Selective Clathrate Inclusion of Primary and Secondary Amines in a New Host Series. Crystallographic Reasoning of the Inclusion Behaviour

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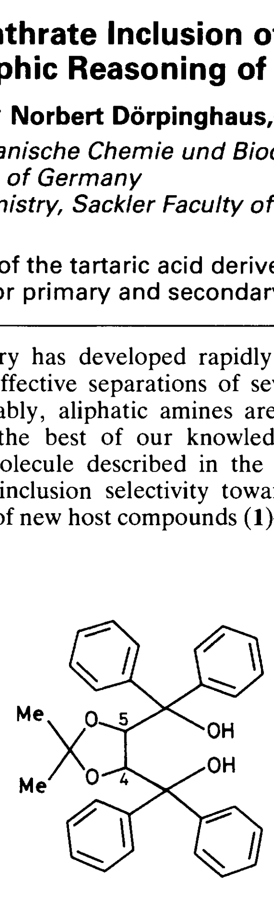
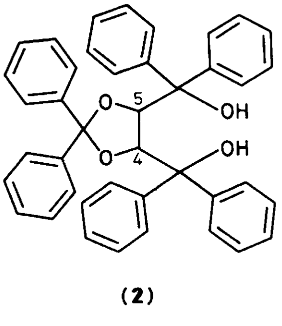
Representatives of the tartaric acid derived host compounds (**1**)—(**3**) are demonstrated to act as highly selective clathrate hosts for primary and secondary amines; this is supported by crystallographic evidence in three cases.

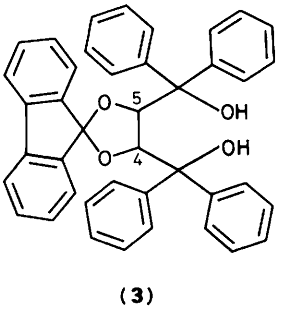
Clathrate chemistry has developed rapidly in the last few years[1] including effective separations of several compound species.[2] Remarkably, aliphatic amines are rarely encountered here.[3] To the best of our knowledge, there is no individual host molecule described in the literature which provides specific inclusion selectivity towards amines. We report on a series of new host compounds (**1**)—(**3**) having this merit and furnish proof of their inclusion behaviour by crystallographic studies. While this work was in progress, Toda and Tanaka provided the first example of this new class of host compounds by introducing (**1a**) and demonstrated part of its inclusion properties.[4]



(**1**) a; (4*R*, 5*R*)
b; (4*RS*,5*RS*)
c; (4*R*, 5*S*)



(**2**)



(**3**)

The present host compounds (**1**)—(**3**) relate to different stereochemical species of tartaric acid (*R*,*R*, racemic, and *meso*). They were obtained as colourless solids† from the corresponding tartaric acid by a sequence of esterification (MeOH, *p*-$MeC_6H_4SO_3H$), transketalization[5] (using the corresponding ketone dimethyl ketal and *p*-$MeC_6H_4SO_3H$ in cyclohexane), and Grignard reaction (PhMgBr, Et_2O)[6] in overall yields between 20 and 60% (*cf.* ref. 4).

Although host molecules (**1a**) and (**1b**) display a surprising variety of clathrate formation ability, including such guests as alcohols, dipolar aprotic molecules, amides, heterocycles, and aromatic hydrocarbons (see also ref. 4), amines (primary, secondary, and tertiary) are highly favoured. Amine inclusions obtained for (**1a**) and (**1b**) are listed in Table 1.

Moreover, from competitive crystallization studies using (**1a**) or (**1b**) and equimolar two-component mixtures of corresponding primary, secondary, and tertiary amines, distinct selectivity in inclusion formation is exhibited (Table 2). In the case of optically active (**1a**), and mixtures including a secondary amine, the secondary amine clathrate is formed with high selectivity. By contrast, racemic (**1b**) is distinctly selective to primary amines in competition with the secondary and tertiary derivatives. In general, tertiary amines are discriminated against primary and secondary ones, from solvent mixtures by the two hosts. Thus, the tartaric acid hosts (**1a**) and (**1b**) are particularly useful for selective crystal inclusion of amines.

Most remarkably, the *meso* analogue (**1c**) is ineffective in

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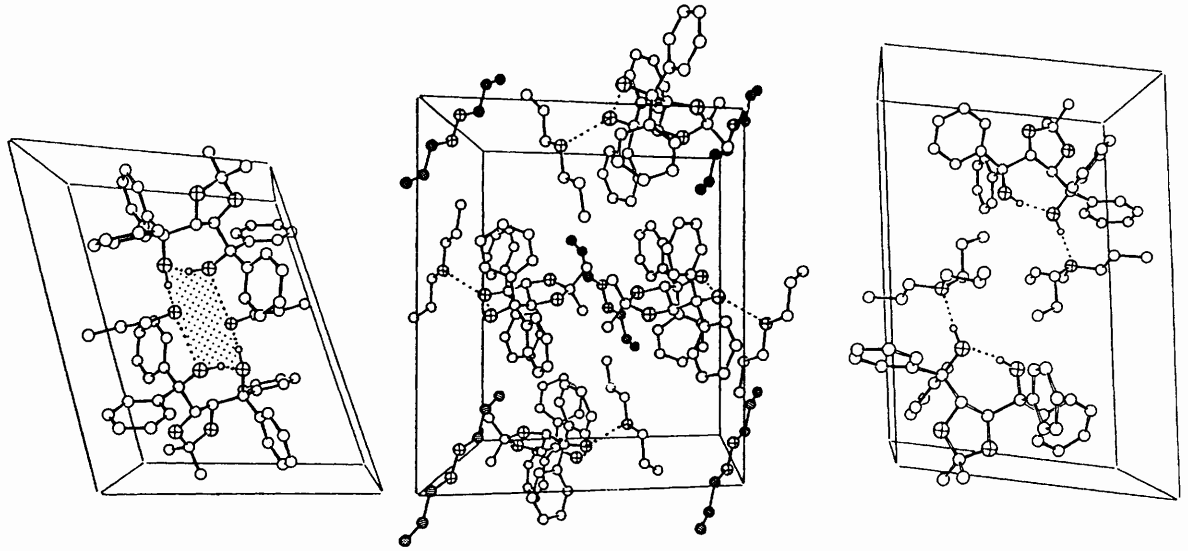
† (**1a**):[4,6] m.p. 192—193 °C, $[\alpha]_D^{20}$ −67° (*c* 1 in $CHCl_3$); (**1b**): m.p. 207—210 °C; (**1c**): m.p. 214—216 °C; (**2a**): m.p. 90—94 °C, $[\alpha]_D^{20}$ +160° (*c* 1 in $CHCl_3$); (**2b**): m.p. 103—106 °C; (**2c**): m.p. 199—201 °C; (**3a**): m.p. 128—130 °C, $[\alpha]_D^{20}$ −40.6° (*c* 1 in $CHCl_3$).



(a) (b) (c)

Figure 1. Crystal structures of (**1b**) with (a) Pr^nNH_2 (1:1), (b) Pr^n_2NH (1:1.5), and (c) Pr^n_3N (1:1). Heteroatoms are marked with filled circles; nonrelevant H atoms are omitted. Especially noteworthy in (a) is the circular H-bonding pattern (dotted region) which does not occur in the other two structures, and in (b) the two different species of Pr^n_2NH (H-bonded and nonbonded type of molecules; the latter are given with shading and are disordered around the inversion centres). Intermolecular H bond distances are in (a) O–H · · · N 2.746, N–H · · · O 3.398; (b) O–H · · · N 2.761; (c) O–H · · · N 2.710 Å. The intramolecular O–H · · · O distances are 2.685, 2.655, and 2.646 Å, respectively.

Table 1. Amines included by (**1a**) and (**1b**) (1:1 host:guest stoicheiometry[a] unless otherwise stated).

Pr^nNH_2, Pr^iNH_2, Bu^nNH_2, Bu^iNH_2, n-OctylNH_2, Cyclopentyl NH_2, Cyclohexyl NH_2, $PhNH_2$
Et_2NH, Pr^n_2NH,[b] Pr^i_2NH, Bu^n_2NH, Bu^i_2NH, piperidine
Et_3N, Pr^n_3N, Bu^n_3N, pyridine, 2-picoline, 3-picoline, 4-picoline[b]

[a] Determined by n.m.r. integration. [b] 1:1.5 host:guest:stoicheiometry.

Table 2. Selective inclusion of primary and secondary amines by (**1a**) and (**1b**) from two-component solvent mixtures.

Equimolar mixture of amines	Host (**1a**)	(**1b**)
RNH_2/R_2NH[a,b]	R_2NH[c]	RNH_2
RNH_2/R_3N[a]	RNH_2	RNH_2
R_2NH/R_3N[a]	R_2NH	R_2NH

[a] R = Pr^n or Bu^n. [b] R = Pr^i or Bu^i. [c] Included amine.

forming amine clathrates under the same conditions. Also, (**1c**) exhibits much lower inclusion capability than (**1a**) and (**1b**) towards other potential guests allowing formation of only a few clathrates of dipolar aprotic guests (dimethylformamide, dimethyl sulphoxide, $MeNO_2$, MeCN, tetrahydrofuran) with (**1c**).

The high preference of (**1a**) and (**1b**) for secondary or primary amines raises questions about the clathrate structures. Crystallographic analyses in the Pr^n amine series revealed that this selectivity can be attributed to a *cyclic* pattern of H bonds that forms within and dominates the preferred clathrate structures of (**1a**) and (**1b**). This pattern involves four host OH groups and one amine NH in the chiral compound, and four host OH groups with two amine functions in the racemic clathrate. In contrast, the less favoured clathrates form a *noncyclic* less extensive system of H bonds with one direct host–guest contact only.

Relevant examples of *X*-ray structures of the racemic clathrates [(**1b**)·Pr^nNH_2 (1:1), (**1b**)·Pr^n_2NH (1:1.5), and (**1b**)·Pr^n_3N (1:1)]‡ are shown in Figures 1a—1c, respectively. The circular pattern of H bonds occurs only in (**1b**)·Pr^nNH_2 (1:1) (Figure 1a). Interestingly, the clathrate of (**1b**) with

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‡ *Crystal data*: (**1b**)·Pr^nNH_2 (1:1) ($C_{31}H_{30}O_4 \cdot C_3H_9N$), M = 525.69, triclinic, space group $P\bar{1}$, a = 9.809(2), b = 11.529(4), c = 15.051(7) Å, α = 104.36(5), β = 101.64(4), γ = 111.00(2)°, Z = 2, D_c = 1.198 g cm^{-3}; (**1b**)·Pr^n_2NH (1:1.5) [$C_{31}H_{30}O_4 \cdot 1.5(C_6H_{15}N)$], M = 618.36, monoclinic, space group $P2_1/n$, a = 14.579(3), b = 16.830(4), c = 15.266(2) Å, β = 103.54(1)°, Z = 4, D_c = 1.128 g cm^{-3}; (**1b**)·Pr^n_3N (1:1) ($C_{31}H_{30}O_4 \cdot C_9H_{21}N$), M = 609.85, triclinic, space group $P\bar{1}$, a = 9.037(2), b = 11.696(7), c = 17.396(5) Å, α = 98.40(4), β = 92.91(2), γ = 102.23(3)°, Z = 2, D_c = 1.143 g cm^{-3}.

Intensity data were measured at room temperature (*ca.* 20 °C) with a CAD4 diffractometer using Mo-K_α (λ = 0.7107 Å) radiation to $2\theta_{max}$ = 50, 46, and 46° for (**1b**) with Pr^nNH_2, Pr^n_2NH, and Pr^n_3N, respectively. The least squares refinement of the first structure converged smoothly at R = 0.062 for 1991 observations above the threshold of $3\sigma(I)$ (out of 4210 unique data above zero); that of the third structure converged at R = 0.055 for 2134 (out of 4152) reflections. In the crystals of (**1b**) with Pr^n_2NH the unco-ordinated amine molecules included in the lattice were found to be disordered around the crystallographic centres of inversion. This affected the amount of significant data that could be measured as well as the precision of the structural analysis. Correspondingly, the refinement of this structure converged only at R = 0.105 for 1667 (out of 3282) observations above the intensity threshold of $3\sigma(I)$; geometric constraints were applied to the disordered fragments to avoid unreliable distortions of the covalent parameters. Most of the hydrogen atoms involved in the co-ordinative interactions were located directly from difference–Fourier maps; the remaining hydrogens were introduced in calculated positions.

The 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.

Pr^n_2NH (1 : 1.5) (Figure 1b), as (**1a**)·Pr^n_2NH (1 : 1),§ contains an additional amine molecule in the crystal matrix, differently situated and lacking polar interaction to both the host molecule and the co-ordinated amine species. This guest may be considered for replacement to allow an intermolecular solid state reaction.[7] We are not aware of any other host system available from the literature which provides a comparable clathrate behaviour toward amines.

Compounds (**2**) and (**3a**) also form clathrates with amines in a way similar to (**1**), but *meso* isomer (**2c**) is just as effective here; however, the observed stoicheiometries are different in most cases. These molecules represent a new host design which can be applied to more extensive problems of molecular separation. For example, compounds outlined here have great potential in chiral resolutions since they can readily be obtained as optically active species from common natural sources. Indeed, Toda and Tanaka[4] have demonstrated already that (**1a**) is effective in the optical resolution of bicyclic enones.

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7 *Cf.* J. Scheffer, 'Organic Chemistry in Anisotropic Media,' Tetrahedron Symposia-in-Print 29, *Tetrahedron*, 1987, **43**, 1197.

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§ Crystallographic data of the corresponding amine clathrates of (**1a**) and of the free hosts (**1a**)—(**1c**) will be given in a future publication.