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Synthesis, Enantiomeric Conformations, and Stereodynamics of Aromatic *ortho*-Substituted Disulfones

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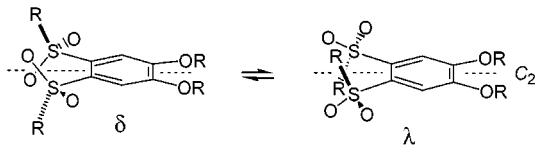
ABSTRACT



Aromatic *ortho*-disulfone derivatives are readily accessible from diiodide precursors by Cu(I)-mediated reactions with sodium sulfinate salts. The sulfone substituents adopt C_2-symmetric enantiomeric conformations (λ and δ) as evidenced by X-ray structural analysis and ^{1}H and ^{31}P NMR on chiral bis(sulfonyl)veratrol derivatives and hexacoordinated tris(benzenediolato)phosphate anions. Slow dynamic conformational isomerism ($\Delta G^{\ddagger} \geq 19.8$ kcal mol^{-1}) was detected in solution.

The octahedral geometry of pentavalent hexacoordinated phosphorus allows the formation of chiral anions—Δ and Λ enantiomers—by complexing the phosphorus with three identical catecholate ligands.[1] Recently, we reported that the introduction of electron-withdrawing groups (chlorine atoms) on the aromatic nuclei increases the configurational stability of the resulting tris(tetrachlorobenzenediolato)phosphate(v) (or TRISPHAT **1**) derivative (Figure 1).

This anion, resolved by association with an enantiopure ammonium cation, is an efficient NMR chiral shift reagent for cationic and neutral molecules, a powerful resolving agent for ruthenium(II) complexes, and chiral inducer onto iron(II) tris(diimine) compounds.[2] To extend the pool of chiral anions for possible asymmetric applications, we decided to prepare a hexacoordinated phosphate anion (**2**) derived from a new catechol ligand substituted with stronger electron-withdrawing *p*-toluenesulfonyl residues (SO_2-*p*Tol). In this letter, we report that the introduction of *ortho p*-toluenesulfonyl groups on the catechol rings of chiral phosphate anion **2** is not asymmetrically innocent. The *ortho* sulfones adopt C_2-symmetric enantiomeric conformations (δ and λ) that interconvert slowly on the NMR time scale. This leads to mixtures of diastereomeric hexacoordinated phosphate anions that can be observed in ^{31}P NMR. This unusual stereodynamic

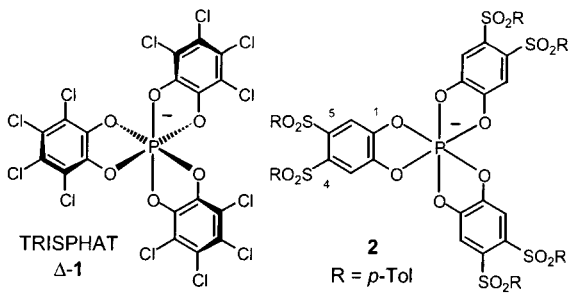


Figure 1. Chiral hexacoordinated phosphate anions.

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(1) Hellwinkel, D.; Wilfinger, H. J. *Chem. Ber.* **1970**, *103*, 1056−1064. Allcock, H. R.; Bissell, E. C. *J. Am. Chem. Soc.* **1973**, *95*, 3154−3157. Hellwinkel, D.; Krapp, W. *Phosphorus* **1976**, *6*, 91−93. Koenig, M.; Klaebe, A.; Munoz, A.; Wolf, R. *J. Chem. Soc., Perkin Trans. 2* **1976**, 955−958. Koenig, M.; Klaebe, A.; Munoz, A.; Wolf, R. *J. Chem. Soc., Perkin Trans. 2* **1979**, 40−44. Cavezzan, J.; Etemad-Moghadam, G.; Koenig, M.; Klaebe, A. *Tetrahedron Lett.* **1979**, 795−798. Lacour, J.; Ginglinger, C.; Grivet, C.; Bernardinelli, G. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 608−609.

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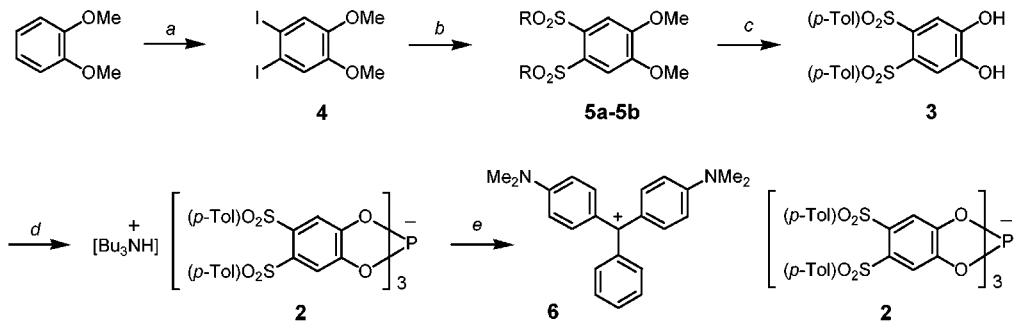
Scheme 1. Synthesis and Isolation of Phosphate Anion **2**[a]



[a] (a) I_2, H_5IO_6, MeOH, 70 °C, **4** (83%); (b) CuI, RSO_2Na, DMF, 110 °C, **5a** (R = *p*-Tol, 88%), **5b** (R = (+)-camphor-10-, 85%); (c) **5a**, BBr_3 (5.0 equiv), CH_2Cl_2, **3** (R = *p*-Tol, 93%); (d) PCl_5 (0.33 equiv), CH_2Cl_2, then DMF, 25 °C; Bu_3N, 25 °C, [Bu_3NH][**2**]; (e) malachite green chromatography (SiO_2, CH_2Cl_2), [**6**][**2**] (two steps, 63%).

behavior was further proved by the synthesis of 4,5-bis((+)-camphor-10-sulfonyl)veratrol, whereas the atropisomers can be simply monitored by ^{1}H NMR.[3]

4,5-Bis(*p*-toluenesulfonyl)catechol **3**, necessary for the making of anion **2**, was prepared in three steps and good overall yield (Scheme 1). From veratrol, diiodination with I_2/H_5IO_6 proceeded smoothly to give **4** (83%).[4] Bis-sulfonylation of **4** by a Cu(I)-mediated reaction with sodium *p*-toluenesulfinate resulted,[5] after optimization, in the synthesis of **5a** (88%). ^{1}H NMR analyses of **5a** did not reveal any particularity except a signal broadening, which could only be understood in the course of this study. Deprotection of **5a** using classical conditions (BBr_3, CH_2Cl_2) led to the 4,5-bis(*p*-toluenesulfonyl)catechol **3** in 93% yield.

Anion **2** was prepared by addition of **3** to PCl_5 in CH_2Cl_2. Concentration in vacuo and addition of DMF and then ^{n}Bu_3N afforded the [^{n}Bu_3NH][**2**] salt along with minor amounts of degradation products (Scheme 1). Purification of the crude reaction mixture was effected by the addition of malachite green and subsequent chromatography (SiO_2, CH_2Cl_2) to give the bis(dimethylaminophenyl)phenylmethinium (**6**) salt, [**6**][**2**], in 63% yield (two steps).[6]

Characterization of salt [**6**][**2**] by ^{31}P NMR was, at first glance, puzzling. Four signals (DMSO-d_6, δ −76.7, −77.3, −77.5, and −78.2, Figure 2) were observed in the −80 ppm region characteristic of the tris(benzenediolato)phosphate anions, while only one was expected. This result was furthermore surprising as only one set of signals corresponding to anion **2** could be observed in ^{1}H NMR. Further characterization of salt [**6**][**2**] by mass spectrometry (ES-MS) confirmed its structural integrity. The four signals in ^{31}P NMR could not be explained by the presence of four different chemical compounds and had to be solely attributed to compound **2**. It appeared to us that this situation for **2** was somewhat reminiscent of what is usually noticed for tris(bidentate) octahedral complexes made of nonplanar chelate rings, such as $[Co(en)_3]^{3+}$. As first noted by Corey and Bailar,[7] when chelate rings adopt chiral conformations (δ and λ), four diastereomers, always appearing in enantiomeric pairs, are generated as a result of the inherent chirality of the octahedral complexes (Δ and Λ): $\Delta(\delta\delta\delta)/\Lambda(\lambda\lambda\lambda)$, $\Delta(\delta\delta\lambda)/\Lambda(\lambda\lambda\delta)$, $\Delta(\delta\lambda\lambda)/\Lambda(\lambda\delta\delta)$, $\Delta(\lambda\lambda\lambda)/\Lambda(\delta\delta\delta)$.[8] However, for **2**, the planarity of the chelating catechol rings was not compatible with such an explanation. If chiral conformations were to be the source of the four signals observed in ^{31}P NMR, they would have to result from the spatial arrangement of the sulfonyl substituents.

It was indeed highly probable that, to minimize strong dipolar interactions, the *ortho* sulfonyl groups would adopt an "up-and-down" arrangement with regard to the aromatic plane (Figure 3). This disposition of the sulfonyl groups imparts a C_2-symmetry and thus the adoption by the *ortho* substituents of two enantiomeric helical conformations (δ

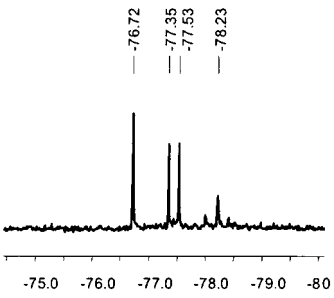


Figure 2. ^{31}P NMR (DMSO-d_6, 162 MHz, parts) of [**6**][**2**].

(2) See Lacour et al. (last reference of footnote 1) and the following: Lacour, J.; Jodry, J. J.; Ginglinger, C.; Torche-Haldimann, S. *Angew. Chem., Int. Ed. Engl.* **1998**, *37*, 2379−2380. Lacour, J.; Goujon-Ginglinger, C.; Torche-Haldimann, S.; Jodry, J. J. *Angew. Chem., Int. Ed.* **2000**, *39*, 3695−3697. Ratni, H.; Jodry, J. J.; Lacour, J.; Kündig, E. P. *Organometallics* **2000**, *19*, 3997−3999.

(3) For a general overview of atropisomerism, see: Eliel, E. L.; Wilen, S. H. *Stereochemistry of Organic Compounds*; John Wiley & Sons: New York, 1994; pp 1142−1155.

(4) Suzuki, H.; Nakamura, K.; Goto, R. *Bull. Chem. Soc. Jpn.* **1966**, *39*, 128−131.

(5) Suzuki, H.; Abe, H. *Tetrahedron Lett.* **1995**, *36*, 6239−6242.

(6) Lacour, J.; Barchéchath, S.; Jodry, J. J.; Ginglinger, C. *Tetrahedron Lett.* **1998**, *39*, 567−570.

(7) Corey, E. J.; Bailar, J. C., Jr. *J. Am. Chem. Soc.* **1959**, *81*, 2620−2629.

(8) Von Zelewsky, A. *Stereochemistry of Coordination Compounds*; John Wiley & Sons: Chichester, U.K., 1996.

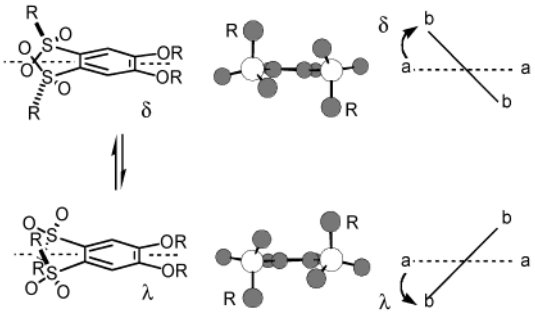


Figure 3. Views of the conformations adopted by *ortho* sulfonyl groups and configurational assignment (δ and λ); a·····a constitutes the plane of the phenyl ring; b·····b is a line passing through the R substituents.

and λ) depending on their left- or right-handed orientation, respectively.[9]

The existence of these chiral conformations was first confirmed by the X-ray structural analysis of **5a**·C_6H_{12}. The molecular conformation observed in the solid state shows a C_2 axis passing through bonds C(1)−C(2) and C(4)−C(5) of **5a** (Figure 4). Both δ and λ configurations of **5a** are

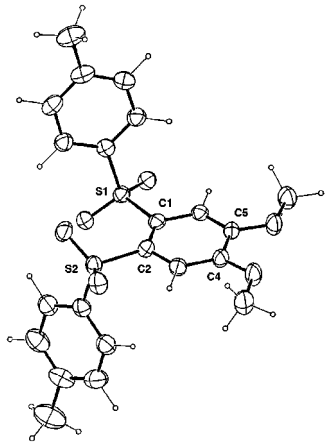


Figure 4. Ortep view (ellipsoids at the 50% probability level) of the crystal structure of **5a** (δ configuration) showing the "up-and-down" orientation of the *p*-tolyl substituents.

observed since the compound crystallizes in the centrosymmetric space group $P\bar{1}$.[10]

The presence of these enantiomeric δ and λ conformations was then confirmed in solution by preparing the 4,5-bis((+)-camphor-10-sulfonyl)veratrol **5b**, whose conformational isomerism could be easily monitored by ^{1}H NMR. The synthesis of **5b** turned out to be more challenging than of **5a** (Scheme 1). Sodium (+)-camphor-10-sulfinate salt **7** was unstable and decomposed slowly at room temperature (monitoring by IR) even under inert conditions (N_2).[11] A large excess of **7** (25 equiv) was required for the Cu(I)-mediated bis(sulfonylation) reaction to proceed with good yield (**5b**, 85%).

^{1}H NMR analysis at room temperature of **5b** revealed two sets of signals, as could be expected from the introduction of new stereogenic centers, corresponding to the diastereomeric δ and λ conformations. Diastereotopic protons H(10) and the geminal methyl groups of the camphorsulfonyl units were split, as well as the aromatic protons H(3′) (Figure 5)

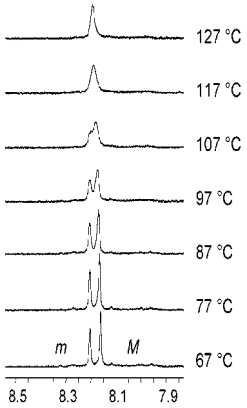
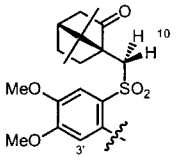


Figure 5. Variable temperature ^{1}H NMR (400 MHz, DMSO-d_6) of **5b**. Proton H(3′) of the major (M) and minor (m) diastereomeric conformations. Coalescence temperature, 117 °C.

and the methoxy groups of the veratrol ring (Table 1). The two diastereomeric δ and λ conformations in **5b** are not evenly populated as the integration of the respective signals reveals a 2.25:1 diastereomeric ratio. The chiral (+)-camphor-10-sulfonyl units lead not only to the magnetic nonequivalency of the conformations but also to an asymmetric induction in favor of one of the λ or δ configurations.[12]

Dynamic conformational isomerism was detected for **5b** in ^{1}H NMR with a coalescence temperature of 117 °C for the signals (400 MHz, Figure 5), demonstrating without ambiguity the slow interconversion at room temperature between diastereomeric δ and λ conformations of the *ortho*

Table 1. Chemical Shifts in ^{1}H NMR (400 MHz, $CDCl_3$) for Selected Protons of the Major (M) and Minor (m) Diastereomeric Conformations of **5b**



	m	M
H(3′)	8.29	8.20
H(10)	5.19	4.98
	4.64	4.63
H(OMe)	3.16	3.28
H(Me)	1.04	1.05
	0.91	0.90

(9) For an example of such chiral conformation in a highly twisted hexasubstituted arene, see: Collard, D. M.; Sadri, M. J.; VanDerveer, D.; Hagen, K. S. *J. Chem. Soc., Chem. Commun.* **1995**, 1357−8.

(10) See the CIF file in the Supporting Information.

disulfones. The corresponding free energy of interconversion is 19.8 kcal mol^{-1}.[13]

Taking thus into account the existence, in the solid state and in solution, of enantiomeric δ and λ conformations for the *ortho* disulfones of each of the three chelating catechols, four diastereomers, always appearing in enantiomeric pairs, can be considered for anion **2**: $\Delta(\delta\delta\delta)/\Lambda(\lambda\lambda\lambda)$, $\Delta(\delta\delta\lambda)/\Lambda(\lambda\lambda\delta)$, $\Delta(\delta\lambda\lambda)/\Lambda(\lambda\delta\delta)$, $\Delta(\lambda\lambda\lambda)/\Lambda(\delta\delta\delta)$. Each of the signals observed in the ^{31}P NMR spectra can thus be assigned to one of the diastereomers, considering that the rate of interconversion of the *p*-toluenesulfonyl groups is slow compared to the NMR time scale. A stereodynamic study was attempted by variable temperature in ^{31}P NMR. Within the range of temperature studied (DMSO-d_6, 25−147 °C, 162 MHz), no variation in the shape of the four signals was observed, showing a very slow equilibration of the δ and λ conformations of the *ortho*-*p*-toluenesulfonyl substituents.[14]

In conclusion, aromatic o*rtho* disulfone derivatives adopt two precise C_2-symmetric enantiomeric conformations, which can be detected by the formation of chiral hexacoordinated tris(benzenediolato) phosphate anions or by the synthesis of enantiopure camphor-10-sulfonyl derivatives. The rate of interconversion is slow on the NMR time scale and depends on the nature of the sulfonyl side chains ($\Delta G^{\ddagger} \geq 19.8$ kcal mol^{-1}).

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Supporting Information Available: ^{1}H, ^{13}C, and/or ^{31}P NMR spectra for compounds [**6**][**2**], **3** and **5a**−**5b** and X-ray crystallographic CIF file for **5a**·C_6H_{12}. This material is available free of charge via the Internet at http://pubs.acs.org.

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(11) Salt **7** was prepared following the directions found in Krauthausen, E. In *Organosulfur Compounds*; fourth ed.; Klamann, D., Ed.; Georg Thieme Verlag: Stuttgart, 1985; Vol. E11, p 619.

(12) No attempts have been made to determine which of the two diastereomeric conformations is preferred.

(13) The relationship $\Delta G^{\ddagger} = RT_c(22.96 + \ln(T_c/\Delta\nu))$ was used to determine the activation energy, $\Delta G^{\ddagger}$, from the coalescence temperature, T_c (K), and the frequency separation of the peaks, $\Delta\nu$ (Hz).

(14) The activation energy $\Delta G^{\ddagger}$ is higher than 21.4 kcal mol^{-1}, considering a $T_c \geq 147$ °C and a minimum $\Delta\nu$ value of 29 Hz ($\Delta\delta$ −77.35 to −77.53).