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Chiral anion-mediated asymmetric induction onto chiral diquats

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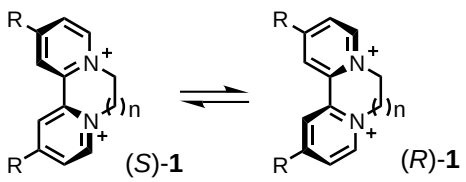
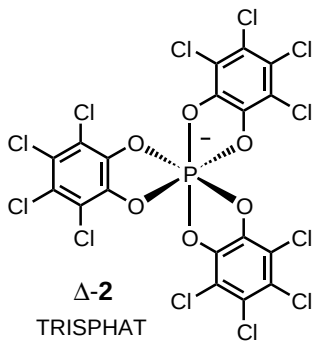
Abstract—Diquats—which are important electron transfer agents in biological and photocatalytic systems, as well as structural templates for efficient supramolecular synthesis—are noteworthy for their axial chirality and have been so far reported only in racemic form due to the rapid interconversion between the atropoisomers. We now report the first example of configurational ordering of chiral diquats through their asymmetric ion pairing with novel hexacoordinated phosphate anions TRISPHAT, HYPHAT and BINPHAT. © 2002 Elsevier Science Ltd. All rights reserved.

Tricyclic diquats (**1**) are important electron transfer agents in biological and photocatalytic systems and have been investigated as structural templates for efficient supramolecular synthesis.[1] Diquat derivatives are also noteworthy for their axial chirality. These compounds, which bridge two pyridinium rings around a central σ bond, possess two enantiomeric (*R* and *S*) conformations, the dihedral angle between the two pyridiniums depending upon the size of the non-aromatic ring.[2]



However, diquats have so far been reported in only racemic form due to the rapid interconversion of the atropoisomers at room temperature in solution. To obtain chiral diquats in a predominant *R* or *S* configuration, a possible strategy would be to add stereogenic elements to the backbone of the compounds; intramolecular diastereoselective interactions would then occur and lead—possibly—to the preferred formation of one diastereomer. An alternative strategy to control the configuration of the charged diquats is to consider their asymmetric ion pairing with chiral counter-ions; intermolecular diastereoselective interactions controlling the stereoselectivity (Pfeiffer effect).[3]

Previously, we reported the synthesis and resolution of tris(tetrachlorobenzenediolato)phosphate(V) anion or TRISPHAT **2**.[4] This D_3-symmetric anion is an efficient NMR chiral shift, resolving and asymmetric inducing reagent onto organic and organometallic derivatives—with a predilection for octahedral metallo-organic complexes.[5] However, with some chiral C_2-symmetric cations, low NMR shifts and asymmetric inducing properties were observed.[6] Assuming that its D_3-symmetry was not suitable for the chiral recognition of such cations, C_2-symmetric BINPHAT **3**[6] and HYPHAT **4**[7]—of configuration controlled by BINOL and hydrobenzoin ligands, respectively—were recently developed. Higher level of asymmetric induction and better chiral shift properties were then obtained using—in rather non-polar solvent conditions—these novel anions as counter-ions.



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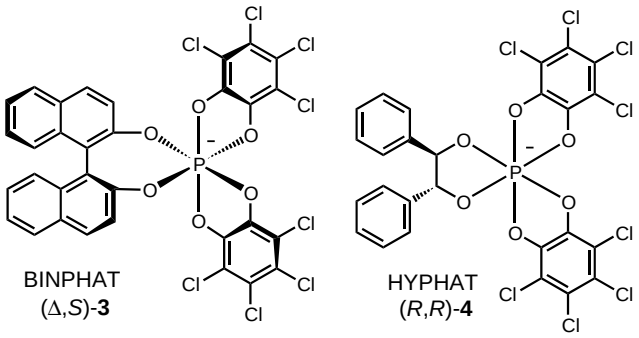
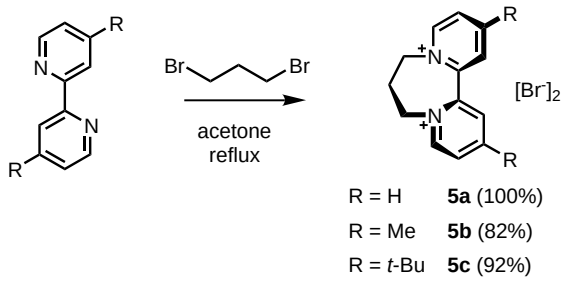


But, doubly charged diquats are noticeably known for their poor solubility in solvents like C_6H_6, $CHCl_3$ or CH_2Cl_2. Polar solvents, e.g. water or methanol, are necessary to dissolve the salts. It was then debatable—in rather polar solvent conditions—whether the coulombic attraction would be sufficiently strong for anions **2**–**4** to behave as NMR chiral shift and asymmetric inducing agents.[8] This is indeed the case and we here report the first example of asymmetric induction onto chiral diquats (d.e. up to 36%); the selectivity being determined without ambiguity by ^{1}H NMR.



Good literature precedents convinced us that seven-membered tricyclic diquat derivatives (**5**) would be best for our study: prior experiments by Calder, Spotswood and Tanzer[2d] have indeed shown that the atropoisomeric conformations of such compounds interconvert slowly on the NMR time scale (e.g. **5a**, ^{1}H NMR in D_2O). Keeping in mind the necessity for the ion pairs containing the chiral anions to be soluble in rather non-polar solvent conditions, we considered from the start the introduction of lipophilic residues on the pyridinium rings. Diquats with extra methyl (**5b**) or *t*-butyl (**5c**) groups were thus prepared and—for ease of synthesis—substitution was realized at the 4,4′-positions. The synthesis was achieved in a single step by treatment at reflux of the corresponding 2,2′-bipyridine with an excess of 1,3-dibromopropane to afford in good to excellent yields (82–100%) salts [**5a**–**c**]Br_2 as white precipitates.

Racemization energies of cations **5b** and **5c** were however unknown and we decided to investigate their configuration stability prior to a study with the chiral anions. NMR spectra (DMSO-d_6) of salts [**5a**–**c**]Br_2 showed at room temperature a magnetic non-equivalency for the diastereotopic protons of the bridge of all three derivatives (Fig. 1, R = H). Dynamic conformational isomerism was then detected for **5a**–**c** with coalescence temperatures of 363 K ($\Delta G^{\neq} = 16.9$ kcal mol^{-1}), 363 K ($\Delta G^{\neq} = 16.9$ kcal mol^{-1}) and 403 K ($\Delta G^{\neq} = 18.8$ kcal mol^{-1}), respectively (400 MHz, Fig. 1), demonstrating the slow interconversion at room temperature between enantiomeric *R* and *S* conformations.[9] However, salts of **5a** proved to be rather insoluble in most organic solvents. Further experiments were therefore performed with [**5b**]Br_2 and [**5c**]Br_2 exclusively.

Initial experiments to determine the efficiency of the TRISPHAT anion as an NMR chiral shift agent were attempted following conditions already reported.[10] Racemic diquat derivatives [**5b**]Br_2 and [**5c**]Br_2 were studied and, as foreseen, salt [**5b**]Br_2 proved to be insoluble in most solvents or solvent combinations of low polarity. Only salt [**5c**]Br_2 could be dissolved in decent amounts in 10% DMSO-d_6/$CDCl_3$. We therefore tested the protocol on such a solution of [**5c**]Br_2 in 10% DMSO-d_6/$CDCl_3$. In a NMR tube, [^{n}Bu$_4$N][Δ-**2**] was added as a solid and, after solubilization, a separation of the signals ($\Delta\delta$) of the enantiomers of **5c** was observed (Fig. 2). It was necessary to add at least 2.0

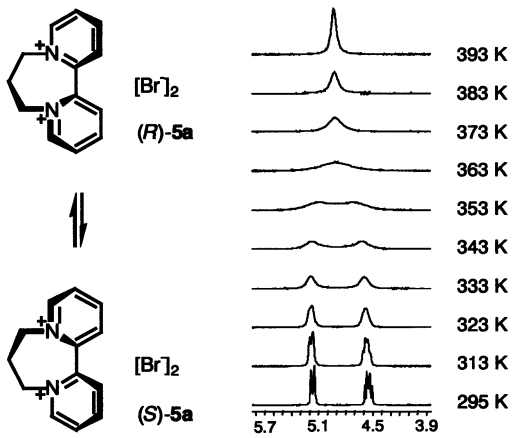


Figure 1. Variable temperature ^{1}H NMR (400 MHz, DMSO-d_6) of [*rac*-**5a**]Br_2. $T_c = 363$ K, $\Delta\nu = 247$ Hz and $J = 14.4$ Hz.

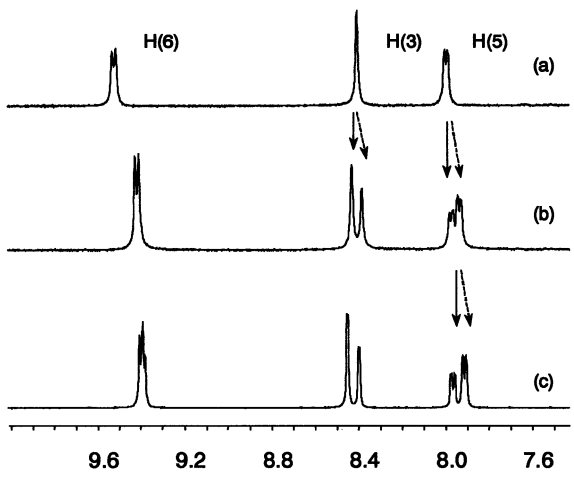


Figure 2. ^{1}H NMR spectra (400 MHz, 10% DMSO-d_6/$CDCl_3$, 22°C, parts) of [**5c**]Br_2 with (a) 0, (b) 2.0 and (c) 6.0 equiv. of [^{n}Bu$_4$N][Δ-**2**].

equiv. of the reagent to observe the beginning of a non-equivalence of the signals and, only with 6.0 equiv. of the shift reagent, could baseline-to-baseline separations be realized for most of the signals ($\Delta\delta_{max}=0.136$ ppm). As mentioned, more polar solvent conditions—28% DMSO-d_6/$CDCl_3$—were required for salt [**5b**]Br_2 and under those conditions the addition of 6.0 equiv. of the shift reagent led to a general broadening for most of the signals except for a couple better resolved ($\Delta\delta_{max}=$ 0.100 ppm). Furthermore, we noticed that—in the presence of the chiral TRISPHAT—the intensities of the two sets of signals of the enantiomers of **5c** were not equivalent, meaning that an asymmetric induction from the anion onto the chiral cation had occurred (Fig. 2, spectrum c, d.e. 25%). With this good preliminary result on our hand, we turned our attention onto the characterization of this effect.

Recently, we have observed that TRISPHAT and the other hexacoordinated phosphate anions **3** and **4** confer to salts an affinity for low polar organic solvents, as they usually dissolve in $CHCl_3$/CH_2Cl_2 and elute rapidly on chromatography over silica gel/alumina.[4b,10] We therefore considered the preparation of the diquats salts of anions **2**–**4**, namely salts [**5b**–**5c**][Δ-**2**]$_2$, [**5b**–**5c**][Δ-**3**]$_2$ and [**5b**–**5c**][(*R*,*R*)-**4**]$_2$, respectively, and expected that the increased lipophilicity of the ion pairs would allow us to dissolve them in less polar NMR solvents—in particular with cation **5b**—leading to better separations of the NMR signals of the enantiomers as well as higher asymmetric inductions.

For the preparation of the salts, solutions in 1:1 methanol/acetone of [ammonium][**2**–**4**] and of [**5b**]Br_2 or [**5c**]Br_2 were prepared and mixed together.[5e,10] Aliquots were adsorbed on analytical basic alumina plates. Development by elution with 10% acetone/CH_2Cl_2 showed as expected a much-reduced affinity of the phosphate salts for basic alumina, as they were retained to a much lower extent (R_f 0.25) than their bromide precursors (R_f ~0). Preparative column chromatography experiments (Al_2O_3, 10% acetone/CH_2Cl_2, 1×8 cm) using mixtures of [**5b**]Br_2 or [**5c**]Br_2 (43 μmol) and the appropriate [ammonium][**2**–**4**] source (2.5 equiv., 166 μmol) were performed and the resulting phosphate salts were isolated in modest to decent yields (50–75%).

Initial experiments were attempted with more robust TRISPHAT anion **2**. As foreseen, TRISPHAT salts exhibited a higher solubility in low polar solvent conditions and could be dissolved in 20% (**5b**) or 8% acetone-d_6/$CDCl_3$ (**5c**). ^{1}H NMR analysis of isolated [**5c**][Δ-**2**]$_2$ salts confirmed our prediction. The signals of both enantiomers of the cations could be observed in the solvent conditions that were used and a 64:36 ratio was measured for the signals of the two enantiomers, (Fig. 3, 8% acetone-d_6/$CDCl_3$, d.e. 28%).

As for anion **2**, association of HYPHAT **4** with diquats (**5b**–**5c**) was realized under the chromatographic exchange conditions. Pure samples of [**5b**][(*R*,*R*)-**4**]$_2$ and [**5c**][(*R*,*R*)-**4**]$_2$ were obtained in decent yields (52 and 61%, respectively). ^{1}H NMR analyses were performed in 8% acetone-d_6/$CDCl_3$ for salts [**5b**][(*R*,*R*)-**4**]$_2$ and [**5c**][(*R*,*R*)-**4**]$_2$ salts, respectively (Fig. 4). A better non-equivalence between the enantiomeric signals (larger $\Delta\delta$) was observed for salt [**5b**][(*R*,*R*)-**4**]$_2$ than for [**5c**][(*R*,*R*)-**4**]$_2$.[11] However, this better NMR separation of the signals did not translate into a better selectivity as diastereomeric excesses of 0 and ~10% were measured for [**5b**][(*R*,*R*)-**4**]$_2$ and [**5c**][(*R*,*R*)-**4**]$_2$ salts, respectively.

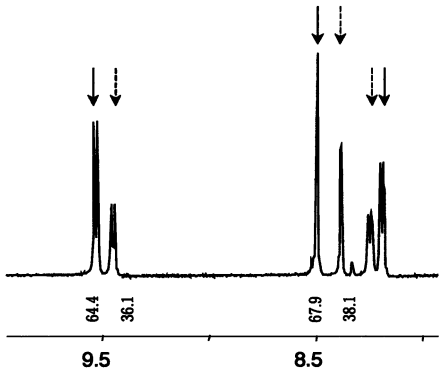


Figure 3. ^{1}H NMR spectra (400 MHz, 8% acetone-d_6/$CDCl_3$, 22°C) of [**5c**][Δ-**2**]$_2$, d.e. 28%.

Association of BINPHAT anion **3** with diquats (**5b**–**5c**) turned out to be more challenging than expected as prolonged exposure to chromatography of the BINPHAT salts led to their decomposition. Only a fraction of [**5c**][Δ-**3**]$_2$ could be isolated; all of the fractions containing the desired ion pair along with some contamination from BINOL. Nevertheless, ^{1}H NMR analyses on a small and not too impure sample of [**5c**][Δ-**3**]$_2$ could be performed and revealed good NMR chiral shift ($\Delta\delta=0.56$ ppm) and asymmetric inducing effects from anion **3**; in 8% acetone-d_6/$CDCl_3$, a 68:32 ratio was measured corresponding to a ~36% diastereoselectivity (Fig. 5).

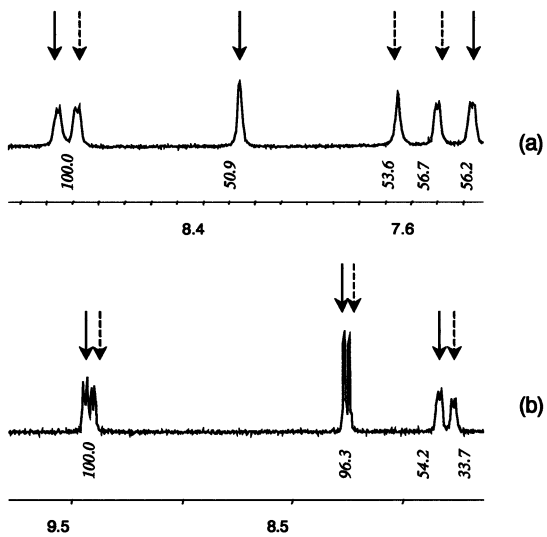


Figure 4. ^{1}H NMR spectra (400 MHz, 8% acetone-d_6/$CDCl_3$, 22°C, parts) of (a) [**5b**][(*R*,*R*)-**4**]$_2$, d.e. 0% and (b) [**5c**][(*R*,*R*)-**4**]$_2$, d.e. ~10%.

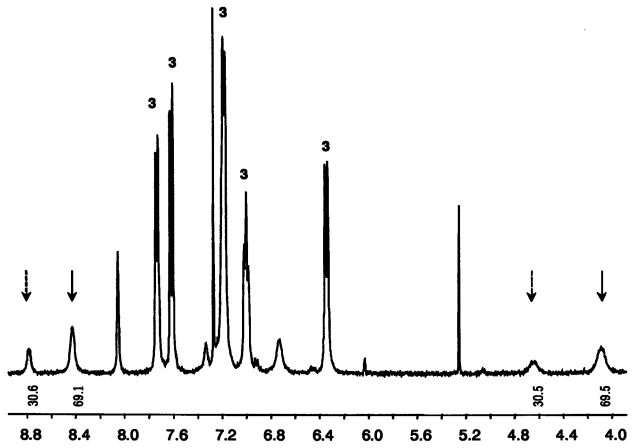


Figure 5. ^{1}H NMR spectra (400 MHz, 8% acetone-d_6/$CDCl_3$, 22°C, parts) of [**5c**][Δ-**3**]$_2$, d.e. ~36%.

In conclusion, association of chiral diquats and hexacoordinated phosphate anions was realized and yielded the first example of configurational ordering of these cationic species. Importantly, we have observed that the overall symmetry of the chiral anion (D_3 or C_2) is not as important as the resulting solubility of the ion pair; anion **4** in spite of its C_2-symmetry is less efficient than TRISPHAT **2**. Nevertheless, C_2-symmetric BINPHAT anion remains the most efficient asymmetric inducting agent.

Acknowledgements

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9. The relationship $\Delta G^{\neq} = RT_c\ (22.96+\ln(T_c/\sqrt{(\Delta v^2+6J^2)})$ was used to determine the activation energy, $\Delta G^{\neq}$, from the coalescence temperature, T_c (K), the frequency separation of the peaks, Δv (Hz), and the coupling constant between the nuclei, J (Hz).
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11. Chemical shifts for each enantiomer of salt [**5b**][(*R*,*R*)-**4**]$_2$ were assigned using COSY experiments and revealed upfield or downfield shifts induced by the phosphate reagent.