Chiral Recognition of Tartaric Acid Derivatives by a Synthetic Receptor

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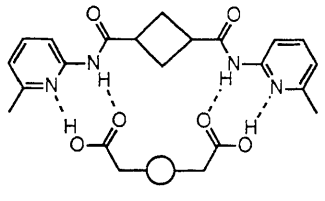
A synthetic receptor containing two acylaminopyridine groups linked through a *R*-(−)-binaphthyl spacer has been prepared and shown to bind to the two enantiomeric forms of diacyl tartaric acids by two very different geometries.

In 1858 Pasteur demonstrated that D-(−)-tartaric acid and L-(+)-tartaric acid could be distinguished by certain micro-organisms[1] and in doing so laid down the principle of chiral recognition by biological receptors. In this paper we report the development of an entirely synthetic receptor that can successfully recognize the two enantiomers of diacyl tartaric acid derivatives.[2] Our strategy involved designing a chiral receptor capable of forming multiple hydrogen bonds to the two carboxylates of tartaric acid. We have previously shown[3] that a molecule containing two acylaminopyridine units

Table 1 ^{1}H NMR Chemical shift values for 1:1 complexes of *R*-(−)-**6** and D-(−)-dibenzoyl tartaric acid or L-(+)-dibenzoyl tartaric acid *in* $CDCl_3$

	NpH_3	NpH_4	NpH_5	NpH_7	NpH_8	BzH_2	BzH_3	BzH_4	TtCH
R-(−)-**6**	7.56	8.14	8.51	7.74	7.19	—	—	—	—
R-(−)-**6**: D-(−)-DBTA	7.58	8.21	8.64	7.85	7.32	7.73	6.91	7.32	6.09
R-(−)-**6**: L-(+)-DBTA	7.49	8.07	8.42	7.71	7.30	7.97	7.30	7.49	5.78
D-(−)-DBTA	—	—	—	—	—	8.05	7.43	7.59	6.02



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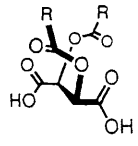

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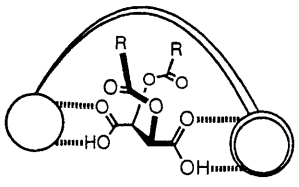

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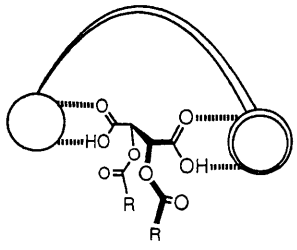

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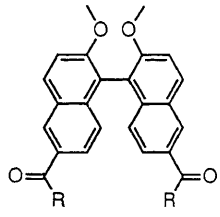
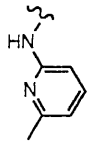


5; R = OH

6; R =



separated by a rigid aromatic spacer binds strongly to dicarboxylic acids as shown in **1**.

Crystal structures of L-(+)- and D-(−)-tartaric acids and their derivatives[4] generally show a conformation in which the carboxylic acid groups are *trans* and the hydroxy groups (or their derivatives) are *gauche* to each other [as shown in **2** for diacyl D-(−)-tartaric acid]. A potential receptor for **2** in this conformation should be of C_2 symmetry and should contain two acylaminopyridine units linked through a chiral spacer such that the two acyloxy substituents of a bound tartaric acid will project into opposite open faces in the binding cavity. In this way, D-(−)-**2** will bind as in **3** with the possibility of repulsive or attractive interactions between the ester groups and the chiral spacer whereas L-(+)-**2** will bind as in **4**. In both **3** and **4** the shape of the receptor is complementary to the position of the two carboxylic acid groups and linear bidentate hydrogen bonds can form. The alternative geometries for the complex, in which the substrates bind upside down compared to those shown in **3** and **4**, will not allow such an effective match of the tartaric acid and cavity shapes.

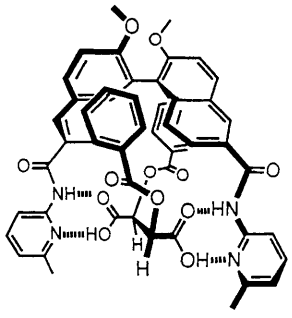
A simple receptor of this type is available from (2,2′-dimethoxy-1,1′-binaphthyl)-6,6′-dicarboxylic acid **5** which can be readily prepared in enantiomerically pure form from *R*-(−)-1,1′-binaphthol *via* bromination (Br_2),[5a] methylation (Me_2SO_4), lithiation (BuLi) and carboxylation (CO_2).[5b] Conversion of the diacid to its diacid chloride [$(COCl)_2$] followed by treatment with 6-methyl-2-aminopyridine gave the receptor *R*-(−)-**6**† in 84% yield from *R*-(−)-**5**. Molecular modelling studies[6] suggested that the position and orientation of the acylaminopyridine groups in **6** were well-suited to bind to succinate derivatives in a *trans* conformation (as in **2**).

The tartrate recognition properties of **6** were studied by ^{1}H NMR spectroscopy. Addition of one equivalent of D-(−)-dibenzoyl tartaric acid (DBTA) to a $CDCl_3$ solution of *R*-(−)-**6** gave a large downfield shift of the amide-NH resonance (2.8 ppm) as expected for the formation of a tetrahydrogen bonded complex.[3] Significantly, the benzoyl-2, -3 and -4 H resonances were shifted upfield by 0.32, 0.52 and 0.27 ppm, respectively, compared to the uncomplexed substrate whereas the C–H resonance barely moved (Table 1). These results indicate a complex structure as shown in **7** in which the benzoyl groups point towards and are influenced by the binaphthyl ring current. An intermolecular NOE is seen between the 2-proton on the benzoyl group and the 8-proton on the naphthalene ring, consistent with the position of the substrate in **7**. In contrast, the complex between *R*-(−)-**6** and L-(+)-dibenzoyl tartaric acid shows a very different structure. A large downfield shift of the amideNH resonance confirms hydrogen bond formation. However, in this case the benzoyl protons experience little ring current effects while the C–H resonance shifts significantly (0.24 ppm) upfield (Table 1); also no NOE was observed between receptor and substrate. The best fit of the L-(+)-diacid into *R*-(−)-**6** involves directing the benzoyloxy substituents out of the cavity, as in **8**. Now, the C–H groups point towards the naphthylenes where they are close enough to experience deshielding but too far to show NOE effects.

Substrate binding was also conveniently followed by fluorescence spectroscopy.‡ Non-linear regression analysis[7] of the binding isotherm in CH_2Cl_2 gave association constant values for the D-(−)-diacid (complex **7**) of $3.0 \pm 0.3 \times 10^5$ dm^3 mol^{-1} and for the L-(+)-acid (complex **8**) of $3.6 \pm 0.4 \times 10^5$ dm^3 mol^{-1}. This small difference presumably reflects increased steric hindrance in **7**. Similar complex geometries are seen with the two enantiomers of dipivaloyl tartaric acid (DPTA) and *R*-(−)-**6**. In the D-(−)-DPTA: *R*-(−)-**6** complex (1:1) an upfield shift (0.22 ppm) of the *tert*-butyl protons and an NOE between them and the 8-naphthyl proton confirm the close positioning of the *tert*-butyl group and the binaphthyl spacer and indicate a similar structure to that seen in **7** for D-(−)-DBTA. However, the association constant for the *R*-(−)-**6**: D-(−)-DPTA is higher ($K_a = 1.01 \pm 0.12 \times 10^6$ dm^3 mol^{-1}) than both the L-(+)-isomer ($3.2 \pm 0.8 \times 10^5$ dm^3 mol^{-1}) or the D-(−)-dibenzoyl analogue. This increased

† All new compounds gave spectroscopic and mass spectral data consistent with their structures.

‡ By following changes in emission intensity at 546 nm (excitation wavelength 339 nm). [*R*-(−)-**6**] = 1.0×10^{-6}, [diacid] = 0–1.2×10^{-5} mol dm^{-3}.



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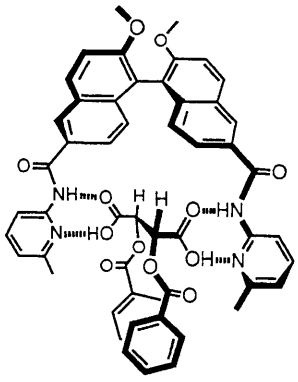

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chiral selectivity for dipivaloyl tartaric acid may indicate a stabilizing of the D-(−)-DPTA complex by Me-π interactions of the type postulated in the solid state[8] and in GC studies.[9,10] The nature of this favourable binding is currently under study.

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