ORGANIC LETTERS

2001
Vol. 3, No. 9
1407−1410

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

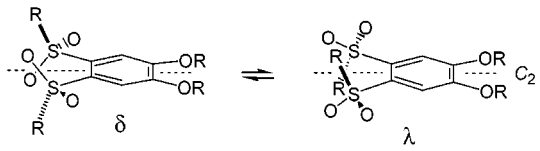
Jérôme Lacour,*,† David Monchaud,† Gérald Bernardinelli,‡ and France Favarger†

Département de Chimie Organique, Université de Genève, quai Ernest-Ansermet 30, CH-1211 Genève 4, Switzerland, and Laboratoire de Cristallographie, Université de Genève, quai Ernest-Ansermet 24, CH-1211 Genève 4, Switzerland

jerome.lacour@chiorg.unige.ch

Received March 7, 2001

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

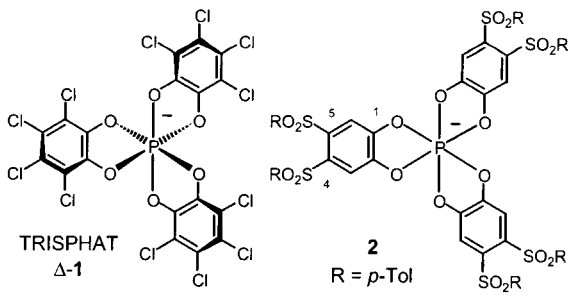


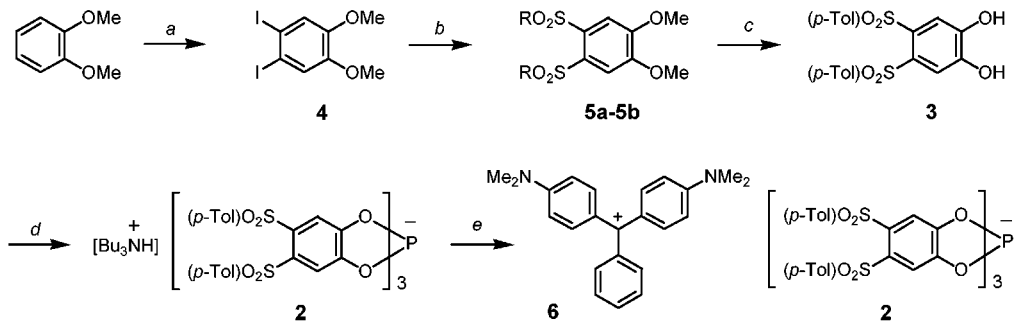
Figure 1. Chiral hexacoordinated phosphate anions.

† Département de Chimie Organique.
‡ Laboratoire de Cristallographie.

(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.

10.1021/ol015804d CCC: $20.00
Published on Web 04/06/2001

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

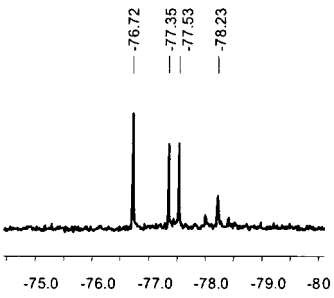


Figure 2. ^{31}P NMR (DMSO-d_6, 162 MHz, parts) of [**6**][**2**].

(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.

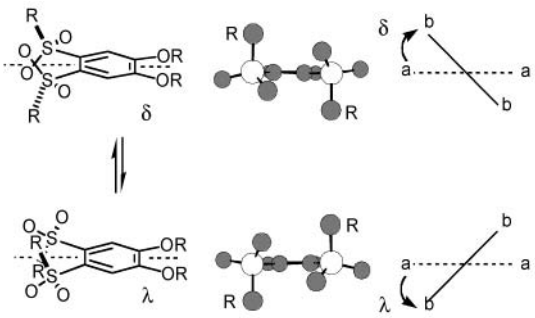


Figure 3. Views of the conformations adopted by *ortho* sulfonyl groups and configurational assignment (δ and λ); a·····a constitutes the plane of the phenyl ring; b·····b is a line passing through the R substituents.

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

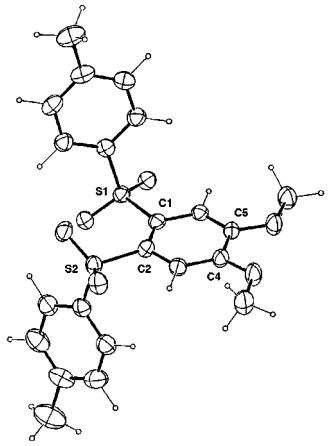


Figure 4. Ortep view (ellipsoids at the 50% probability level) of the crystal structure of **5a** (δ configuration) showing the "up-and-down" orientation of the *p*-tolyl substituents.

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)

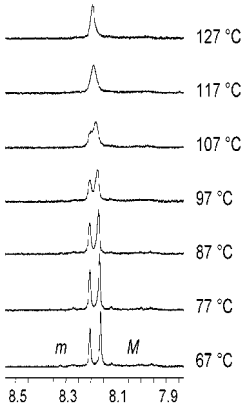
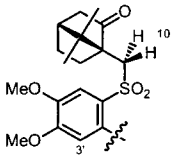


Figure 5. Variable temperature ^{1}H NMR (400 MHz, DMSO-d_6) of **5b**. Proton H(3′) of the major (M) and minor (m) diastereomeric conformations. Coalescence temperature, 117 °C.

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}).

Acknowledgment. We are grateful for financial support of this work by the Swiss National Science Foundation and Federal Office for Education and Science (J.L., COST D11). We thank Mr. A. Pinto, Mr. J.-P. Saulnier, Mr. W. Kloeti, and Mrs. E. Sandmeyer for NMR and MS measurements.

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.

OL015804D

(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).