied, and their structural properties have attracted much attention in addition to their transannular $\pi-\pi$ interaction or inclusion properties.[1]

Semmelhack et al.[2] and our group[3] independently elucidated that the temperature-dependent ^{1}H NMR phenomena of [3.3]metacyclophane (Figure 1, X = H, Y = CH_2) originated from a flipping of the trimethylene bridges. Furthermore, we clarified that inversion of the benzene ring is also responsible for the conformational isomerism of the [3.3]metacyclophane and that its energy barrier is much lower than that of the flipping process of the trimethylene bridges.[3] The most stable conformer of the [3.3]metacyclophane is the syn(chair−chair) one in solution and in the crystalline state.[2,3] The relative stability order of the three conformers with syn geometry is syn(chair−chair), syn(chair−boat), and syn(boat−boat), whereas the anti isomers are much less stable than the syn isomers.[3] Related compounds, the dithia- and diselena-[3.3]metacyclophanes, and the diaza- and diselena[3.3]-pyridinophanes are known and their solid-state structures and conformational analysis in solution have also been reported.[4] Particularly, the dithia[3.3]metacyclophanes with several substituents were synthesized and the syn or anti isomers were isolated.[5] In the case of X = H, the syn ⇌ anti interconversion process is rapid at room temperature, whereas the syn and anti isomers can be isolated by introducing a bulky group such as X = Me at the 9 and 18 positions.[5b] A borderline case is observed when X is a fluorine atom (van der Waals radius, 1.47 Å), which is larger than a hydrogen atom (1.20 Å).[6] In the case of 9,18-difluoro-2,11-dithia[3.3]metacyclophane (X = F, Y = S), the syn isomer was isolated as a stable conformer.[4a,b,5a]

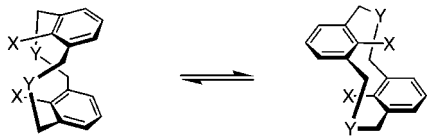

Figure 1. The structure of [3.3]metacyclophanes.

We previously reported the design and synthesis of fluorine-containing macrocyclic compounds.[7] During the course of that study, we noticed that 9,18-difluoro-2,11-diaza[3.3]metacyclophane, **1**, is an interesting molecule for conformational analysis; the syn and anti isomers can be isolated and the *anti*-**1** slowly converts into the *syn*-**1** in solution. We describe here the conformational analysis of **1** in solution.

Results and Discussion

The synthesis of **1** has already been reported by Plenio et al.,[8] and we also reported an alternative synthesis via

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the *p*-toluenesulfonamide.[7] Removing the tosyl groups from *N*,*N*′-ditosyl-9,18-difluoro-2,11-diaza[3.3]metacyclophane with HBr−phenol afforded *syn*- and *anti*-**1** in ca. 1:1 ratio, separable by silica gel chromatography (CH_2Cl_2/MeOH/aqueous NH_3 = 95/4/1). Heating an aqueous HCl solution of the syn or anti isomer at 80 °C followed by alkali treatment gives a mixture of *syn*- and *anti*-**1** in a 3:1 ratio. Thus, the syn or anti isomer can be recycled by this method.

Boekelheide and Anderson reported the identification of the anti and syn isomers of 9,18-difluoro-2,11-dithia-[3.3]metacyclophane based on dipole moment measurements.[4b] We employed ^{19}F NMR spectra for the identification of the isomers of **1**. The ^{19}F signal of *anti*-**1** appeared at a higher field than that of *syn*-**1** by 2 ppm in $CDCl_3$. Plenio et al. reported the spectral data and identification of the *syn*- and *anti*-**1**, and our data completely coincided with theirs.[8] In the ^1H NMR spectrum, the methylene and the aromatic signal of the *syn*-**1** appeared as an A_2X_2 pattern and a singlet, respectively, while the corresponding signals of the *anti*-**1** appeared as an A_2B_2 pattern and a multiplet. In the ^{13}C NMR spectrum, the methylene carbon of *syn*-**1** appeared as a broad singlet which shows the slow motion of the methylene moiety due to chair−boat interconversion. On the other hand, the methylene carbon signal of *anti*-**1** appeared as a sharp signal at higher field by ca. 6 ppm than that of *syn*-**1**. The chemical shifts of the aromatic carbons of *syn*-**1** are quite similar to those of *anti*-**1**, but J_{C-F} coupling constants are smaller than those of *anti*-**1** ($^2J_{C-F}$ < 9 Hz for syn, 16 Hz for anti; $^3J_{C-F}$ = 3 Hz for syn, 6 Hz for anti; $^4J_{C-F}$ = singlet for syn, 4 Hz for anti), while the $^1J_{C-F}$ was the same (246.5 Hz).

The energy barrier of the syn → anti conversion of 9,-18-difluoro-2,11-dithia[3.3]metacyclophane (X = F, Y = S) was reported to be 21.1 ± 0.5 kcal/mol.[5a] In the case of **1**, *anti*-**1** gradually converted to *syn*-**1** in solution. The energy barrier of the anti → syn conversion can be estimated by determination of the kinetic constants of this reaction. The kinetic measurements were performed in acetonitrile and gave the results of $k = 3.28(\pm0.07) \times 10^{-4}$ mol/dm^3/h (328 K) and $k = 1.01(\pm0.02) \times 10^{-3}$ mol/dm^3/h (338 K). The Arrhenius activation energy was estimated to be $E_a = 24.8 \pm 0.9$ kcal/mol on the basis of these data. In addition, in a solution of *syn*-**1** in DMSO-d_6, the generation of *anti*-**1** could be observed by ^1H NMR at high temperatures. Thus, the relative stability of the *syn*- and *anti*-**1** can be estimated. Isomer ratios were observed in the range of 110−170 °C, and each equilibrium constant was used for the calculation of the thermodynamic parameters using van't Hoff's plots to give $\Delta H = 1.42 \pm 0.11$ kcal/mol and $\Delta S = -1.9 \pm 0.2$ cal/mol K. These results are illustrated in Figure 2.

Conformation of Methylene Bridges in *syn*-1. By flipping of the methylene unit, $-CH_2NHCH_2-$, conformational isomers (chair−chair, chair−boat, boat−boat) occur in the *syn*-**1**. In the case of the [3.3]metacyclophane (X = H, Y = CH_2), the relative stability order of these conformers is chair−chair, chair−boat, boat−boat,[2,3a] while the relative stability order of boat−boat, chair−boat, chair−chair is observed in 2,11-diaza[3.3](2,6)-pyridinophane.[9] We also carried out variable temperature NMR analyses and MO (ab initio) calculations on 2,11-diaza[3.3]metacyclophane and its *N*-Me derivative, and clarified that the most stable conformers are boat−boat and chair−boat, respectively.[10] In the case of the *syn*-**1**, these conformers could be easily observed in the NMR spectra. In the ^1H NMR spectra at low temperatures, the methylene signal of the *syn*-**1** coalesced at −10 °C (CD_2Cl_2) and then split into three sets of double doublets below −70 °C (Figure 3a). The chair−chair and boat−boat conformers each exhibit one AB due to the molecular symmetry. The chair−boat conformer is seen as two AB

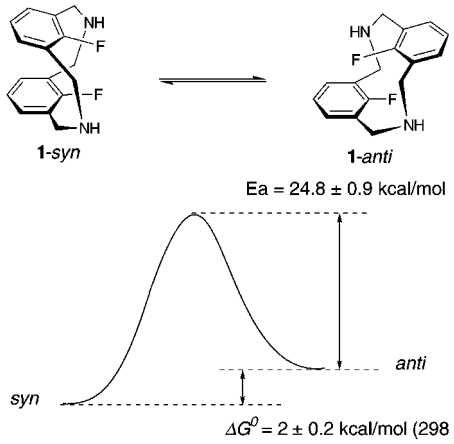

Figure 2. The energy diagram of syn−anti interconversion of **1**.

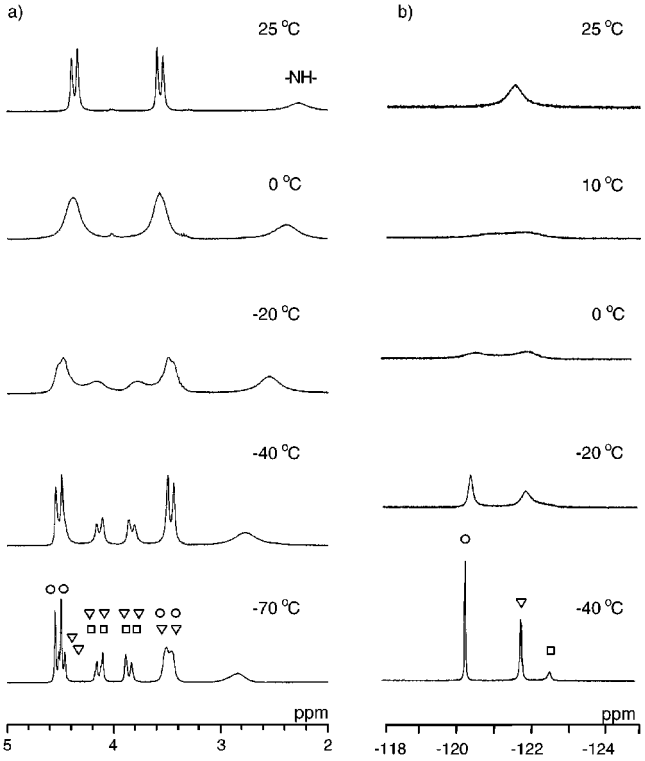

Figure 3. Variable temperature NMR spectra: (a) ^1H ($-CH_2-$) signal, (b) ^{19}F signal. Open circle, triangle, and square show the signals of the boat−boat, chair−boat, and chair−chair, respectively.

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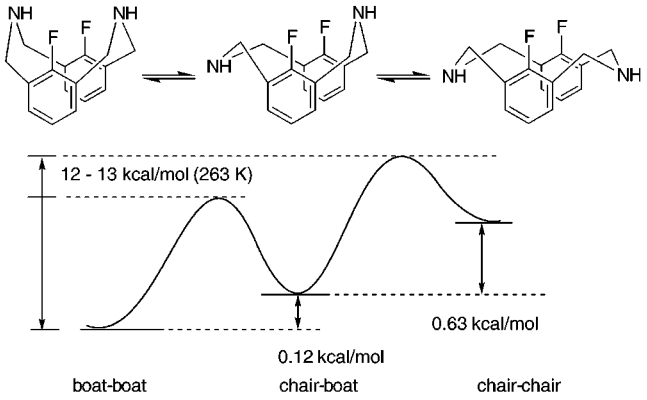

Figure 4. The energy diagram of boat−boat, chair−boat, and chair−chair interconversion at 203 K.

Table 1. Thermodynamic Parameters of the Equilibria among Boat−Boat (bb), Chair−Boat (cb), and Chair−Chair (cc) Conformations (errors are within 5%)

	bb ⇌ cb	cb ⇌ cc	bb ⇌ cc
ΔH (kcal/mol)	−0.49	−0.73	−1.23
ΔS (cal/mol K)	−1.9	−0.5	−2.4

patterns resulting from the methylene groups held in the chair and the boat regions. The boat and chair conformers could be distinguished by comparing the geminal coupling constants of the methylene proton signal. We previously reported that the methylene proton signal of the boat isomer of [3.3]metacyclophane derivative has ca. 1 Hz larger geminal coupling constant (J = 14.7 Hz) than that of the chair isomer (J = 13.8 Hz).[3a] A similar result was clearly shown in the oxaselenophane and its derivative (cyclic selenurane dication), in which the methylene moieties are fixed in the chair−chair (13.0 and 12.3 Hz) and boat−boat (15.9 and 16.1 Hz) conformation, respectively.[11] Thus, the three sets of double doublets of **1** at low temperatures were assigned as those of boat−boat, chair−boat, chair−chair (J_{boat} = 15.6 Hz, J_{chair} = 14.7 Hz) as shown in Figure 3a. The ratio of these signal intensities could be determined by separating each signal, or by observing the three isomers as well-resolved signals in VT ^{19}F NMR spectra (Figure 3b). The fluorine signal coalesced at 10 °C, and the three isomers were apparent at −40 °C. Taking into account the steric compression effect caused by compression of the fluorine nuclei by the NH proton or the nitrogen atom, the most deshielded fluorine signal is assigned to the boat−boat conformer, and the most shielded signal is due to the chair−chair conformer. The dipoles of the NH groups also result in the deshielding of the fluorine nuclei in the boat−boat conformation, more so than in the chair−boat and chair−chair conformers.[12] The obtained isomer ratios coincided with those from the ^{1}H NMR spectra within acceptable errors. The ratios of the three isomers were measured at −40 to −90 °C, and each equilibrium constant was used for the estimation of the thermodynamic parameters

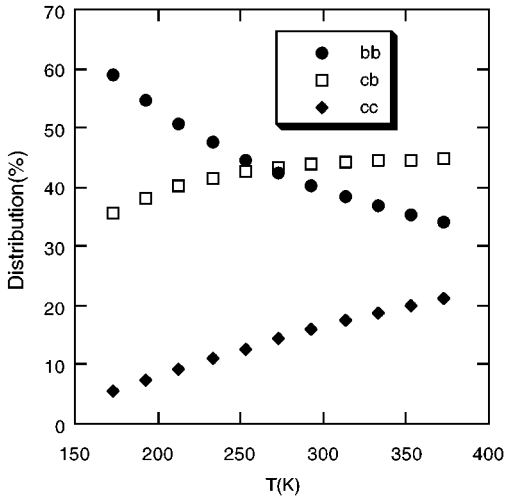

Figure 5. Distribution of boat−boat (bb), chair−boat (cb), and chair−chair (cc) conformations at 173−373 K.

ΔH and ΔS by van't Hoff's plots (Table 1). In addition, the overall activation energy of the boat ⇌ chair interconversion was estimated to be ΔG = 12−13 kcal/mol (263 K) on the basis of the coalescence temperature (263 K) of the methylene signal. The relative stability of each isomer at 203 K is illustrated in Figure 4. On the basis of the ΔH and ΔS values thus obtained, the distribution of each conformer at −100 to 100 °C was calculated (Figure 5). The boat−boat conformer is predominant at low temperatures, but the ratios of the chair−boat and chair−chair isomers increase as the temperature is raised. We should note that the relative stability of these isomers is dependent on temperature.

Experimental Section

The ^{1}H, ^{13}C, and ^{19}F NMR spectra were recorded at 400.1, 100.6, and 376.5 MHz, with TMS and $CFCl_3$ as internal references, respectively. The *syn*- and *anti*-**1** were recrystallized from CH_2Cl_2−CH_3CN. The kinetic measurements were performed in a temperature-controlled water bath at 55 and 65 ± 0.1 °C using a mixture of the *syn*- and *anti*-**1** (ca. 1:8) at the concentration of 1.97×10^{-2} mol dm^{-3} in CD_3CN. NMR spectra were recorded at intervals of 4 (55 °C) and 2 h (65 °C) until over the half-life period. The high-temperature NMR spectra in DMSO-d_6 were recorded every 10 °C in the range of 110−170 °C, and the syn/anti ratios were measured. The chair and boat isomers were observed by the ^{1}H and ^{19}F NMR spectra in the range from 25 to −90 °C, but the ratios of the isomers were measured by ^{19}F NMR at 10 °C intervals in the range from −40 to −90 °C.

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