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Conformational Preference and Configurational Control of Highly Symmetric Spirobi[dibenzazepinium] Cation

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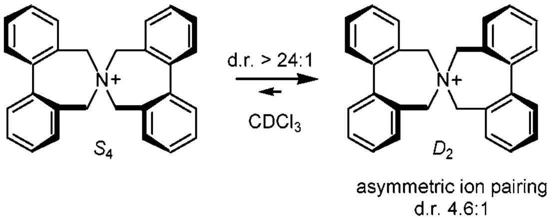
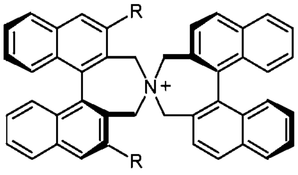
ABSTRACT



Stereodynamics were detected in solution for salts of the simple spirobi[dibenzazepinium] cation in favor of the homochiral (D_2) conformer as evidenced by chiral TRISPHAT and BINPHAT counterions; asymmetric induction was furthermore observed in ^{1}H and ^{15}N NMR spectroscopy.

Chiral quaternary ammonium cations or *quats* have been much studied due to the potential of these derivatives to serve as efficient asymmetric phase transfer catalysts.[1] Most examples of highly stereoselective reactions have employed cations derived from the chiral pool.[2] Recently, successful transformations mediated by purely synthetic chiral *quats*, in particular those of type **1** and **2** (Figure 1), have been reported.[3] These robust reagents permit low-catalyst loadings and large scope of reactions. For their stereoselective synthesis, enantiopure BINOL is used as a starting material and the high kinetic barrier to racemization of the binaphthyl moieties ensures the configurational stability of the adducts.[4]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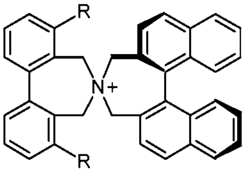
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Figure 1. Quaternary ammonium cations **1** and **2** (R = H, Ar).

It occurred to us that the parent 5,5′,7,7′-tetrahydro-6,6′-spirobi[6*H*-dibenz[*c*,*e*]azepinium] cation **3** (Scheme 1), reported in the literature as early as 1951,[5] had never been studied from a stereochemical point of view.[6] Herein, we report on the stereodynamics of **3** detected by variable-

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[1] Nelson, A. *Angew. Chem., Int. Ed.* **1999**, *38*, 1583−1585.

[2] Dolling, U. H.; Davis, P.; Grabowski, E. J. J. *J. Am. Chem. Soc.* **1984**, *106*, 446−447. Corey, E. J.; Zhang, F.-Y. *Angew. Chem., Int. Ed.* **1999**, *38*, 1931−1934. Zhang, F.; Corey, E. J. *Org. Lett.* **2001**, *3*, 639−641. Lygo, B.; Crosby, J.; Peterson, J. A. *Tetrahedron* **2001**, *57*, 6447−6453. Thierry, B.; Perrard, T.; Audouard, C.; Plaquevent, J. C.; Cahard, D. *Synthesis* **2001**, 1742−1746.

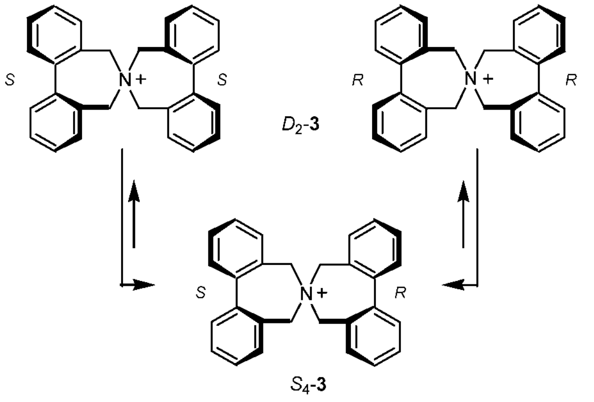
[3] (a) Ooi, T.; Kameda, M.; Maruoka, K. *J. Am. Chem. Soc.* **1999**, *121*, 6519−6520. (b) Ooi, T.; Takeuchi, M.; Kameda, M.; Maruoka, K. *J. Am. Chem. Soc.* **2000**, *122*, 5228−5229. (c) Maruoka, K. *J. Fluorine Chem.* **2001**, *112*, 95−99. (d) Ooi, T.; Uematsu, Y.; Kameda, M.; Maruoka, K. *Angew. Chem., Int. Ed.* **2002**, *41*, 1551−1554. (e) Ooi, T.; Takahashi, M.; Doda, K.; Maruoka, K. *J. Am. Chem. Soc.* **2002**, *124*, 7640−7641.

[4] For compound **2**, the biphenyl ring is flexible and, in the case of R = 3,5-diphenylphenyl, two diastereoisomers in a 1:1 ratio are detected by VT-NMR (243 K). See ref 3d.

[5] Wenner, W. *J. Org. Chem.* **1951**, *16*, 1475−1480. Wittig, G.; Koenig, G.; Clauss, K. *Liebigs Ann. Chem.* **1955**, *593*, 127−156.

10.1021/ol026800r CCC: $22.00

Scheme 1. Equilibrium among Chiral D_2 [(*S*,*S*) and (*R*,*R*) Enantiomers] and *Meso* S_4 Symmetric (*S*,*R*) Conformers of **3**



temperature (VT) NMR and on the preferred nature of the homochiral conformer (diastereomeric ratio, d.r. >24:1 at −40 °C). Partial control over the configuration of **3** by its ion pairing with (bis(tetrachlorobenzenediolato)mono([1,1′]-binaphthalenyl-2,2′-diolato)phosphate(V)) anion **4**, known as BINPHAT, is evidenced by NMR and circular dichroism (CD) spectroscopy.

Spirobi[6*H*-dibenz[*c*,*e*]azepinium] cation **3** is made up of two stereogenic dibenz[*c*,*e*]azepinium rings that are joined together at the charged nitrogen atom. Each of these two halves presents an axial chirality with preferred *S* or *R* atropisomeric conformations. Their association in the construction of spiro compound **3** results in the formation of two predominant diastereomers that have chiral D_2 and achiral (*meso*) S_4 symmetry (Scheme 1).[7] Studies performed on diphenylazepines have revealed that the *S* and *R* atropisomeric conformations interconvert freely in solution by rotation around the biphenyl axis with rather low kinetic barriers ($\Delta G^{\ddagger} \sim 12-14$ kcal·mol^{-1}).[3d,8] It was thus expected that the homochiral (D_2) and heterochiral (S_4) isomers of **3** would interconvert rapidly in solution, the equilibrium occurring between them being possibly shifted toward a thermodynamically preferred diastereoisomer, the nature of which was unknown before the start of this study. The probability of a simultaneous change of configuration ($S \rightleftarrows R$) of each of the two halves of **3** was considered to be low and the equilibrium between the D_2 symmetric enantiomers would thus occur in a two-step process via the formation of the *meso* compound. Before proceeding with the experiments, we realized that both the chiral and *meso* diastereoisomers would reveal AB systems for the diastereotopic methylene protons in ^{1}H NMR and that it would be difficult to distinguish between them.

Previously, chiral hexacoordinated phosphate anions BINPHAT (**4**)[9] and TRISPHAT (**5**, tris(tetrachlorobenzenediolato)phosphate(V))[10] have been shown to be readily prepared in one or two steps from commercially available starting materials (Figure 2). These diamagnetic anions are efficient NMR chiral shift agents for cationic metalloorganic and organometallic substrates.[11] Anion **4** often has superior chiral shift properties than **5** when associated with organic cations.[9,12]

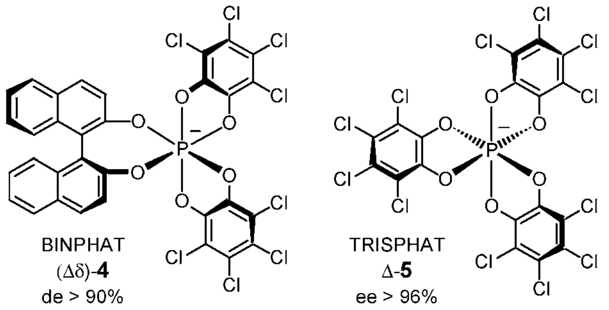


Figure 2. Chiral BINPHAT **4** and TRISPHAT **5** anions.

Their association with spiro compound **3** was therefore considered for the distinction of the *meso* (S_4) and the chiral (D_2) conformers as the signals of the latter could be split into two sets in ^{1}H and ^{15}N NMR spectroscopy.[13] However, we realized that the ion pairing of cation **3** in its *meso* form with enantiopure anions might not be asymmetrically innocent as it could lead to an NMR desymmetrization of the two chiral halves of the cation since they would become "diastereoisomeric" upon salt formation.[14] In ^{1}H NMR, this would mean the appearance of two sets of signals (1:1 ratio) for the benzylic protons, one for each half of the *meso* molecule. Distinction of the separated signals of diastereo-

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[6] For other highly symmetrical cations of type **3**, see: Matarasso-Tchiroukhine, E.; Quelet, R. *Bull. Soc. Chim. Fr.* **1959**, 630−633. Kashiwada, Y.; Huang, L.; Ballas, L. M.; Jiang, J. B.; Janzen, W. P.; Lee, K. H. *J. Med. Chem.* **1994**, *37*, 195−200.

[7] For a recent study on the stereodynamics of D_2- and S_4-symmetric conformers of tetraisopropylmethane and tetracyclopropylmethane, see: Anderson, J. E.; de Meijere, A.; Kozhushkov, S. I.; Lunazzi, L.; Mazzanti, A. *J. Am. Chem. Soc.* **2002**, *124*, 6706−6713.

[8] (a) Tichy, M.; Budesinsky, M.; Gunterova, J.; Zavada, J.; Podlaha, J.; Cisarova, I. *Tetrahedron* **1999**, *55*, 7893−7906. (b) Saudan, L. A.; Bernardinelli, G.; Kundig, E. P. *Synlett* **2000**, 483−486. See also: (c) Superchi, S.; Casarini, D.; Laurita, A.; Bavoso, A.; Rosini, C. *Angew. Chem., Int. Ed.* **2001**, *40*, 451−454. (d) Rashidi-Ranjbar, P.; Taghvaei-Ganjali, S.; Wang, S. L.; Liao, F. L.; Heydari, A. *J. Chem. Soc., Perkin Trans. 2* **2001**, 1255−1260. (e) Kiupel, B.; Niederalt, C.; Nieger, M.; Grimme, S.; Vögtle, F. *Angew. Chem., Int. Ed.* **1998**, *37*, 3031−3034. (f) Sutherland, I. O.; Ramsay, M. V. J. *Tetrahedron* **1965**, *21*, 3401−3408.

[9] Lacour, J.; Londez, A.; Goujon-Ginglinger, C.; Bu*β*, V.; Bernardinelli, G. *Org. Lett.* **2000**, *2*, 4185−4188.

[10] Lacour, J.; Ginglinger, C.; Grivet, C.; Bernardinelli, G. *Angew. Chem., Int. Ed.* **1997**, *36*, 608−609.

[11] Amouri, H.; Thouvenot, R.; Gruselle, M.; Malezieux, B.; Vaissermann, J. *Organometallics* **2001**, *20*, 1904−1906. Monchaud, D.; Jodry, J. J.; Pomeranc, D.; Heitz, V.; Chambron, J.-C.; Sauvage, J.-P.; Lacour, J. *Angew. Chem., Int. Ed.* **2002**, *43*, 2317−2319 and references therein.

[12] (a) Lacour, J.; Vial, L.; Herse, C. *Org. Lett.* **2002**, *4*, 1351−1354. (b) Pasquini, C.; Desvergnes-Breuil, V.; Jodry, J. J.; Dalla Cort, A.; Lacour, J. *Tetrahedron Lett.* **2002**, *43*, 423−426. (c) Pasquato, L.; Herse, C.; Lacour, J. *Tetrahedron Lett.* **2002**, *43*, 5517−5520.

[13] Parker, D. *Chem. Rev.* **1991**, *91*, 1441−1457.

[14] NMR desymmetrization of *meso* derivatives can occur upon the addition of external chiral shift agents. See: Reetz, M. T. *Pure Appl. Chem.* **1996**, *68*, 1279−1283. Huskens, J.; Reetz, M. T. *Eur. J. Org. Chem.* **1999**, 1775−1786. Zhang, X. X.; Bradshaw, J. S.; Izatt, R. M. *Chem. Rev.* **1997**, *97*, 3313−3361. Reetz, M. T.; Rudolph, J.; Mynott, R. *J. Am. Chem. Soc.* **1996**, *118*, 4494−4495.

isomeric [(*S*,*S*)-**3**][Δ-**4**] and [(*R*,*R*)-**3**][Δ-**4**] ion pairs from the split signals within the [(*S*,*R*)-**3**][Δ-**4**] salt would then be difficult. We reasoned that ^{15}N NMR spectroscopy might provide the solution to this problem as the nitrogen atoms of D_2 symmetric enantiomers could be differentiated by the presence of the chiral anions while the N-atom of the *meso* (S_4) conformer would never be split.[15]

Nitrogen-labeled [**3**][Br] was synthesized in good yield (90%) by the reaction of $^{15}NH_4OH$ (>98%, 3.3 N in water, 5 equiv, Cambridge Isotope Laboratories, Inc.) and 2,2′-bis(bromomethyl)biphenyl in refluxing MeOH (1 h). Salts [**3**][Δ-**4**], [**3**][*rac*-**5**], and [**3**][Δ-**5**] were prepared following previously reported conditions.[16] In all cases, initial room temperature NMR analyses revealed broad resonances or lack of signal separation. The existence of a dynamic conformational isomerism was therefore considered with the spectra being recorded around or above the coalescence temperatures (see Supporting Information). A variable-temperature experiment was then performed on salt [**3**][Br] in ^{1}H NMR ($CDCl_3$) and an AB system appeared at low temperature for the benzylic protons demonstrating without ambiguity the existence of stereodynamics (Figure 3, $\Delta G^{\ddagger} = 13.1$ kcal·mol^{-1}).[17]

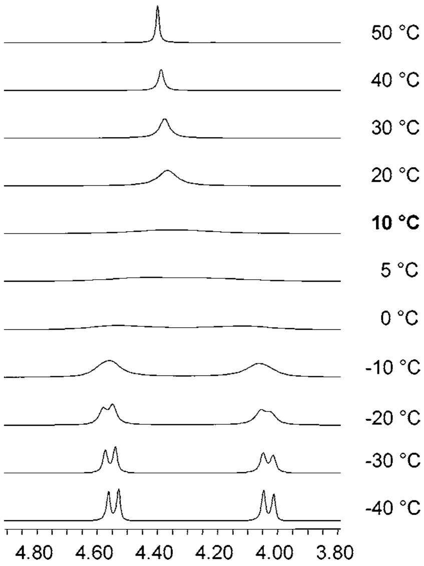

Figure 3. Stereodynamics of salt [**3**][Br] as evidenced by VT-NMR (400 MHz, $CDCl_3$, 323−223 K). Coalescence temperature (T_c) = 283 K, $\Delta\nu$ = 206.2 Hz, J = 13.4 Hz. $\Delta G^{\ddagger}$ = 13.1 kcal·mol^{-1}.

To our surprise, only one set of signals was observed whereas two series of resonances were expected. ^{1}H, ^{13}C, and ^{15}N NMR spectroscopic studies on salt [**3**][*rac*-**5**] at −40 °C also indicated the presence of a single diastereoisomer in solution (d.r. >24:1, Figure 4 spectrum b, Figure 5 spectrum a).[18]

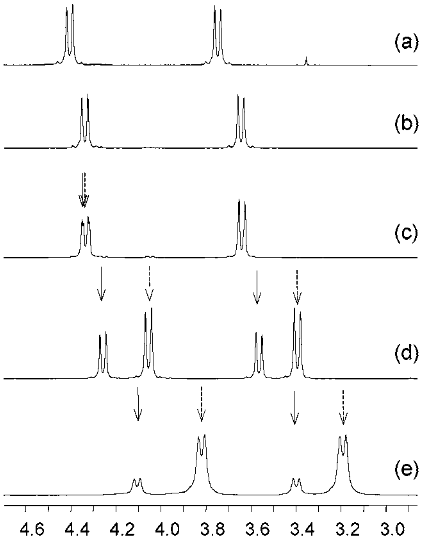

Figure 4. ^{1}H NMR (500 MHz, parts, 233K) of salts (a) [**3**][Br], CD_2Cl_2; (b) [**3**][*rac*-**5**], CD_2Cl_2; (c) [**3**][Δ-**5**], CD_2Cl_2, d.r. 1:1; (d) [**3**][Δ-**4**], CD_2Cl_2, d.r. 1.6:1; and (e) [**3**][Δ-**4**], $CDCl_3$, d.r. 4.6:1.

Evidently, one of the D_2 or S_4 conformers was singly present in solution at low temperature unless considering an isochronicity of all signals, and this for all the nuclei studied.[19,20]

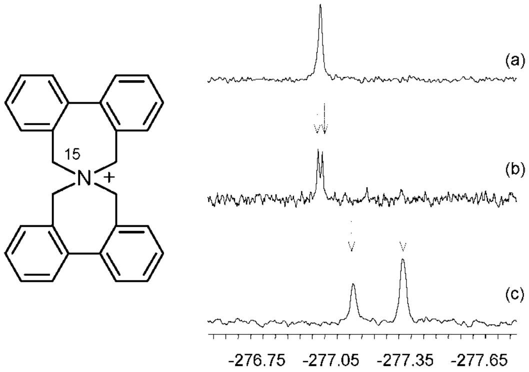

Figure 5. ^{15}N NMR (51 MHz, CD_2Cl_2) of salts (a) [**3**][*rac*-**5**]; (b) [**3**][Δ-**5**], d.r. 1:1; and (c) [**3**][Δ-**4**], d.r. 1.6:1.

Salts [**3**][Δ-**4**] and [**3**][Δ-**5**] were then studied. For the latter compound, only a very small enantiodifferentiation ($\Delta\delta$ =

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[15] Lloyd-Jones, G. C. *Synlett* **2001**, 161−183.

[16] Prepared by metathesis of [**3**][Br] and [Me_2NH_2][Δ-**4**], [Bu_3NH][*rac*-**5**], and [cinchonidinium][Δ-**5**], respectively, and isolated in chemically pure form by chromatography (Al_2O_3 or SiO_2, CH_2Cl_2). See ref 12 and Supporting Information.

[17] The relationship $\Delta G^{\ddagger} = RT_c(22.96 + \ln(T_c/\sqrt{(\Delta\nu^2 + 6J^2)}))$ was used to determine the activation energy, $\Delta G^{\ddagger}$, from the coalescence temperature, T_c (K), the frequency separation of the peaks, $\Delta\nu$ (Hz), and the coupling constant between the nuclei, J (Hz).

[18] With [**3**][*rac*-**5**], the VT-NMR experiment was hampered by the large $\Delta\nu$ (346.6 Hz) and T_c (~313 K) values which limited the study in $CDCl_3$ at high temperatures.

[19] This is rather improbable considering the results of Maruoka et al. See ref 4.

[20] Preliminary DFT calculations with different functionals/basis sets combinations have shown that the homochiral (D_2) conformer is preferred by about 1.5 kcal·mol^{-1}.

0.007 ppm, Figure 4, spectrum c) was observed in ^{1}H NMR, which was confirmed in ^{15}N spectroscopy by the splitting of the nitrogen signal ($\Delta\delta = 0.017$ ppm, Figure 5, spectrum b). For salt [**3**][Δ-**4**], a more noticeable effect was monitored as the signals of the benzylic protons were completely split in two sets at −40 °C ($\Delta\delta_{max} = 0.202$ and 0.286 ppm in CD_2Cl_2 and $CDCl_3$, respectively; Figure 4, spectra d and e). The enantiodifferentiation was also evidenced in ^{15}N NMR spectroscopy ($\Delta\delta = 0.20$ ppm, Figure 5, spectrum c). All these results advocate for a chiral D_2 symmetry for the thermodynamically preferred conformer.

Interestingly, the low-temperature NMR experiments on [**3**][Δ-**4**] revealed not only a separation of the signals of the D_2 symmetric enantiomers but also an induction of chirality from the anion onto the cation as the integration of the signals gave 1.6:1 and 4.6:1 ratios in pure CD_2Cl_2 and $CDCl_3$ respectively. This observation is clearly the result of a *Pfeiffer* effect,[21] in which one of the diastereoisomeric [(*S*,*S*)-**3**][Δ-**4**] and [(*R*,*R*)-**3**][Δ-**4**] ion pairs is thermodynamically favored in solution. The higher diastereoselectivity in chloroform is probably the result of a tighter ion pairing in this lower polarity solvent.[22]

Finally, assignment of the configuration of cation **3** in the preferred [**3**][Δ-**4**] ion pair was attempted by circular dichroism. UV spectra of salt [**3**][Br] were recorded and revealed the absorption characteristics of biphenyl containing moieties, including the A band at 249 nm in CH_2Cl_2. As shown by Mislow and Sandström, positive and negative *Cotton* effects can arise from the A band if the twisted biphenyls have predominant *M* and *P* torsions, respectively.[23] CD spectra of enantioenriched **3** should thus reveal such an effect. However, we realized that the CD active chromophores of **4** would appear on the spectrum and mask the induced CD spectrum of **3**. We therefore prepared a sample of [Bu_4N][Δ-**4**],[12a] containing the CD inactive tetrabutylammonium cation, and decided to subtract its CD spectra from those of [**3**][Δ-**4**] so as to observe the induced CD of cation **3** only. To benefit also from the *Pfeiffer* effect, which sees the diastereoselectivity of the induction increase with the lowering of the polarity of the solvent medium, CD spectra of salts [**3**][Δ-**4**] and [Bu_4N][Δ-**4**] were recorded in mixtures of $CHCl_3$ (0−75%) in CH_2Cl_2 (Figure 6). As expected, an absorbance in the region of the A band was detected on the calculated spectra which intensified with the increase of the chloroform content (lower polarity), its positive sign indicating a preferred *M* torsion for the twisted biphenyl chromophores of **3**. Salt [(*R*,*R*)-**3**][Δ-**4**] is therefore the preferred diastereomer in solution.

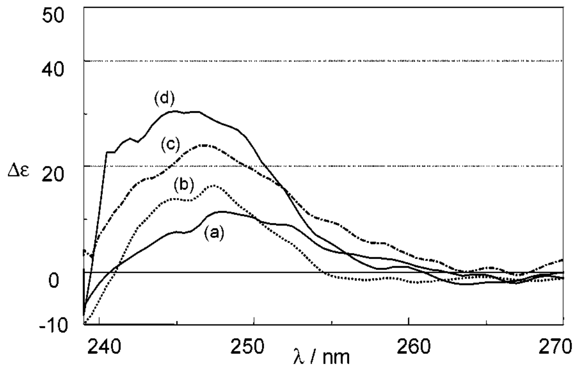

Figure 6. Calculated CD spectra of {[**3**][Δ-**4**]−[Bu_4N][Δ-**4**]} in mixtures of $CHCl_3/CH_2Cl_2$: (a) 0%; (b) 25% $CHCl_3$; (c) 50% $CHCl_3$; and (d) 75% $CHCl_3$. Concentration 2.13×10^{-6} M.

In conclusion, the highly symmetric spirobi[dibenzazepinium] cation exits in a preferred homochiral conformation in solution. Partial control over its configuration can be realized by an asymmetric ion pairing with the chiral BINPHAT anion. Studies directed toward the use of salt [**3**][Δ-**4**] in asymmetric chemistry are being pursued.

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Supporting Information Available: Preparation and spectral data for salts [**3**][Br], [**3**][Δ-**4**], [**3**][*rac*-**5**], and [**3**][Δ-**5**]. This material is available free of charge via the Internet at http://pubs.acs.org.

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