ORGANIC
LETTERS

2002
Vol. 4, No. 14
2309−2312

One-Step Stereoselective Synthesis and NMR Chiral Shift Properties of a Novel Hexacoordinated Phosphorus Cation

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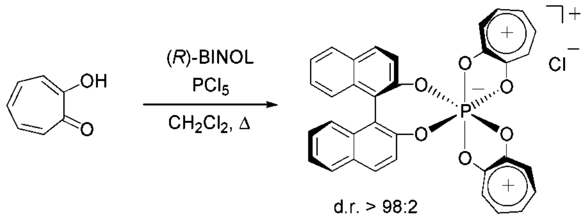
Received May 8, 2002

ABSTRACT

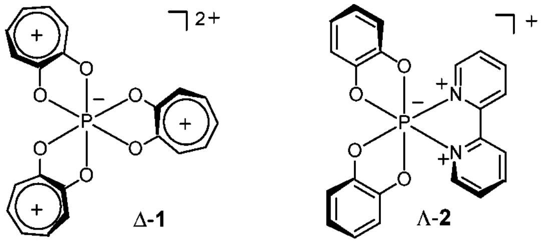


Tropolone, binol, and PCl_5 react in CH_2Cl_2 at reflux to generate in one step a novel C_2-symmetric hexacoordinated phosphorus cation of configuration controlled by the binol ligand. It behaves as an efficient NMR chiral shift agent for chiral anionic phosphate and borate anions.

The octahedral geometry of pentavalent hexacoordinated phosphorus allows the formation of chiral species by complexation of the phosphorus atom with three bidentate ligands (Δ and Λ enantiomers).[1] Depending upon the nature of the chelating moieties, the resulting phosphates are anionic, neutral, or cationic,[2] compounds **1** and **2** being representative examples of the latter class of compounds (Figure 1).[3]

However, such chiral cationic hexacoordinated derivatives have been prepared as racemates, and to our knowledge, no attempts have been made to resolve them.[4] As hexacoordinated phosphates often lack configurational stability, it was debatable whether these cationic structures could be isolated in one predominant stereoisomeric form and used for asymmetric applications. Herein, we report that hexacoordinated BINTROP cation **3**, made from binol, tropolone, and PCl_5, can be prepared in one step and isolated as a single diastereomer. Application of **3** as an NMR chiral shift agent is detailed.

Previously, it was shown that the configurational stability of hexacoordinated phosphate anions can be increased by the introduction of electron-poor chelating ligands.[5] For the synthesis of a configurationally stable cationic derivative, strong electron-withdrawing and positively charged ligands were therefore considered, the introduction of two such moieties around the central phosphorus atom being sufficient



Δ-**1**

Λ-**2**

Figure 1. Chiral hexacoordinated phosphate cations.

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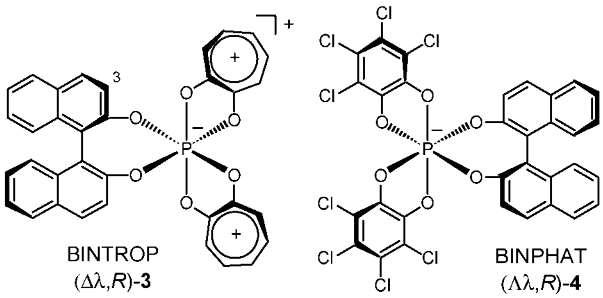
10.1021/ol026152b CCC: $22.00

to upset the negative charge and generate a possibly stable cationic derivative. Among potential chelates, tropolone,[6] which binds in a cationic 1,2-dihydroxy-tropylium form, was selected for its ease of preparation and well-established main group chemistry.[7,8] Recently, the one-pot synthesis of C_2-symmetric hexacoordinated BINPHAT anion **4** made of two tetrachlorocatechols and one chiral binol ligand was reported (Figure 2).[9] Using (*R*)-binol, only one of the four possible diastereomers (Λλ) was detected and isolated,[10] the chiral ligand predetermining completely the configuration of **4**.[11,12] For this reason, binol was selected as the third ligand around the phosphorus atom.



BINTROP
(Δλ,*R*)-**3**

BINPHAT
(Λλ,*R*)-**4**

Figure 2. Binol-derived chiral hexacoordinated phosphate cation **3** and anion **4**.

Preparation of novel bis(tropyliumdiolato)mono([1,1′]-binaphthalenyl-2,2′-diolato)phosphate(v) cation or BINTROP **3** was performed under conditions similar to those reported by Muetterties for the synthesis of **1**.[3a] Tropolone (2.0 equiv), PCl_5, and (*R*)-binol (1.0 equiv each) were heated in CH_2Cl_2 at reflux for 2 h. Addition of hexane and chromatography (SiO_2, CH_2Cl_2/MeOH 9:1) of the resulting precipitate afforded pure [**3**]Cl salt in modest to decent yield (44−70%). Surprisingly, the ^1H NMR spectrum of [**3**]Cl revealed two sets of signals indicating the presence of two diastereomers in the precipitate, whereas by analogy with the synthesis of **4**, only one was expected (Figure 3, spectra a and d). ^{31}P NMR confirmed this analysis, as two signals (δ −82.1 and −83.3 ppm, $CDCl_3$) could be observed in the −80 ppm region characteristic for such hexacoordinated phosphorus species. COSY and NOESY experiments allowed us to assign the ^1H NMR signals of each diastereomer. The diastereomeric ratio (dr 2:1) was determined by the integration of the respective signals.

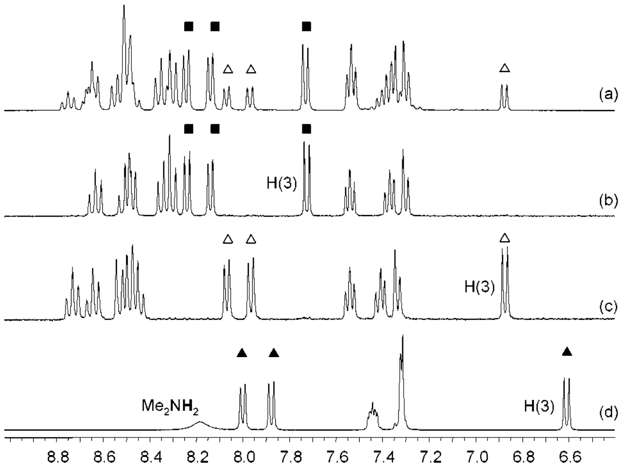


Figure 3. ^1H NMR spectra (400 MHz, DMSO-d_6, parts): (a) [**3**]Cl, dr 2:1 (**3*M***:**3*m***); (b) [**3*M***][*rac*-**5**]; (c) [**3*m***][*rac*-**5**], and (d) [Me_2NH_2][**Λλ-4**]. Selected binol protons of **3*M***, **3*m***, and **4** marked as ■, △, and ▲, respectively.

Separation of major **3*M*** and minor **3*m*** diastereomers of cation **3** was realized by a chromatographic exchange of the chloride counterion with previously reported tris(tetrachlorobenzenediolato)phosphate(v) anion **5** or TRISPHAT.[5,13]

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[8] pK_a for first ionization can be used as a measure of the electronic effect of the substituents on a aromatic diol. 1,2-Dihydroxy-tropylium: pK_{a1} = −0.53. Tetrachlorocatechol: pK_{a1} = 6.63. Pyrocatechol: pK_{a1} = 10.87. See: Beauchamp, A.; Benoit, R. L. *Can. J. Chem.* **1966**, *44*, 1607−1614. Rosenblatt, D. H.; Epstein, J.; Levitch, M. *J. Am. Chem. Soc.* **1953**, *75*, 3277−3278.

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Solutions of racemic $[Bu_3NH]$[*rac*-**5**] (acetone) and [**3**]Cl (CH_2Cl_2/MeOH 19:1) were prepared, mixed together, and analyzed by thin-layer chromatography (TLC). Development by elution (CH_2Cl_2) showed a much reduced affinity for silica gel of diastereomeric [**3*M***][*rac*-**5**] and [**3*m***][*rac*-**5**] salts, as they were retained (R_f 0.66 and 0.51, respectively) to a much lower extent than their chloride precursor (R_f ~0).[14] Preparative TLC (SiO_2, 20 cm × 20 cm, CH_2Cl_2) using a mixture of $[Bu_3NH]$[*rac*-**5**] and [**3**]Cl (2:1 ratio of **3*M***:**3*m***) afforded ion pairs [**3*M***][*rac*-**5**] and [**3*m***][*rac*-**5**] as the most and least eluted fractions, respectively.

The configurations of BINTROP cation **3** were first evaluated by comparison of the ^{1}H NMR spectra of diastereomerically pure BINPHAT **4** ($\Lambda\lambda$,*R*) and of the major **3*M*** and minor **3*m*** diastereomers.[15] Stronger analogies, in particular for the signal of proton H(3) of the binol moieties, were observed between the spectra of anion **4** and minor diastereomer **3*m*** (Figure 3, spectra d and c) and not with predominant isomer **3*M*** (spectra b). Assuming little influence of the tropolone-derived ligands on the chemical shifts of the protons of the binol moiety, this seemed to indicate that the configurations of **4** and **3*m*** were identical and thus a Λ configuration for these ions derived from (*R*)-binol. This would also mean that the (*R*)-binol ligand would favor two different relative configurations in the anionic (Λ for **4**) and cationic series (Δ for **3*M***).

The result of this NMR comparison was confirmed by X-ray diffraction analysis of a crystal obtained by slow diffusion of Et_2O to a solution (MeOH) of pure [**3*M***]Cl (vide infra).[16] The asymmetric unit contained six independent molecules, all $\Delta\lambda$ configuration (Flack parameter $x^{17} = -0.03\ (12)$). Only moderate differences were observed between the structures of the phosphate cations (Figure 4).

To improve the ratio between [**3*M***]Cl and [**3*m***]Cl and understand why the (*R*)-binol leads to different preferred configurations in the cationic (Δ, **3*M***) and anionic (Λ, **4**) series, experiments were performed to determine the thermodynamic or kinetic nature of stereochemical control. Preparation of salt [**3**]Cl was repeated under the same conditions but with prolonged reaction time (24 h). Diastereomer [**3*M***]Cl or [($\Delta\lambda$,*R*)-**3**]Cl was again obtained in the precipitate as the major product (same overall yield) with, however, an increase from 2:1 to 9:1 of the **3*M***:**3*m*** diastereomeric ratio. Further improvement of the diastereoselectivity was not achieved with longer reaction times (48 h).

In another experiment, an isolated 2:1 mixture of [**3*M***]Cl and [**3*m***]Cl was heated in CH_2Cl_2 at reflux for 24 h and a 9:1 ratio resulted with virtually no loss of chemical yield. Recrystallization of mixtures of [**3*M***]Cl and [**3*m***]Cl in MeOH/Et_2O afforded pure [**3*M***]Cl salt (dr > 98:2), which yielded again the 9:1 ratio of diastereomers when heated at reflux in CH_2Cl_2. All of these experiments indicate that diastereomer [($\Delta\lambda$,*R*)-**3**]Cl is generated under thermodynamic control and corresponds to the most stable diastereomer (Figure 5). BINPHAT **4** is then most probably generated under kinetic control and isolated in the Λ configuration.

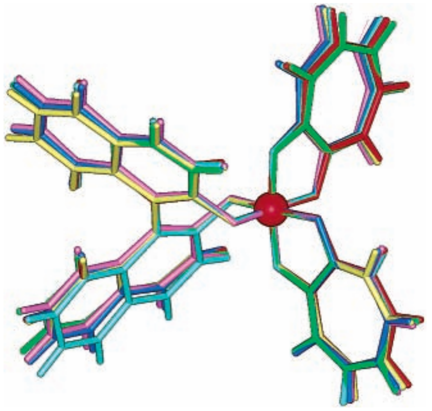

Figure 4. Superposition of the six molecules of **3*M*** ($\Delta\lambda$ configuration) contained in the asymmetric unit of crystal [($\Delta\lambda$,*R*)-**3**]Cl·$Et_2O(MeOH)_6(EtOH)_2(H_2O)_3$.

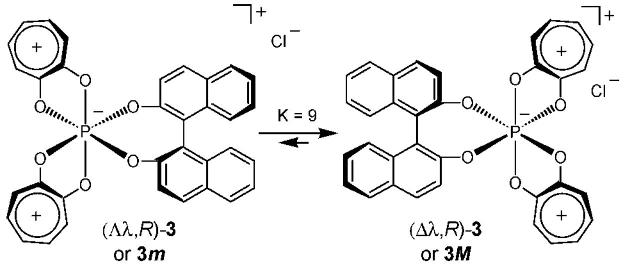

Figure 5. Equilibrium between diastereomeric [($\Lambda\lambda$,*R*)-**3**]Cl and [($\Delta\lambda$,*R*)-**3**]Cl salts in CH_2Cl_2 at reflux. *K* is the equilibrium constant.

The ^{31}P NMR characterization of [**3*M***][*rac*-**5**] as the result of the chromatographic separation of the diastereomers revealed a first application for BINTROP cation. In $CDCl_3$, three signals in the −80 ppm region were observed (−79.90, −79.98, −83.10), indicating that cation **3** behaved as an NMR chiral shift agent for chiral TRISPHAT anion **5**.[18] This was confirmed by addition of pure [**3*M***]Cl to $CDCl_3$ solutions of racemic, enantiomerically enriched, and pure $[Bu_3NH]$[**5**] (Figure 6). ^{31}P NMR spectra revealed without ambiguity an enantiodifferentiation for the Λ and Δ enan-

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(14) Using racemic **5** as counterion, four bands could in principle be observed on TLC, corresponding to the four possible diastereomeric ion pairs [**3*M***][Δ-**5**], [**3*M***][Λ-**5**], [**3*m***][Δ-**5**], and [**3*m***][Λ-**5**]. However, it was not the case.

(15) In the following experiments care was taken to use samples made all from (*R*)-binol, although this precaution is not necessary for the NMR experiments.

(16) All recrystallization attempts with other solvents led to poorer quality crystals. The molecular packing shows “channels” in which are located the solvents molecules showing large disorders. Crystallographic data are available as Supporting Information.

(17) Flack, H. D.; Bernardinelli, G. *Acta Crystallogr. Sect. A* **1999**, *55*, 908−915; *J. Appl. Crystallogr.* **2000**, *33*, 1143−1148.

(18) In DMSO-d_6, the signal of racemic TRISPHAT anion is not split by the chiral cation, as the polarity of the solvent medium most probably generates separated ion pairs.

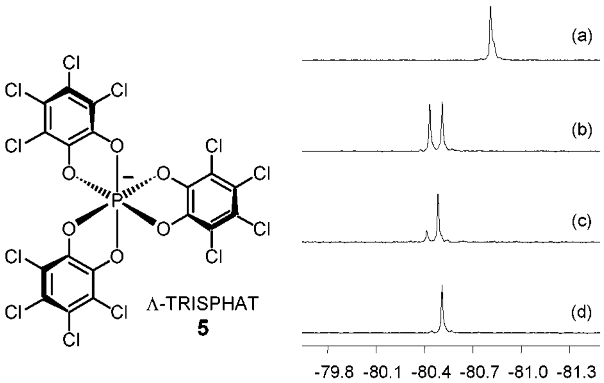

Figure 6. ^{31}P NMR spectra (162 MHz, $CDCl_3$). (a) [$n$$Bu_3NH$][*rac*-**5**], no additive. 4.8 equiv of [**3*M***]Cl and [$n$$Bu_3NH$][Λ-**5**]: (b) 0% ee, (c) 56% ee, and (d) > 96% ee.

tiomers of **5** and allowed the determination of the enantiomeric purity of the optically enriched sample (spectrum c). This efficiency of the BINTROP cation as an NMR chiral shift agent for chiral anions was further proven with chiral bis(3,5-di-*tert*-butylbenzenediolato)borate **6**. Recently, the interest in such chiral anions has been revived because of the potential of these anions to serve as anionic chiral auxiliaries.[19] Here, we show that the determination of a possible enantiomeric purity using BINTROP **3** is simple. A low amount, as little as 0.07 equiv, of chiral shift agent is sufficient to lead to a split of the NMR signals of the enantiomers of **6** (Figure 7, spectra b−d).

In conclusion, we reason that the fact that both Λ and Δ diastereomers of BINTROP **3** can be observed and isolated separately is the result of a remarkable chemical and configurational stability of cation **3**. As for TRISPHAT anion **5**, we propose that the electron-poor nature of the tropylium

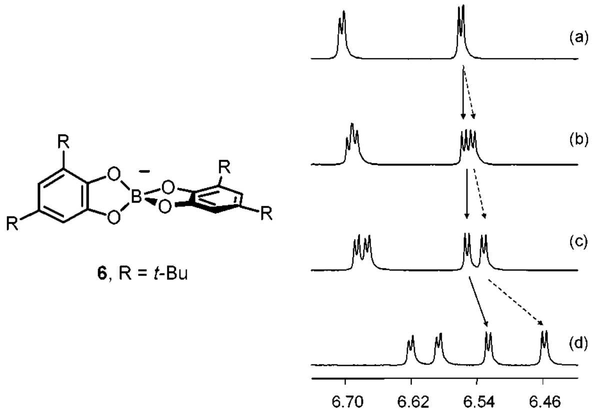

Figure 7. ^{1}H NMR spectra (400 MHz, $CDCl_3$, parts): [$n$$Bu_3NH$][*rac*-**6**] with (a) 0, (b) 0.07, (c) 0.14, and (d) 0.58 equiv of [**3*M***]Cl.

ligands strongly stabilizes the hexacoordinated structure. This also allows us to explain the relative instability of BINPHAT anion in solution, as this compound is most probably generated, although highly selectively, as the “kinetic” isomer. Further stereoselective applications of BINTROP **3** are currently in progress.

Acknowledgment. We thank Mrs. Torche-Haldimann and Mr. Luca Torelli for the large scale preparation of tropolone. We are grateful for financial support of this work by the Swiss National Science Foundation, the Federal Office for Education and Science (COST D11), the Société Académique de Genève, the Schmidheiny Foundation, and the Sandoz Family Foundation (J.L.).

Supporting Information Available: Spectral data for compounds [**3**]Cl, [**3**][**5**], and [Bu_3NH][**6**] and X-ray crystallographic data for [($\Delta\lambda$,R)-**3**]Cl·$Et_2O(MeOH)_6(EtOH)_2(H_2O)_3$ in CIF format. This material is available free of charge via the Internet at http://pubs.acs.org.

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