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Efficient NMR Enantiodifferentiation of Chiral Quats with BINPHAT Anion

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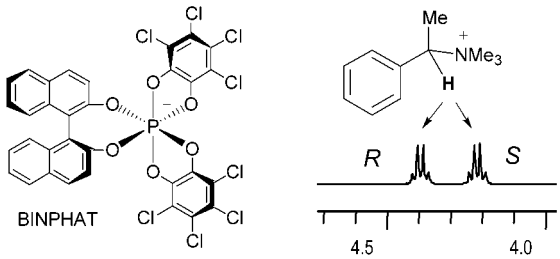
ABSTRACT



Hexacoordinated phosphorus BINPHAT anion is an efficient NMR chiral shift agent for quaternary ammonium cations (quats) leading to large separations ($\Delta\Delta\delta$ up to 0.29 ppm) of the proton signals of the enantiomers.

Chiral quaternary ammonium cations or quats have been the subject of much attention due to the potential of these derivatives to serve as efficient chiral phase transfer catalysts.[1] Whereas most examples of highly stereoselective reactions have employed cations derived from the chiral pool[2]—for which the enantiomeric purity is ascertained—recent reports of successful transformations mediated by purely synthetic chiral quats, e.g., **1** (Figure 1),[3] raises the general question of the determination of the enantiomeric purity of such synthetic derivatives.[4]

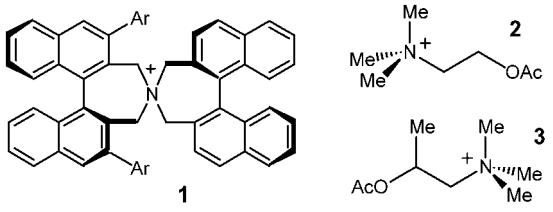


Figure 1. Quaternary ammonium cations (quats) **1**−**3**.

Quats, such as acetylcholine **2** (Figure 1), have also been recently studied for their binding with aromatic natural and artificial receptors with the goal to develop a better understanding of the biologically important cation−π interactions.[5,6] In several of these reports, the aromatic hosts have been chiral.[7] It is therefore conceivable that stereoselective

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(4) This is not the case for cations of type **1**; the enantiomeric purity is directly correlated to the BINOL starting material.

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discriminating interactions could occur between them and chiral quats such as biologically active methacholine **3**.[7i−l] It appeared to us that such studies would strongly benefit from the use of salts in which the two enantiomers of the chiral quaternary ammonium cations could be directly detected in ^{1}H NMR spectroscopy as titration experiments could be performed with racemic quats for which the pure enantiomers are not readily available.[8]

Herein, we report that the ion pairing of chiral quaternary ammonium cations and recently developed BINPHAT (Figure 3) allows the strong enantiodifferentiation of the proton NMR signals of the ammonium cations; rather large difference in chemical shifts ($\Delta\Delta\delta$)—up to 0.29 ppm—were observed upon asymmetric ion pairing. This allows for the efficient determination of the enantiomeric purity of chiral quats.[9]

Several chiral quaternary ammonium cations (**4**−**8**) were chosen along with methacholine **3** (Figure 2). Care was taken

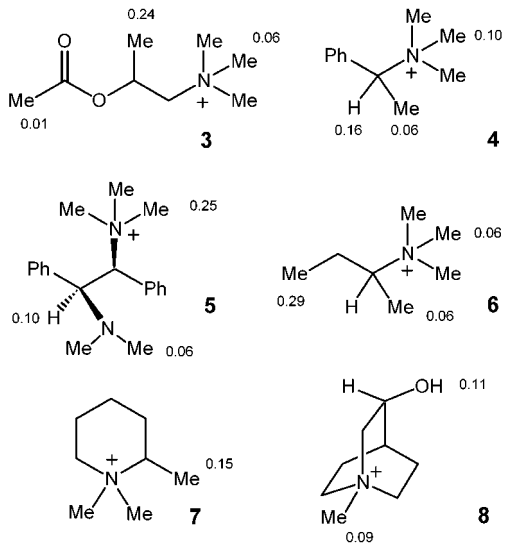

Figure 2. Chiral quaternary ammonium cations **3**−**8** and magnitude of the difference in chemical shifts ($\Delta\Delta\delta$ in small figures) for well-separated signals of the BINPHAT salts.

to select rather different backbones with stereogenic center(s) in α and/or β positions to the positive nitrogen atom. Chiral quats **4**−**8** were prepared as racemates—when possible in enantiopure form—by the reaction of the amine precursors with an excess of MeI/$NaHCO_3$ in MeOH, affording chemically pure starting materials in moderate to good yields (42−98%). Racemic methacholine **3** was commercially available as its bromide salt.

Recently, chiral hexacoordinated phosphate anions, BINPHAT **9** (bis(tetrachlorobenzenediolato)mono([1,1′]binaphthalenyl-2,2′-diolato)phosphate(V)), TRISPHAT **10** (tris(tetrachlorobenzenediolato)phosphate(V)), and HYPHAT **11** (bis(tetrachlorobenzenediolato)mono(1,2-diphenylethane-1,2-diolato)phosphate(V)), were shown to be readily prepared in one or two steps from commercially available starting materials (Figure 3).[10] These diamagnetic anions are efficient

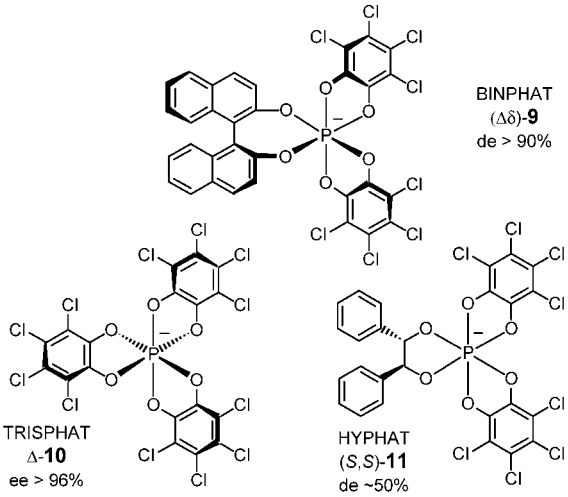

Figure 3. Chiral phosphate anions BINPHAT **9**, TRISPHAT **10**, and HYPHAT **11**.

NMR chiral shift agents, with a predilection for cationic metallo-organic and organo-metallic substrates.[11] The efficiency of the anions is explained by the formation of diastereomeric contact ion pairs. In most of the studies, the chiral shift experiments were performed by the addition of [Bu_3NH][Λ-**10**] or [Bu_4N][Δ-**10**] to solutions of the chiral cations.[11] However, recent results have shown that C_2-symmetric BINPHAT **9** and HYPHAT **11** anions often possess better chiral shift properties than TRISPHAT **10** when associated with organic cations.[10b,12]

Initial experiments were performed with racemic trimethyl(1-phenylethyl)ammonium iodide salt. In an NMR tube,

Tamura, T.; Okhkubo, H.; Kobayashi, K.; Morikawa, O. *Chem. Lett.* **1996**, 685−686. (k) Ito, K.; Kida, A.; Ohba, Y.; Sone, T. *Chem. Lett.* **1998**, 1221−1222. (l) Ito, K.; Ohta, T.; Ohba, Y.; Sone, T. *J. Heterocycl. Chem.* **2000**, *37*, 79−85 and references therein.

(8) A modest split ($\Delta\Delta\delta$ < 0.015) was observed by Ito for cation *rac*-**4** in the presence of modified calixarene hosts: refs 7k and 7l.

(9) In situ generated anionic lanthanide complexes have been used as chiral shift reagents onto chiral cations. However, to our knowledge, their use on quaternary ammonium derivatives has not been reported: Vining, M. S.; Weinstein, S. E.; Wenzel, T. J. In *Book of Abstracts*, 216th National Meeting of the American Chemical Society, Boston, August 23−27, 1998; American Chemical Society: Washington, DC, 1998; Abstract ANYL-124. Green, T. K.; Pesterfield, L. L.; Radmard, B.; Whetstine, J. R. *Magn. Reson. Chem.* **1998**, *36*, 79−86. Green, T. K.; Whetstine, J. R.; Son, E. J. R. *Tetrahedron: Asymmetry* **1997**, *8*, 3175−3181. Wenzel, T. J.; Zaia, J. *Anal. Chem.* **1987**, *59*, 562−567.

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[^{n}Bu$_4$N][(Δ,*S*)-**9**][13] was added to a $CDCl_3$ solution of [*rac*-**4**][I] (Figure 4). Although efficient (Δδ = 0.13 ppm), the

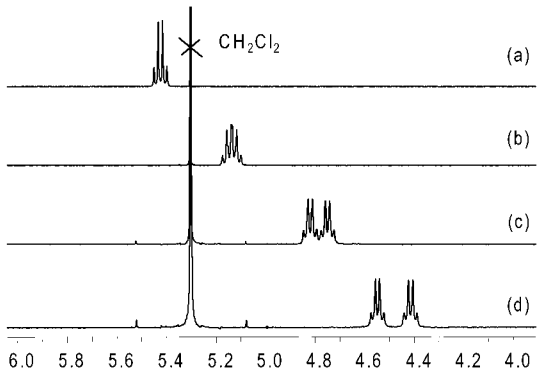

Figure 4. ^{1}H NMR spectra (400 MHz, $CDCl_3$, parts) of [*rac*-**4**][I] with (a) 0, (b) 0.5, (c) 1.5, and (d) 4.8 equiv of [^{n}Bu$_4$N][(Δ,*S*)-**9**].

separation of the signals of the benzilic proton of **4** could only be achieved with a substantial amount of chiral shift salt (4.8 equiv), and a rather large spectral window was perturbed in the aliphatic region (2.93−0.54 ppm) by the protons of the tetra-*n*-butylammonium counterion. While this was acceptable for this particular example, strong overlaps—which would prevent any measurements—were foreseen to happen with chiral cations depleted of signals outside this region, e.g., **6**−**7**. The direct association of cations **3**−**8** and anionic chiral shift agent **9** in preformed [**3**−**8**][(Δ,*S*)-**9**] salts was thus considered to be a better solution, as a much larger spectral window would be available.

Recently, we observed that hexacoordinated phosphate anions **9**−**11** confer to their salts a poor affinity for polar chromatographic phases as they elute rapidly over silica gel/alumina.[14] For the preparation of salts [**3**−**8**][(Δ,*S*)-**9**], solutions of [Me_2NH_2][(Δ,*S*)-**9**] (1.2 equiv) in acetone and of 5.0 mg of salts [**3**][Br] or [**4**−**8**][I] in CH_2Cl_2 were prepared and mixed together. Aliquots were adsorbed on basic alumina (5 × 30 mm, Pasteur pipet) and eluted with a few milliliters of CH_2Cl_2 (∼5 mL) to afford salts [**3**−**8**]-[(Δ,*S*)-**9**] as the only eluted compounds.[15]

BINPHAT salts of trimethyl(1-phenylethyl)ammonium **4** were thus prepared with the racemic, the *R*, the *S*, and an undetermined mixture of the enantiomers of the cation. Parts of the NMR spectra are shown in Figure 5 and are compared to the iodide salt (spectrum a). All aliphatic protons were easily monitored; observed chemical shifts (δ), upfield shifts induced by the phosphate anion (Δδ), and the magnitude of the difference in chemical shifts (ΔΔδ) of analogous protons of the two enantiomers of **4** are summarized in Table 1. A

Table 1. Chemical Shifts (δ), Induced Changes (Δδ), and Magnitude of the Changes (ΔΔδ) for Salts [*rac*-**4**][I], [*R*-**4**][(Δ,*S*)-**9**], and [*S*-**4**][(Δ,*S*)-**9**] ($CDCl_3$, 400 MHz)

proton	δ^a	δ^b	δ^c	$\Delta\delta^b$	$\Delta\delta^c$	ΔΔδ
C**H**Me	5.40	4.38	4.22	−1.02	−1.18	0.16
N(**Me**)$_3$	3.38	2.36	2.46	−1.02	−0.92	−0.10
CH**Me**	1.85	1.09	1.15	−0.76	−0.70	−0.06

[a] [*rac*-**4**][I]. [b] [*R*-**4**][(Δ,*S*)-**9**]. [c] [*S*-**4**][(Δ,*S*)-**9**].

rather large difference in chemical shifts ($\Delta\Delta\delta_{max}$ ∼0.16 ppm) was observed for the benzylic proton, allowing—for the enantioenriched sample—the facile determination of its enantiomeric purity by integration of the respective signals (Figure 5, spectrum e, er 78:22 in favor of *R*-**4**). To ensure that BINPHAT anion was indeed the best anionic chiral shift agent, salts [*rac*-**4**][(*S*,*S*)-**11**] and [*rac*-**4**][Δ-**10**] were prepared (Figure 5, spectra f and g). Little or no separation of the signals of cation **4** was obtained with these anions, validating the initial choice.

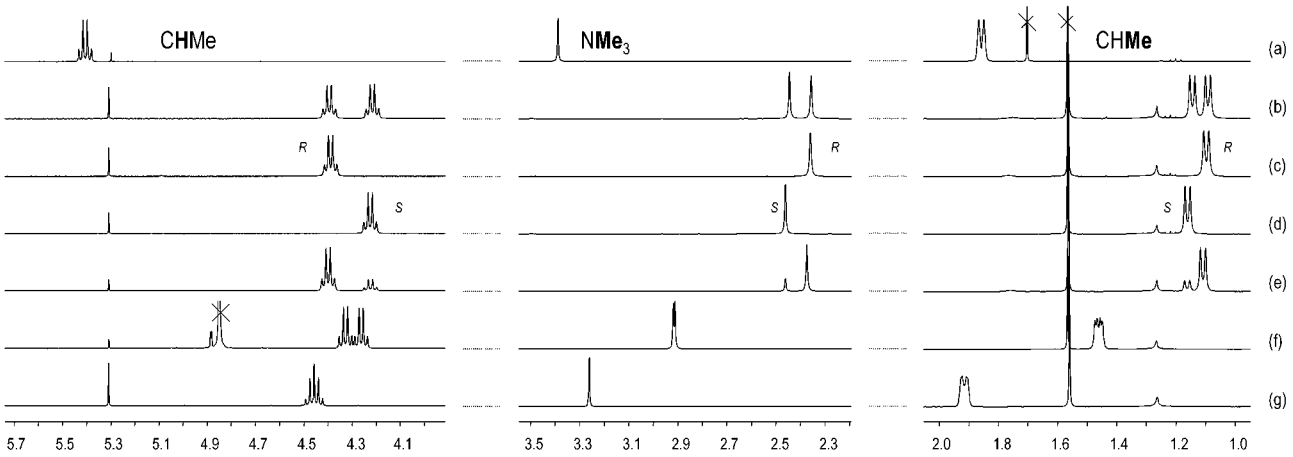

Figure 5. ^{1}H NMR spectra (400 MHz, $CDCl_3$, parts) of (a) [*rac*-**4**][I], (b) [*rac*-**4**][(Δ,*S*)-**9**], (c) [*R*-**4**][(Δ,*S*)-**9**], (d) [*S*-**4**][(Δ,*S*)-**9**], (e) [*R*-**4**][(Δ,*S*)-**9**] (er 78:22), (f) [*rac*-**4**][(*S*,*S*)-**11**], and (g) [*rac*-**4**][Δ-**10**].

With cation **5**, upfield shifts induced by the phosphate reagent and large differences in chemical shifts for the analogous protons of the two enantiomers were also observed (Figures 3 and 6). The signals of the N^+Me_3 protons ($\Delta\Delta\delta$ = 0.25 ppm) were the most perturbed. For *sec*-butyltrimethylammonium cation **6**, several signals of the ammonium cation were fully split upon the association with **9** (Figure 2 ($\Delta\Delta\delta$) and Supporting Information). Interestingly, the most shifted signals are those of the methyl group positioned γ to the charged nitrogen atom ($\Delta\Delta\delta$ = 0.29 ppm) and not α or β ($\Delta\Delta\delta$ = 0.06 ppm). This example and the next (cation **7**, see Supporting Information) clearly indicate that the efficiency of the BINPHAT anion is not tempered by the lack of aromatic substituents. For salt [*rac*-**7**][(Δ,*S*)-**9**], the overall spectrum was complex. Nevertheless, the methyl group β to the charged nitrogen atom was sufficiently split by the chiral counterion (baseline-to-baseline separation, $\Delta\Delta\delta$ = 0.15 ppm) and the lack of overlap with other signals would allow—if necessary—a possible determination of the enantiomeric purity. For compound **8**, more polar solvent conditions for the preparation, the elution, and the final characterization of [*rac*-**8**][(Δ,*S*)-**9**] salt were required. Splits of the N-Me signal and, more interestingly, of the OH proton ($\Delta\Delta\delta$ = 0.11 ppm, see Supporting Information) were observed, with the rest of the spectrum being complex.

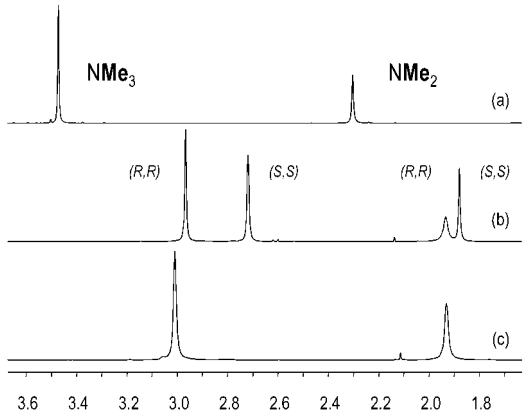

Figure 6. ^{1}H NMR spectra (400 MHz, $CDCl_3$, parts) of (a) [*rac*-**5**][I], (b) [*rac*-**5**][(Δ,*S*)-**9**], and (c) [(*R*,*R*)-**5**][(Δ,*S*)-**9**].

Interestingly, this methodology could also be applied for biologically active methacholine **3** as the two enantiomers of the cation could be easily observed upon ion pairing with **9**; signals N^+**Me**$_3$ and CH**Me** ($\Delta\Delta\delta$ = 0.06 and 0.24 ppm, respectively) were the most separated. The methyl group of the acetate moiety—although positioned ϵ to the charged nitrogen atom—was slightly split by the chiral shift anion ($\Delta\Delta\delta$ = 0.01 ppm, Supporting Information).

Since a purification step is involved in this protocol, care was and should be taken to verify that this method does not lead to any resolution of the ammonium cations upon chromatography, as one of the two diastereomeric BINPHAT ion pairs could be more retained over Al_2O_3. Further studies on the interaction of these BINPHAT salts and chiral aromatic receptors are currently in progress.

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Supporting Information Available: Preparation and spectral data for salts [**4**−**8**][I] and [^{n}Bu$_4$N][(Δ,*S*)-**9**]. ^{1}H NMR spectra of compounds [**3**−**8**][(Δ,*S*)-**9**]. This material is available free of charge via the Internet at http://pubs.acs.org.

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(13) Reagent [^{n}Bu$_4$N][(Δ,*S*)-**9**] was prepared by metathesis from [Me_2NH_2][(Δ,*S*)-**9**] and [^{n}Bu$_4$N][Cl]. Salt [Me_2NH_2][**9**], and the resulting [Me_2NH_2][Cl] are completely retained on Al_2O_3 using CH_2Cl_2 as eluent.

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(15) For salt [**8**][I], a minimum amount of MeOH was required to dissolve it in CH_2Cl_2; 5% acetone in CH_2Cl_2 was required for its elution on Al_2O_3.