Degenerate Racemization of Chiral Saddle Conformations in a Cyclic Dioxadithia Aryl Polyether

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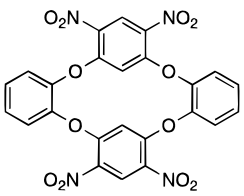
Introduction

The cyclic aryl polyether **1** derived from the base-mediated reaction of catechol with 1,3-difluoro-4,6-dinitrobenzene has been proposed by Lehmann to exist exclusively in a saddle-shaped conformation.[1] This conclusion was based on a single experimental observation; namely, the relatively high-field chemical shift observed for the inner-ring protons of **1** (5.67 ppm, DMSO-d_6). Studies with space-filling molecular models also supported this hypothesis.

Despite a potential saddle−saddle conformational inversion of **1**, evidence for such a process in alternating *ortho, meta*-linked cyclic aryl ethers of this type has not been reported. The regioselective preparation of analogs of **1** leading to chiral saddle conformers and, hence, pairs of conformational enantiomers has, to the best of our knowledge, also not been described. Ring inversion barriers in chiral saddle conformations of this type will dictate the feasibility of resolving conformational enantiomers,[2] or atropisomers,[3] which could ultimately provide intriguing homochiral scaffolds for use in synthesis and conformational studies. For these reasons, evidence of ring inversion in analogs of **1** displaying chiral saddle conformations and determination of the corresponding inversion barriers are of interest.



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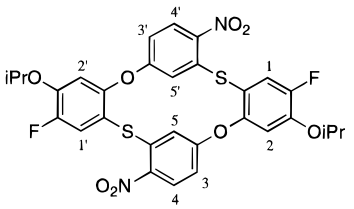
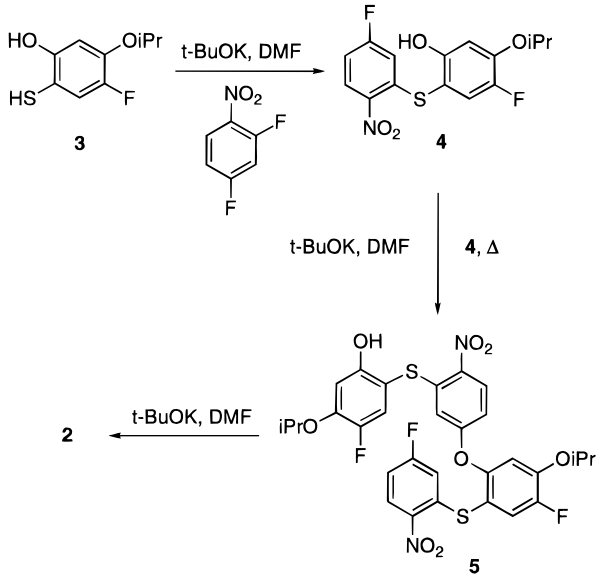


2

We have prepared the isopropoxy-substituted dioxadithia analog **2** by a route similar to that described for **1**.[1] If the macrocycle **2** exists in a saddle conformation similar to **1**, then the homotopic nitro, fluorine, sulfur, and isopropoxy substituents will independently render the saddle conformation of **2** chiral, leading to a pair of conformational enantiomers. In addition, the isopropoxy groups of **2** will serve as a prochiral probe for investigating conformational inversion in this ring system. Herein, we relate molecular modeling results together with ^{1}H NMR data which support the conclusion that macrocycle **2** exists in a chiral saddle-shaped conformation. In addition to the anisotropic shielding of the inner-ring protons of **2** (H-5/5′), we describe NOEs in **2** that strengthen the saddle conformation argument. More significantly, dynamic ^{1}H NMR spectra of **2**, utilizing the homotopic isopropoxy groups as a prochiral probe, support a rapid equilibration of saddle-shaped conformational enantiomers (a degenerate racemization) at elevated temperatures.

Scheme 1. Synthesis of the Cyclic Dioxadithia Aryl Polyether 2



Results and Discussion

The macrocycle **2** was formed by reaction of 3-fluoro-6-hydroxy-4-isopropoxythiophenol (**3**)[4] with 2,4-difluoronitrobenzene and 2 equiv of potassium *tert*-butoxide in DMF.[5] The high reactivity of the thiolate anion directs the regioselectivity in this reaction. Presumably, the 2-nitrophenyl sulfide (**4**) is formed as an intermediate[6] which then undergoes dimerization to **5** followed by cyclization to **2** (Scheme 1). Mass spectrometry of the product established a molecular weight of 642 amu, and the chemical shifts in the ^{13}C NMR spectrum ($CDCl_3$) were consistent with structure **2**. The ^{1}H NMR spectrum (DMSO-d_6) exhibited five aromatic protons, indicative of a symmetrical dimeric structure. In order to simplify the discussion, these protons are numbered H-1/1′ to H-5/5′ (see structure **2**). An unusually low chemical shift of 5.70

† Author to whom correspondence concerning the theoretical computations should be addressed.

(1) Lehmann F., P. A. *Tetrahedron* **1974**, *30*, 727−733.

(2) Conformational isomers with energy barriers between them of less than *ca.* 20 kcal/mol are typically inseparable under normal conditions; see reference 3 and (a) Lowry, T. H.; Richardson, K. S. *Mechanism and Theory in Organic Chemistry*, 2nd ed.; Harper & Row: New York, 1981; pp 115−130. (b) Gilman, N. W.; Rosen, P.; Earley, J. V.; Cook, C.; Todaro, L. J. *J. Am. Chem. Soc.* **1990**, *112*, 3969−3978 and references cited therein.

(3) For a review of atropisomerism, see: Oki, M. *Topics Stereochem.* **1983**, *14*, 1−81.

(4) Compound **3** was prepared by fluorination of commercially available 6-hydroxy-1,3-benzoxathiol-2-one with 1-fluoro-3,5-dichloropyridinium triflate,[2a] isopropylation of the resulting 5-fluoro derivative,[2b] and basic hydrolysis of the oxathiolone moiety, respectively. (a) Umemoto, T.; Fukami, S.; Tomizawa, G.; Harasawa, K.; Kawada, K.; Tomita, K. *J. Am. Chem. Soc.* **1990**, *112*, 8563−8575. (b) Cresp, T. M.; Sargent, M. V. *J. Chem. Soc., Perkin Trans. 1* **1974**, 2145−2153.

(5) A minor impurity in **2** was detected by HPLC/UV and by ^{1}H NMR. Attempts at further purification by recrystallization and flash chromatography were unsuccessful owing to the poor solubility properties of this compound.

(6) (a) Anions of 2-hydroxythiophenols react preferentially at the thiolate position with 2-halonitrobenzenes; see: Martin, G. E.; Turley, J. C.; Williams, L.; Steenberg, M. L.; Buckley, J. P. *J. Heterocycl. Chem.* **1977**, *14*, 1067−1069. (b) 2,4-Dihalonitrobenzenes react preferentially at the 2-position with nucleophiles; see: Galbreath, R. J.; Ingham, R. K. *J. Org. Chem.* **1958**, *23*, 1804−1806 and references cited therein.

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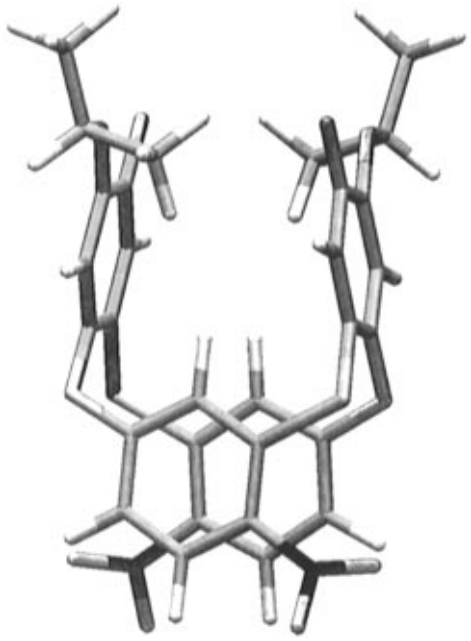
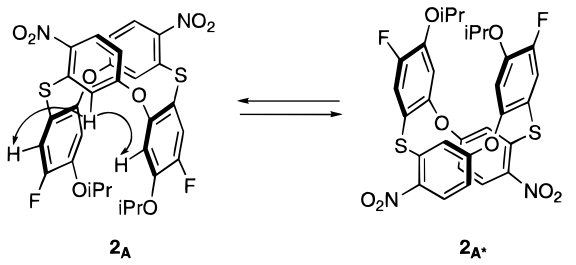


Figure 1. Global energy minimum of structure **2** obtained from a Monte Carlo conformational search.

ppm was observed for the inner-ring protons (H-5/5′) which appeared as a doublet (J = 2.6 Hz). This is nearly identical to the chemical shift reported for the corresponding inner-ring protons of **1**.[1] The nonequivalence of the geminal isopropyl methyls of **2** was evidenced by the presence of two distinct doublets at 1.37 and 1.34 ppm (J = 6.0 Hz); this anisochrony was more pronounced in benzene-d_6 in which the two methyl doublets appeared at 1.17 and 0.94 ppm (J = 6.0 Hz).[7]

In order to determine a theoretical ground state conformation for comparison with our ^{1}H NMR data, we performed a Monte Carlo global conformational search of structure **2** (see Experimental Section). A search of 1000 conformations produced the chiral saddle conformation shown in Figure 1 as the global minimum,[8] indicating a pair of ground state saddle-shaped enantiomers. In this saddle-like arrangement, the inner-ring protons of **2** are exposed to the shielding cones of both flanking isopropoxy-substituted aromatic rings. This anisotropic shielding explains the relatively high-field chemical shift observed for the inner-ring nuclei of **1**[1] and **2**.[9] The presence of two methyl resonances in the ^{1}H NMR spectrum of **2** is also consistent with the diastereotopic relationship between the pro-*R* and pro-*S* methyl groups in the saddle-like conformation. Another noteworthy feature of the saddle conformation, not exploited in the analysis of **1**, is the proximity of each inner-ring proton to the two flanking protons on the adjacent isopropoxy-substituted aromatic rings. The internuclear distances

Scheme 2. Saddle−Saddle Inversion and ^{1}H NOEs of 2



2A **2A***

from H-5 to H-1′ (H-5′ to H-1) and H-5 to H-2 (H-5′ to H-2′) in the global minimum conformation of **2** are 3.0 and 2.8 Å, respectively. The proximity of these nuclei in **2** were confirmed by an NOE experiment in which irradiation of the signal at 5.70 ppm (H-5/5′) produced strong enhancements of near equal intensity in the signals at 7.61 (H-1/1′) and 7.39 ppm (H-2/2′) (Scheme 2). This result served to further substantiate a saddle conformation of **2** in solution.

A potential conformational inversion of **2** was investigated by dynamic ^{1}H NMR spectroscopy utilizing the homotopic isopropoxy substituents as a prochiral probe. Two methyl doublets were observed in the ^{1}H NMR spectrum of **2** in DMSO-d_6 at 298 and 323 K. When the sample was heated to 353 K, a single broad methyl signal was observed; this became a sharp doublet at 373 K. When the isopropyl methine proton was decoupled during the variable temperature studies, we observed the coalescence of two methyl singlets at 353 K. The resulting broad singlet continued to sharpen up to 393 K, the highest temperature studied. The remaining signals in the spectrum remained sharp and unchanged throughout the course of the experiment, with the exception of a slight decrease in the chemical shifts of the outer-ring protons and a slight increase in the chemical shift of the inner-ring protons from 298 to 393 K (±0.12 ppm).

At ambient temperature, equilibration of the isopropoxy rotomers of **2** is assumed to be rapid on the NMR time scale relative to conformational inversion. The nitro-substituted rings in the saddle conformer may also oscillate slightly about the nitro aryl C−O and C−S bonds, but ring inversion to an enantiomeric saddle conformer is impeded by interference involving the two inner-ring protons (H-5/5′) and ring heteroatoms. At elevated temperatures, a rapid equilibration of enantiotopic saddle conformers explains the coalescence of the methyl signals observed in the ^{1}H NMR spectrum.[10] As illustrated in Scheme 2, ring inversion of saddle conformer $\mathbf{2_A}$ produces its enantiomer $\mathbf{2_{A^*}}$, and this degenerate racemization mechanism enables the pro-*R* and pro-*S* methyl groups to exchange stereoenvironments. If this process is rapid on the NMR time scale, a maximum of one methyl signal would be predicted, as observed experimentally. From the peak separation of 9.5 Hz between the methyl singlets in the methine-decoupled spectrum of **2** at 323 K, a first-order rate constant (k_{coal}) of 21.1 s^{-1} at the coalescence temperature (T_c = 353 K) was obtained for the ring inversion of **2**, from which a free energy of activation $\Delta G^{\ddagger}$ = 18.6 kcal/mol was calculated.[11] This energy barrier is lower than that

(7) For a brief discussion of the effects of solvent on chemical shift nonequivalence of prochiral groups, including aromatic solvent induced shift (ASIS), see Jennings, W. B. *Chem. Rev.* **1975**, *75*, 307−322.

(8) A similar Monte Carlo global conformational search of structure **2** *minus the isopropoxy and nitro groups* also produced the saddle-shaped arrangement as the global minimum.

(9) The calculated chemical shifts for the inner-ring protons of **1** and **2** using NO_2, SPh, and OPh benzene substituent effects are 7.20 and 7.29 ppm, respectively. This indicates similar anisotropic shielding in both systems. For the effects of substituents on the chemical shift of benzene ring protons, see: Pretsch, E.; Clerc, T.; Seibl, J.; Simon, W. In *Tables of Spectral Data for Structure Determination of Organic Compounds*; Fresenius, W., Huber, J. F. K., Pungor, E., Rechnitz, G. A., Simon, W., West, T. S., Eds.; Springer-Verlag: Berlin, Germany, 1989; pp H255−H260.

(10) For examples involving the use of prochiral probes to investigate ring inversion phenomena, see reference 7 and (a) Anet, F. A. L. *J. Am. Chem. Soc.* **1964**, *86*, 458−460. (b) Downing, A. P.; Ollis, W. D.; Sutherland, I. O. *J. Chem. Soc. (B)* **1970**, 24−34. (c) Ollis, W. D.; Stoddart, J. F. *J. Chem. Soc., Chem. Commun.* **1973**, 571−572.

typically required for separation of conformational isomers at ambient temperature.[2]

Summary

^{1}H NMR, NOE, and molecular modeling results support the conclusion that macrocycle **2** preferentially adopts a chiral saddle-shaped conformation, leading to a pair of ground state conformational enantiomers. Dynamic ^{1}H NMR spectra support a saddle-saddle conformational inversion of **2** (a degenerate racemization) at elevated temperatures with a free energy of activation $\Delta G^{\ddagger} = 18.6$ kcal/mol. Steric interactions involving the inner-ring protons of **2** (H-5/5′) are likely during ring inversion, and the incorporation of substituents larger than hydrogen at these positions should dramatically increase conformational inversion barriers in these heterocycles.

Experimental Section

General. ^{1}H, ^{13}C, and ^{19}F NMR were recorded at 300, 75, and 282 MHz, respectively. ^{1}H NMR coupling constants are ^{1}H−^{1}H unless otherwise noted. ^{1}H NMR chemical shifts are reported in ppm relative to the residual protonated solvent resonance: δ 2.50 (DMSO-d_6) and δ 7.15 (C_6D_6). ^{13}C NMR chemical shifts are reported in ppm relative to the solvent resonance at δ 76.9 ($CDCl_3$). ^{19}F NMR chemical shifts are reported in ppm relative to a trifluoroacetic acid external standard. Mass spectral analyses were performed by Oneida Research Services, Whitesboro, NY. Elemental analyses were performed by Atlantic Microlabs, Norcross, GA.

2,13-Difluoro-3,14-diisopropoxy-9,20-dinitro-6,10:17,21-dimethenodibenzo[*b*,*k*][5,16]dioxa[11,22]dithiacyclooctadecin (2). A solution of 3-fluoro-6-hydroxy-4-isopropoxythiophenol[4] (**3**) (233 mg, 1.15 mmol) in DMF (3 mL) was added dropwise to an ice-cooled stirring mixture of potassium *tert*-butoxide (129 mg, 1.15 mmol) in DMF (3 mL), and the resulting mixture was stirred for 5 min. A solution of 2,4-difluoronitrobenzene (129 mg, 1.15 mmol) in DMF (3 mL) was added dropwise, and, after stirring an additional 5 min at 0 °C, the mixture was allowed to warm to rt. HPLC analysis indicated complete conversion to an intermediate assigned structure **4** based on the UV spectrum[12] obtained from the photodiode array detector. Additional potassium *tert*-butoxide (128 mg, 1.14 mmol) was added *via* spatula, and the mixture was stirred overnight at rt at which point HPLC indicated mostly unreacted **4**. The reaction mixture was heated at reflux for 1 h, allowed to cool, and then concentrated at reduced pressure. The crude material was washed with CH_2Cl_2/H_2O and filtered, collecting **2** (110 mg, 0.17 mmol, 30% yield) as a yellow solid: mp 279−284 °C dec; ^{1}H NMR (DMSO-d_6) δ 8.11 (2H, d, $J = 9.2$), 7.61 (2H, d, $J_{HF} = 10.5$), 7.39 (2H, d, $J_{HF} = 7.6$), 7.05 (2H, dd, $J = 9.2, 2.6$), 5.70 (2H, d, $J = 2.6$), 4.73 (2H, sept, $J = 6.0$), 1.37 (6H, d, $J = 6.0$), 1.34 (6H, d, $J = 6.0$); ^{1}H NMR (C_6D_6) δ 7.63 (2H, d, $J = 9.2$), 6.79 (2H, d, $J_{HF} = 10.5$), 6.41 (2H, dd, $J = 9.2, 2.6$), 6.26 (2H, d, $J_{HF} = 7.3$), 5.51 (2H, d, $J = 2.6$), 3.86 (2H, sept, $J = 6.0$), 1.17 (6H, d, $J = 6.0$), 0.94 (6H, d, $J = 6.0$); ^{19}F NMR ($CDCl_3$) δ −54.7 (2F, t, $J_{FH} \sim 8$); ^{13}C NMR ($CDCl_3$) δ 161.5, 152.4 (d, $J_{CF} = 3$), 150.2 (d, $J_{CF} = 250$), 149.7 (d, $J_{CF} = 11$), 140.4, 138.3, 128.4, 125.4 (d, $J_{CF} = 20$), 114.8, 112.8 (d, $J_{CF} = 6$), 112.5, 110.6 (d, $J_{CF} = 2$), 72.6, 21.6; CIMS *m*/*z* 643 (M + 1, 100); HPLC mobile phase: 80% MeOH/H_2O/0.1%TEA/0.1%TFA; stationary phase: 4 μm Waters Nova-Pak Phenyl (major peak: 95%, $K' = 10.2$). Anal. Calcd for $C_{30}H_{24}F_2N_2O_8S_2 \cdot 0.5H_2O$: C, 55.29; H, 3.87; N, 4.30; S, 9.84. Found: C, 55.09; H, 3.84; N, 4.29; S, 9.84.

Molecular Modeling Procedure for 2. The structure of **2** was built in MacroModel 4.0[13] and minimized with the MM3* force field.[14] It was then subjected to Monte Carlo global conformational searching using the default MCMM (Monte Carlo Multiple Minimum) setup in MacroModel. MacroModel identifies rotatable bonds for Monte Carlo scanning, selects the number of rotatable bonds which are varied during each Monte Carlo step, minimizes each Monte Carlo candidate, manages the population of low energy conformations within a 0−50 kJ window, and selects a starting conformation for the next Monte Carlo step from this population on the basis of least usage. The Truncated Newton (TNCG) minimization method[15] was chosen to achieve good convergence in minimization.

Acknowledgment. The authors thank Professor Ernest L. Eliel for helpful discussion and for a preliminary review of this manuscript. We also thank William R. Hall for performing the analytical HPLC analyses.

Supporting Information Available: Copies of 300 MHz ^{1}H NMR spectra for **2** including NOE and dynamic NMR (6 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

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(11) Determined from $k_{coal} = {}^1/_2\pi\Delta\nu(2)^{1/2} = (kT/h)e^{-\Delta G/RT}$; see: Eliel, E. L. *Topics Curr. Chem.* **1982**, *105*, 1−76 and references cited therein.

(12) UV maxima of **4** were observed at 205, 233, 290, and 363 nm. For the UV absorption spectrum of the 2-nitrophenyl phenyl sulfide chromophore, see: Koch, H. P. *J. Chem. Soc.* **1949**, 387−394.

(13) Mohamadi, F.; Richards, N. G. J.; Guida, W. C.; Liskamp, R.; Lipton, M.; Caufield, C.; Chang, G.; Hendrickson, T.; Still, W. C. *J. Comput. Chem.* **1990**, *11*, 440−467.

(14) (a) Allinger, N. L.; Yuh, Y. H.; Lii, J.-H. *J. Am. Chem. Soc.* **1989**, *111*, 8551−8566. (b) Lii, J.-H.; Allinger, N. L. *Ibid.* **1989**, *111*, 8566−8575. (c) Lii, J.-H.; Allinger, N. L. *Ibid.* **1989**, *111*, 8576−8582.

(15) Ponders, J. W.; Richards, F. M. *J. Comput. Chem.* **1987**, *8*, 1016−1024.