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^{1}H and ^{31}P NMR Determination of the Enantiomeric Purity of Quaternary Phosphonium Cations Using TRISPHAT as Chiral Shift Agent

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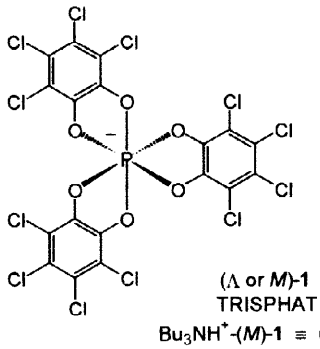
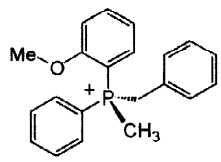
Abstract: The enantiomeric purity of quaternary phosphonium cations can be easily determined in ^{1}H and ^{31}P-NMR using TRISPHAT anion as chiral shift agent.

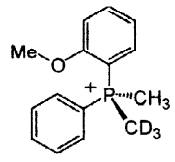
Since the initial works of Mc Ewen, Horner and Luckenbach,[1] few studies have been performed on chiral quaternary phosphonium salts in asymmetric synthesis,[2] certainly due to the difficulty of their preparation in enantiopure form. Significant progresses have been recently described for the direct formation of quaternary phosphonium salts from chiral phosphine-borane complexes,[3] whose asymmetric preparation from oxazaphospholidine derived from ephedrine is now well established.[4] This efficient route to chiral phosphonium salts opens new fields of application, but also poses the problem of the determination of their enantiomeric purity. As few methods have already been described,[5] we report herein the application of TRISPHAT anion **1** as an efficient chiral NMR shift reagent for quaternary phosphonium salts.[6]



(Λ or *M*)-**1**
TRISPHAT
Bu_3NH^+-(*M*)-**1** ≡ (+)-**1a**



2
(*R*)-AnPhBnMeP$^+$



3
(*S*)-AnPh(CH$_3$)(CD$_3$)P$^+$

Recently, we have shown that chiral (Δ or Λ) D_3-symmetric tris(tetrachlorobenzenediolato)phosphate(V) anion **1** (or TRISPHAT) is configurationally stable in solution associated with ammonium counterions.[7] Anion **1** is an efficient NMR chiral shift agent for ruthenium(II) tris(bis-imine) complexes [8] and a valuable host in molecular

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recognition studies conferring unique properties to its ion pairs.[9] Although anion **1** and cations **2**, **3** are topologically different, we thought that diastereoselective interactions would still occur between the ions (R^+-Λ^- *vs.* S^+-Λ^-) and lead, consequently, to a magnetic non-equivalence of ^1H and ^{31}P NMR signals. We have verified this hypothesis with racemic and optically active quaternary phosphonium salts **2** and **3**, prepared in a single step by quaternization of (±)-, (*S*)- and (±)-, (*R*)-*o*-anisyl methyl phenyl phosphine borane with benzyl bromide and CD_3I respectively.[3] Readily prepared Bu_3NH^+-(*M*)-**1** salt ((+)-**1a**, 96% ee) was used as the chiral shift reagent.[8,9b]

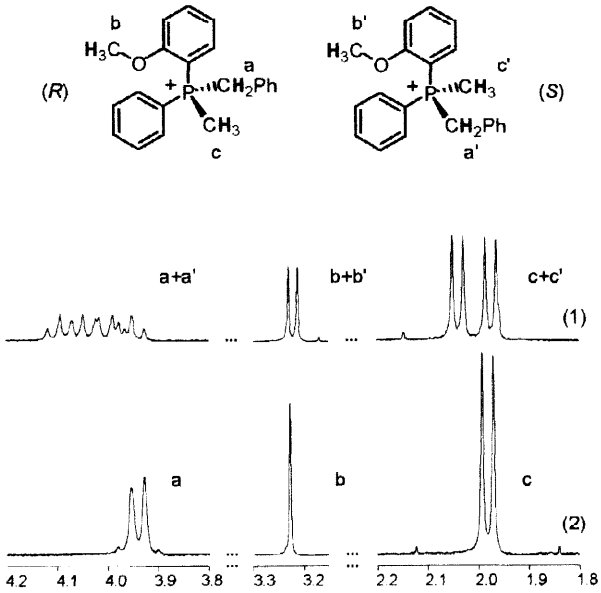

Figure 1. ^1H NMR spectra (600 MHz, C_6D_6, parts) of 2(bromide) in the presence of 1.0 equiv. of **1a**: (1) (±)-**2** and (2) (+)-**2**. Signals (a,a'), (b,b') and (c,c') correspond to the protons of groups CH_2Ph, OCH_3 and P^+CH_3 respectively. Signals (b,b') are reduced in size by a factor of four.

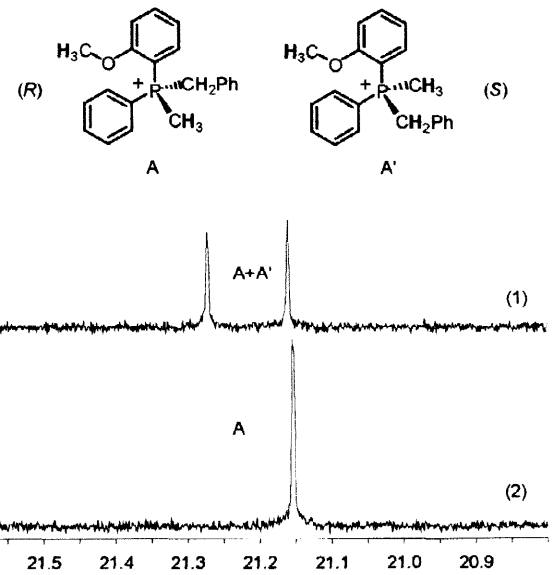

Figure 2. ^{31}P NMR spectra (243 MHz, C_6D_6, part) of 2(bromide) in the presence of 1.0 equiv. of **1a**: (1) (±)-**2** and (2) (+)-**2**.

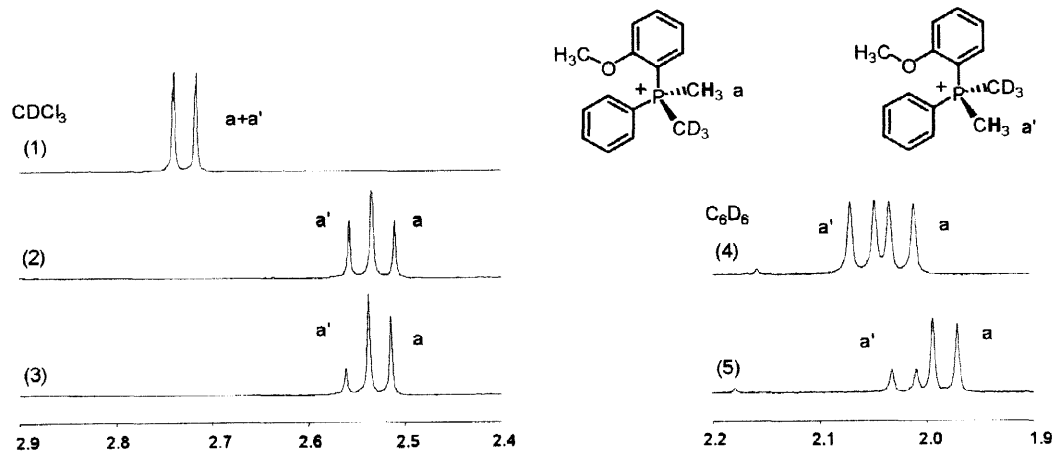

Figure 3. ^1H NMR spectra (600 MHz, part) of 3(iodide) in the absence (1, in $CDCl_3$) and presence of 1.0 equiv. of **1a**: (±)-**3** [(2) in $CDCl_3$ and (4) in C_6D_6]; (-)-**3** [(3) in $CDCl_3$ and (5) in C_6D_6].

As expected, addition of ~1.0 equiv. of (*M* or Λ)-**1** to solutions of (±)-**2**, (*R*)-(+)-**2** in $CDCl_3$, $CDCl_3$:C_6D_6 (1:1) or C_6D_6 led to the signal separation in ^1H and ^{31}P-NMR spectra of the two enantiomers of phosphonium **2**. We were able to distinguish between the two enantiomers and show that sample (+)-**2** is indeed enantiomerically pure. Parts of the resulting spectra of **2** in C_6D_6 upon addition of the shift reagent are shown in Figure 1 (^1H, 600 MHz) and Figure 2 (^{31}P, 243 MHz). In ^1H-NMR, the magnitude of the induced difference in chemical shifts (ΔΔδ in ppm) of some analogous protons (OCH_3 and P^+CH_3) of the two enantiomers of **2** are summarized in Table 1. Fairly strong solvent effect was observed as the use of less polar C_6D_6 (ε 2.27) led to better signal separation than $CHCl_3$ (ε 4.81) or a mixture of these solvents (Table 1, entries 2, 3).[10] It is reasonable to think that it is due to closer interactions within the diastereomeric ion pairs in the less polar solvent C_6D_6, increasing the non-equivalence of the signals of the two enantiomers of **2**. We may point out that the phosphonium salts **2**(bromide) and **3**(iodide) are insoluble in C_6D_6 and that their solubilization occurs only in the presence of TRISPHAT proving the formation of new ion pair species. Simple observation is enough to verify that sample (+)-**2** is enantiopure as no trace of the other enantiomer can be observed in the NMR spectra. However the analysis of the aromatic and the diastereotopic benzylic protons (although quite well resolved, Figure 1) is complicated enough not to be used for the determination of the enantiomeric purity of **2**. In the case of ^{31}P-NMR spectra, the signal corresponding to the phosphonium cation was also well resolved in C_6D_6 (Table 1, entry 3, figure 2) and offers an alternative method for the determination of the enantiomeric purity of these compounds.

The determination of the enantiomeric purity of phosphonium cation **3** was *a priori* more challenging, as its P chirality resides only in an isotopic difference for the hydrogen atoms of the two methyl groups. Addition of ~1.0 equiv. of **1a** to solutions of (±)-**3** and (*S*)-(-)-**3** in $CDCl_3$ or C_6D_6, still led to the non-equivalence of the ^1H-NMR signals of the two enantiomers as shown in Figure 3. However if the signal of P-CH_3 group shows a magnetic non-equivalence for the two enantiomers in ^1H-NMR ($\Delta\Delta\delta_{CDCl3}$ ~0.024 and $\Delta\Delta\delta_{C6D6}$ 0.036), curiously no difference appears for the signals in ^{31}P-NMR neither in $CDCl_3$ nor in C_6D_6. So in C_6D_6, we were thus able to distinguish between the two enantiomers in ^1H-NMR and determine by integration of the respective signals that sample (-)-**3** is enantiomerically enriched (ee 54% ± 2%).

Table 1

Signals	ΔΔδ in $CHCl_3$ [c]	ΔΔδ in 50% $CHCl_3/C_6D_6$ [c]	ΔΔδ in C_6D_6 [c]
OCH_3 [a]	0.00	0.00	0.018
P^+CH_3 [a]	0.00	0.022	0.065
P^+ [b]	0.019	0.012	0.112

[a] ^1H NMR (600 MHz); [b] ^{31}P NMR (243 MHz); [c] With 1.0 equiv. of (+)-**1a**.

In summary, by addition of chiral TRISPHAT anion **1** to the quaternary phosphonium cations **2** or **3**, we have observed the magnetic non-equivalence of the signals for each enantiomer, using the readily accessible ^1H and ^{31}P nuclei. The difference observed is the best in the less polar solvent C_6D_6 and permits the easy determination of the enantiomeric excess by simple integration. We think that the NMR method using chiral TRISPHAT

anion **1** is of particular interest in order to observe the enantiomers of species bearing the chirality on the cationic center.

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