Enantiodifferentiation of Carboxylates by Chiral Building Blocks for Abiotic Anion Receptors

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The chiral bicyclic guanidinium compound (**2b**) binds oxoanionic guests by a unique ion pairing pattern, which is confirmed by the *X*-ray crystal structure of the nitrate salt (2*S*, 8*S*)-2,8-bis(t-butyldiphenylsilyloxymethyl)-3,4,6,7,8,9-hexahydro-2*H*-pyrimido[1,2a]pyrimidine hydronitrate, and allows enantiodifferentiation of racemic carboxylic acids by NMR.

Molecular recognition of polyfunctional organic substrates may be achieved by linearly connected polytopic host molecules.[1] The underlying concept deliberately abandons utmost preorganization of binding groups in the molecular host, but rests instead on their strong enthalpic interactions with substructures of the guest. This serves to organize the host–guest complex in space. A particularly favourable interaction mode on theoretical grounds,[2] as well as shown by abundant biological examples,[3] is the complexation of oxoanionic functions by guanidinium groups, which has been exploited by cyclic[4] and acyclic[5] artificial receptors. Incorporation of a guanidinium group into a bicyclic framework as in (**1**)[6] paves the way towards polytopic hosts capable of positively dedicated enantioselective recognition of, *e.g.*, chiral carboxylates.[7] Chiral recognition of aromatic carboxylates by similar guanidinium compounds has been recently described.[8] The respective chiral guanidinium compounds have been synthesized starting from L-amino acids.[9] Based on the optical rotation data our synthesis[9b] of (2*S*,8*S*)-2,8-bis(hydroxymethyl)-3,4,6,7,8,9-hexahydro-2*H*-pyrimido[1,2-*a*]pyrimidine hydrochloride (**2a**)·Cl^- produced a configurationally purer compound ($[\alpha]_D^{20}$ = +96.8°, H_2O, *c* 0.2) than the published procedure ($[\alpha]_D^{20}$ = +61.8°, H_2O, *c* 1.3).[9a] The idea that replacement of the hydroxyfunctions by bulky substituents could yield a chiral recognition unit for carboxylates in organic solvents led us to test compound (**2b**) in this respect.

As indicated by the *X*-ray crystal structure† of the nitrate salt of (**2b**) (Figure 1) the counter anion is bound by two virtually parallel hydrogen bonds to both of the protonated guanidinium nitrogen atoms. This binding site is central to the

† *Crystal data* for (**2b**)·NO_3^-; $C_{41}H_{54}N_4O_5Si_2$, M = 789.083, orthorhombic, space group $P2_12_12_1$ (No.19), a = 10.021(1), b = 12.983(1), c = 31.651(2) Å, U = 4117.9 Å^3, Z = 4, D_c = 1.192 g cm^{-3}, μ(Cu-K_α) = 11.4 cm^{-1}, F(000) = 1584, T = 23 °C. The integrated intensities of 8920 reflexions were measured up to $(\sin\theta/\lambda)_{max.}$ = 0.629 Å^{-1}, corrected for Lorentz-polarization effects, and averaged to give 8420 unique structure factors (R_{int} = 0.018), 7475 of which with $F_o \geq 4.0\ \sigma(F_o)$ were considered 'observed' and used for all further calculations (Enraf-Nonius CAD4, Cu-K_α radiation, λ = 1.54178 Å, Ni-filter, θ–2θ scans, $\Delta\omega = 0.7 + 0.15 \tan\theta$; *hkl* range: ±13, +17, +40). The structure was solved by direct methods (SHELXS-86). Refinement converged at $R(R_w)$ = 0.056(0.052), $w = 1/\sigma^2(F_o)$ for 477 refined parameters in one block (anisotropic, H(2N)/H(3N) isotropic, all other H atoms in constant position with U_{iso} = 0.05 Å^2; SHELX-76). $\Delta\rho_{fin}$ (max/min) = +0.45/−0.57 e Å^{-3}. The correct absolute configuration was verified by comparison with that of the starting material (L-aspartic acid). It was independently checked by refinement of the inverse co-ordinate set of the final model which gave substantially higher R values [R (R_w) = 0.059 (0.055); during all stages of the refinement the scattering factors of all atoms except hydrogen were corrected for anomalous dispersion[11]]. Atomic co-ordinates, bond lengths and angles, and thermal parameters have been deposited at the Cambridge Crystallographic Data Centre. See Notice to Authors, Issue No. 1.

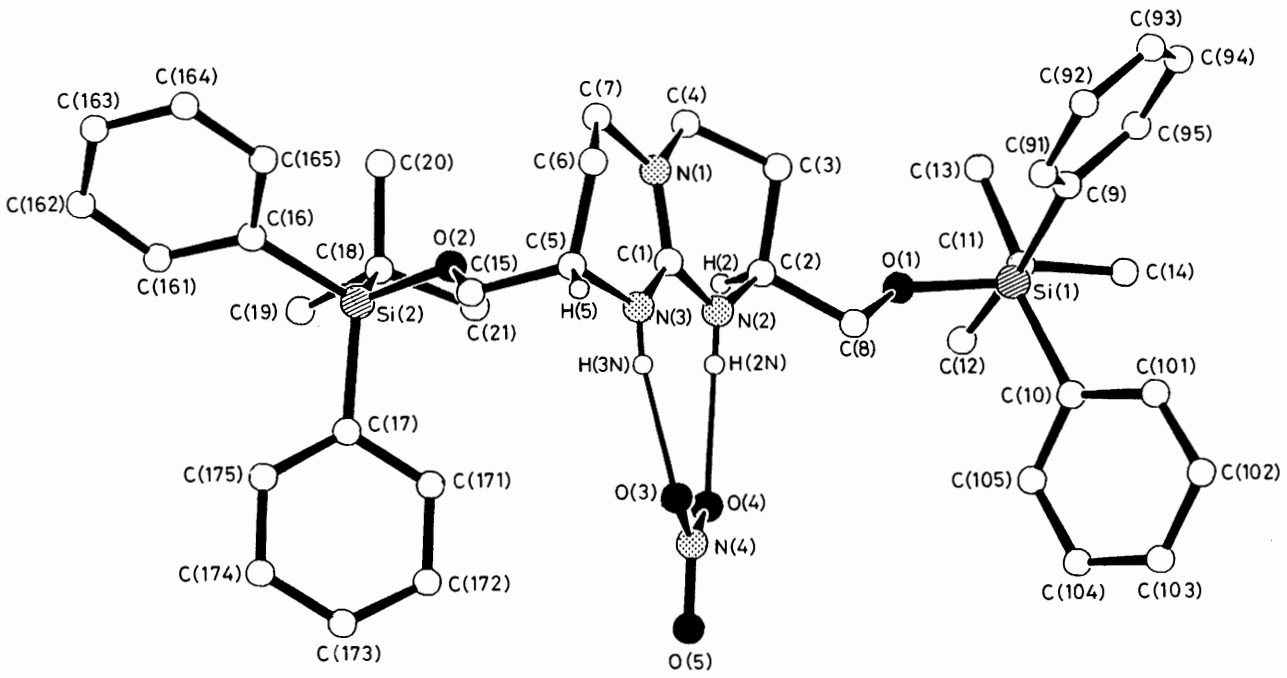


Figure 1. Molecular structure (**2b**)·NO_3^- (SCHAKAL plot; H atoms omitted, except those at C(2), C(5), N(2), and N(3); arbitrary radii; dotted = N atoms, black = O atoms, shaded = Si atoms). Important distances (Å): N(2)–H(2N) 0.77(3), N(3)—H(3N) 0.83(3), H(2N)–O(4) 2.06, H3N–O(3) 2.00, N(2) · · · O(4) 2.823(5), N(3) · · · O(3) 2.810(5); angle between planes N(1), N(2), N(3), C(1)/N(4), O(3), O(4), O(5); 20.8°.

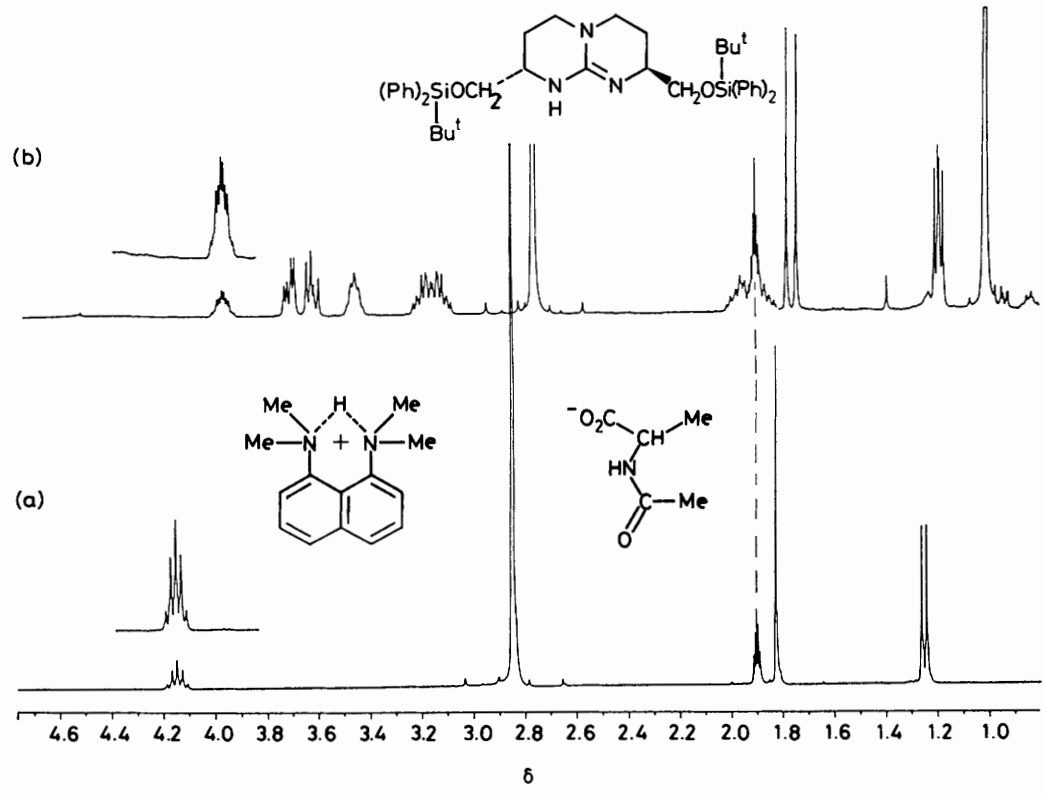
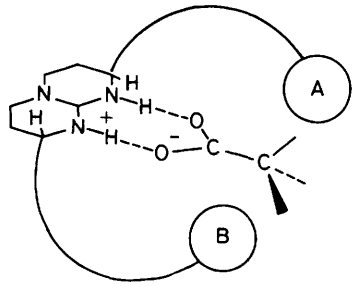
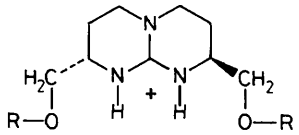


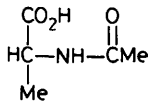
Figure 2. High field region of the 360 MHz ^1H NMR of acetyl-D,L-alanine as the salt with 1,8-bis(dimethylamino)naphthalene in CD_3CN (a) and after addition of 100 mol% (**2b**) as a free base (b).



(1)



	R
(2a)	H
(2b)	$Si(Ph)_2Bu^t$



(3)

molecular cleft lined by the club-like silyl substituents. By virtue of the chirality at C(2) and C(5), the cleft itself is asymmetric.

Inspection of Figure 1 shows that the molecular structure does not even obey C_2 symmetry, which in principle would be possible for both ions (**2**). The molecular cleft is formed predominantly by phenyl rings. The nitrate ion in the cleft is not coplanar with the guanidinium system but rather tilted by 20.8° with respect to the plane through the atoms N(1), N(2), N(3), and C(1). It should be noted, however, that the atoms of the NO_3^- ion have by far the largest displacement parameters, indicating that the guest ion has enough space in the cleft to be still thermally mobile or slightly disordered. This is substantiated by the distances between the phenyl rings and the nitrate ion which are all above the van der Waals limit. It thus seems that the molecular cleft in the solid state structure of (**2b**)·NO_3^- is even better suited for the accommodation of larger guest ions, although it should be remembered that in solution the siloxy methyl substituents at C(2)/C(5) may well take up a large number of different conformations.

The observation of a relatively large chiral cleft in the solid state structure of the ion (**2b**) fostered our suspicion that diastereoisomeric complexes with racemic carboxylates can be formed in solution. *N*-acetyl-D,L-alanine (**3**) was examined by ^1H NMR as an example (Figure 2). If to an acetonitrile solution containing the salt of (**3**) with 1,8-bis(dimethylamino)naphthalene (proton sponge), (spectrum a, Figure 2) an equimolar amount of the free base of (**2b**) in CD_3CN is added (spectrum b, Figure 2), three effects become obvious. The singlet of the *N*-methyl protons at δ 2.85 is shifted upfield indicating the almost complete deprotonation of the proton sponge cation. This emphasizes the extraordinary basicity of these bicyclic guanidines.[10] In addition all resonances of the anionic guest appear at higher field (Δδ = 0.05—0.2 p.p.m.), while the shift of the α-CH-signal is most pronounced. However, all signals of the guest show up in duplicate, which reveals the formation of diastereoisomeric host–guest complexes. The distinct separation of corresponding resonances, in particular for the *N*-acetyl-group at approximately δ 1.75 would easily allow the determination of enantiomeric excess-values by integration without the interference of line broadening effects commonly seen with *e.g.* chiral lanthanide shift reagents in use for the same purpose. Other chiral α-disubstituted acids (examples: D,L-2-methylbutyric acid, D,L-lactic acid, D,-L-2-bromobutyric acid, D,L-phenylalanine) show similar effects although not in every case as striking. Clearly the unique mode of pairing single charged ions creates host–guest complexes of definite structure and sufficient stability to allow enantiodifferentiation of guest species even in solvents of high electrical permittivity [ε (acetonitrile) = 35.8].

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