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A homochiral tripodal receptor with selectivity for sodium (*R*)-2-aminopropionate over sodium (*S*)-2-aminopropionate

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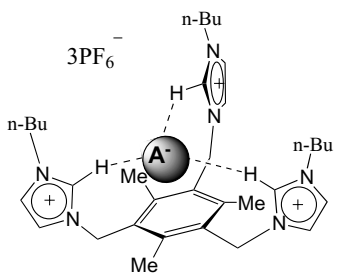
Abstract—This paper describes the synthesis and use of a homochiral tripodal imidazolium salt that can distinguish between sodium (*R*)-2-aminopropionate and sodium (*S*)-2-aminopropionate. The imidazolium salt complexes with the (*R*) enantiomer but not with the (*S*) enantiomer. © 2001 Elsevier Science Ltd. All rights reserved.

In spite of their very important roles in chemistry and biology, substrates or cofactors for enzymes,[1] nucleophiles, bases, redox agents and phase transfer catalysts, the synthesis of receptors designed to recognise and coordinate anions has only relatively recently become an area of intense research activity. The combination of a metal unit as a Lewis acid together with an amide N–H group as a hydrogen bond donor have been demonstrated to be the essential components for anion recognition. As such this combination has been widely applied to the design of anion receptors.[2] Recently the ability of 1,3-disubstituted imidazolium cations to enter into hydrogen bonds with halide ions[3–7] has led to the design of new systems based on the azolium entity that have anion recognition properties, such as molecules **1** and **2**.[8–10]

We were intrigued by the tripodal anion receptor **1** used by Sato[8] and the possibility that it could be modified to incorporate chirality. A homochiral tripodal anion receptor may have the potential ability to distinguish between chiral anions and therefore hold promise in biomedical applications.

Therefore, we synthesised four novel homochiral molecules **3**–**6** according to a similar procedure used by Sato and Dias,[11] but incorporating chirality into the compounds. The general synthesis of compounds **3**–**6** is given in Scheme 1. The *N*-((−)-*cis*-myrtanyl) imidazole (**7**), for example, was formed using a modified Arduengo[12] protocol whereby an amine can react with aqueous formaldehyde, glyoxal and aqueous ammonia to effect a ring closure and produce a *N*-substituted imidazole. This was subsequently reacted with 1,3,5-tris(bromomethyl)-2,4,6-trimethyl benzene **8**[13] to form the 1,3,5-tris[*N*-((−)-*cis*-myrtanyl imidazolium)methyl]-



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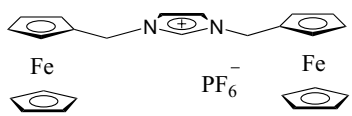

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Keywords: anion recognition; homochiral; coordination.

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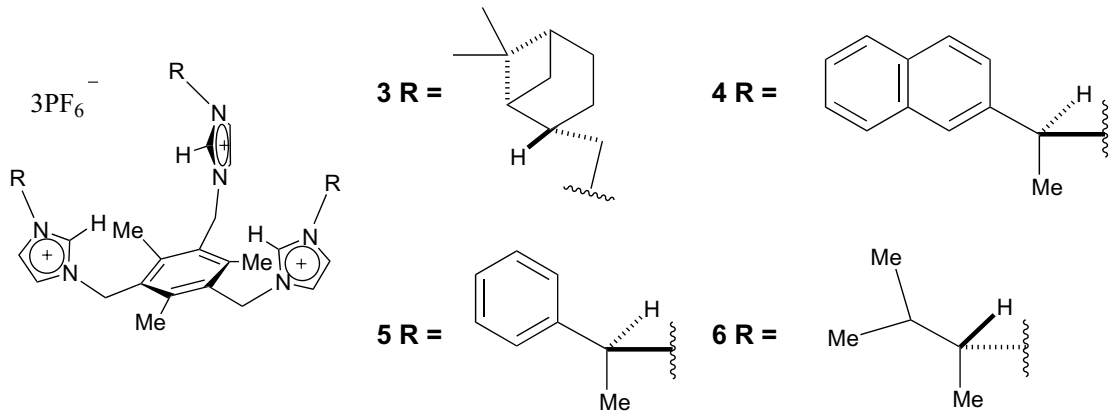
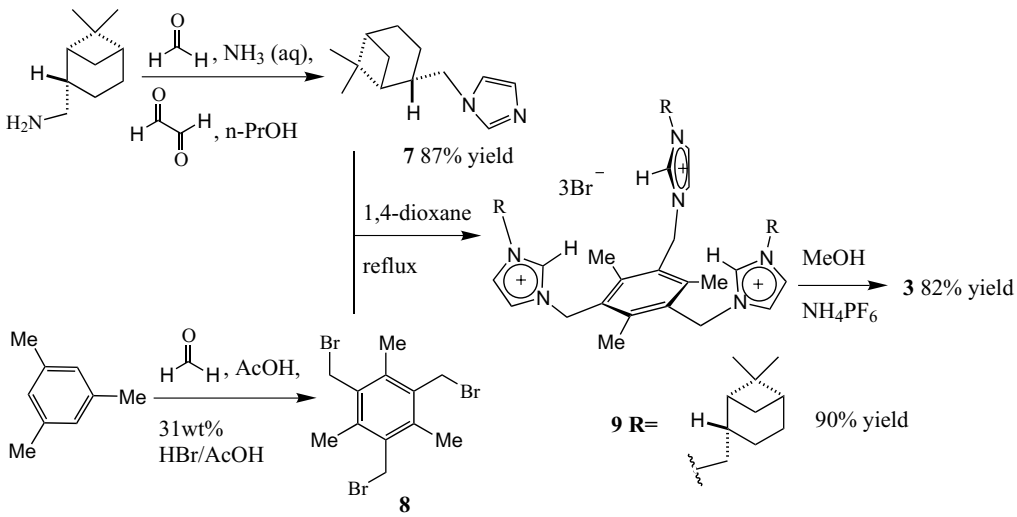


2,4,6-trimethyl benzene trisbromide salt (**9**).[9] Finally this was converted to the corresponding trishexafluorophosphate salt **3**.

In series of ^{1}H HMR experiments[14] sodium (*R*)-2-aminopropionate, sodium (*S*)-2-aminopropionate or a racemic mixture were added separately to each of the four tripodal molecules **3**–**6** in an 1:1 ratio [1:1:1 for the racemic system (tripodal compound:(*R*)-anion:(*S*)-anion)]. The rational behind these experiments was that if the tripodal molecules act as receptors for the anion enantiomers, a diastereomeric complex would be formed. The formation of a diastereomeric complex would possibly lead to differences in the ^{1}H NMR spectra for either the anion enantiomer or that of the tripodal molecule component of the complex, and those of the uncomplexed components. Should the potential receptor distinguish between anion enantiomers we might see a shift difference in the δ value for a particular proton in the complex, and the magnitude of the shift could depend on which one of the two possible diastereomic complexes is formed. If this were the case, we can establish which complex is formed preferentially.

The results from these experiments were very interesting. For tripodal compounds **4**–**6**, we observed no difference in the ^{1}H NMR spectra when mixed with either of the anion enantiomers or the racemic mixture. However, when compound **3** was mixed with the anions there was a distinct down-field shift of the δ value of the α proton for the sodium (*R*)-2-aminopropionate anion to 4.42 ppm and broadening of the signal was observed, indicating the formation of a diastereomeric complex. In the absence of **3** this proton has a δ value of 3.62 ppm and is a distinct quartet. In the corresponding experiment with the sodium (*S*)-2-aminopropionate there was no shift in the δ value for the corresponding proton and the signal remained as a quartet. When the experiment was carried out with the 1:1:1 (compound **3**:(*R*)-anion:(*S*)-anion) system both the shifted signal at 4.42 ppm and the unshifted signal at 3.62 ppm were observed in an 1:1 ratio, indicating that all the (*R*)-anion enantiomer has been complexed over the (*S*)-anion enantiomer. Although these are preliminary observations, they suggest that the tripodal homochiral imidazolium salt **3** can distinguish between sodium (*R*)-2-aminopropionate and sodium (*S*)-2-aminopropionate.



Scheme 1.

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^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) = 0.83 (1H, d, J = 9.6 Hz), 1.02 (3H, s), 1.3 (3H, s), 1.45 (1H, m), 1.70 (1H, m), 1.84 (4H, m), 2.27 (1H, m), 2.39 (1H, m), 3.84 (1H, d, J = 8.4 Hz) overlapping 3.85 (1H, d, J = 8.0 Hz), 6.81 (1H, s, NCHC<u>H</u>), 6.97 (1H, s, NCHC<u>H</u>), 7.36 (1H, s, NCHN).
^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) = 19.8 (CH_3), 23.8 (CH_3), 26.1 (CH_2), 28.2 (CH_2), 33.2 (CH_2), 38.9 (CH_2), 41.5 (CH), 43.0 (CH), 43.4 (CH), 52.9 (C), 119.4 (N<u>C</u>HCH), 129.6 (N<u>C</u>HCH), 137.6 (NCHN).
1,3,5-Tris(bromomethyl)-2,4,6-trimethyl benzene (0.50 g, 1.35 mmol) and (−)-*cis*-myrtanyl imidazole (1.00 g, 4.80 mmol) in 1,4-dioxane (15 mL) were heated to 100°C for 24 h. The resulting solid, 1,3,5-tris[*N*-((−)-*cis*-myrtanyl imidazolium)methyl]-2,4,6-trimethyl benzene trisbromide, was collected, rinsed with diethylether (3×100 mL) and dried to leave a light brown solid in 90% yield. The trisbromide salt was converted to the trihexafluorophosphate salt by dissolving the trisbromide salt in methanol (ca. 5% w/v) and adding a saturated aqueous solution of ammonium hexafluorophosphate until no further precipitation occurred. The precipitate was filtered, washed with methanol and dried, to yield **3** (82%) with the following analytical data, mp = 260–262°C.
^{1}H NMR (400 MHz, CD_3COCD_3) δ (ppm) = 0.94 (3H, d, J = 9.6 Hz), 1.10 (9H, s), 1.20 (9H, s), 1.61 (3H, m), 1.93 (21H, m), 2.39 (3H, m), 2.65 (3H, m), 4.31 (6H, d, J = 8.8 Hz), 5.77 (9H, s) 7.63 (3H, s, NC<u>H</u>CH), 7.81 (3H, s, NC<u>H</u>CH), 8.92 (3H, s, NCHN).
^{13}C NMR (100 MHz, CH_3COCH_3) δ (ppm) = 17.1 (CH_3), 19.9 (CH_3), 23.8 (CH_3), 26.6 (CH_2), 28.4 (CH_2), 33.8 (CH_2), 39.6 (CH_2), 42.3 (CH_2), 43.1 (CH), 44.5 (CH), 49.6 (CH), 56.3 (C), 123.8 (CH_3), 124.5 (CH_2), 130.7 (NCH), 136.7 (NCH), 143.1 (NCHN).
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14. A 2×10^{-2} molar stock solution for each of the four homochiral imidazolium hexafluorophosphate salts **3**–**6** in deuterated acetonitrile was prepared. For each salt four ^{1}H NMR experiments were run. To equal aliquots of the stock solution, no chiral anion, (*R*)-2-aminopropionate anion, (*S*)-2-aminopropionate anion, and both (*R*)- and (*S*)-2-aminopropionate anions were added in an 1:1 ratio (1:1:1 for the racemic mixture), the anions being dissolved in deuterated water. The experiments were then run on a Bruker ADVANCE 400 MHz spectrometer. 2-Aminopropionate: ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) = 1.36 (3H, d, J = 7.2 Hz), 3.62 (1H, q, J = 7.2 Hz).