Weak Hydrogen Bonding as a Basis for Concentration-Dependent Guest Selectivity by a Cyclophane Host

Sylke Apel,[a] Michael Lennartz,[b] Luigi R. Nassimbeni,[c] and Edwin Weber*[a]

Abstract: Crystalline inclusion complexes between the cyclophane **1** and three isomers of picoline and lutidine were grown and their properties and structures were studied by X-ray analysis, thermal gravimetry (TG), and differential scanning calorimetry (DSC). In competition experiments, the cyclophane host, which by itself is only able to form weak C–H ··· acceptor hydrogen bonds, is able to discriminate between the different picoline or lutidine isomers, although in some cases a strong concentration dependence of the preferred isomer is observed. In the three-component experiments, inclusion of 4-picoline is strongly favored when $X(\text{4-picoline}) > 0.35 - 0.39$. Very similar results were obtained in the lutidine series. The fact that 2,4-lutidine is favored when $X(\text{2,4-lutidine}) > 0.2$ indicates that the host prefers the isomer with the methyl group in 4-position relative to the nitrogen atom. The selectivities observed can be explained based on the assignment of the inclusion complexes to different adduct classes. In the case of the picoline isomers, the preference of 4-picoline was in good agreement with the calculated lattice energies for this series. The present work also shows that caution is advisable when deducing selectivity of crystalline inclusion compounds from guest competition experiments.

Keywords: crystal engineering · host-guest systems · inclusion compounds · macrocycles · separation of isomers

Introduction

Crystalline inclusion compounds (clathrates) and similar co-crystalline systems have attracted considerable interest over recent years as they are typical examples for the assembly of organic molecules into larger supramolecular structures.[1] Our knowledge about supramolecular synthesis, and our understanding of the weak intramolecular attractive forces associated with crystal engineering are still limited.[2, 3] So far, most studies in this area have been directed to the use of polar host compounds containing strategically positioned hydroxy or carboxy groups in a rigid framework,[4] often as part of a macrocyclic compound.[5] The C–H group itself can also serve as a hydrogen-bond donor and plays an important role in the determination of crystal structures in the form of weak nonclassical hydrogen bonding such as C–H ··· N–,[6] C–H ··· O–,[7] or C–H ··· π interactions.[8] But so far, these have only been used to a small extent in rational supramolecular synthesis.[9]

An important application of macrocyclic ligands and host–guest chemistry in general is the selective recognition of ions or uncharged organic molecules including even the separation of close isomers.[10] This last process is industrially attractive as the procedure only requires the recrystallization of the targeted isomer in the presence of the host. The crystalline inclusion complex is filtered, and the enriched guest mixture is released by gentle warming, while the host is recovered and recycled. As mentioned above, strong hydrogen bonding is usually involved in achieving high selectivity.[11]

Herein, we present the inclusion properties of the cyclophane **1**[12] (Scheme 1) when co-crystallized with the picoline and lutidine isomers. Assignment of the crystal structures to different adduct classes prompted us to perform two- and three-component competition experiments which revealed strong concentration dependence. Here, we point out that the remarkable selectivities observed are only based on weak C–H ··· N– and C–H ··· O– interactions, and that the common method to determine the selectivity of crystalline inclusion compounds starting with an equimolar mixture of the guests under study can yield erroneous results.

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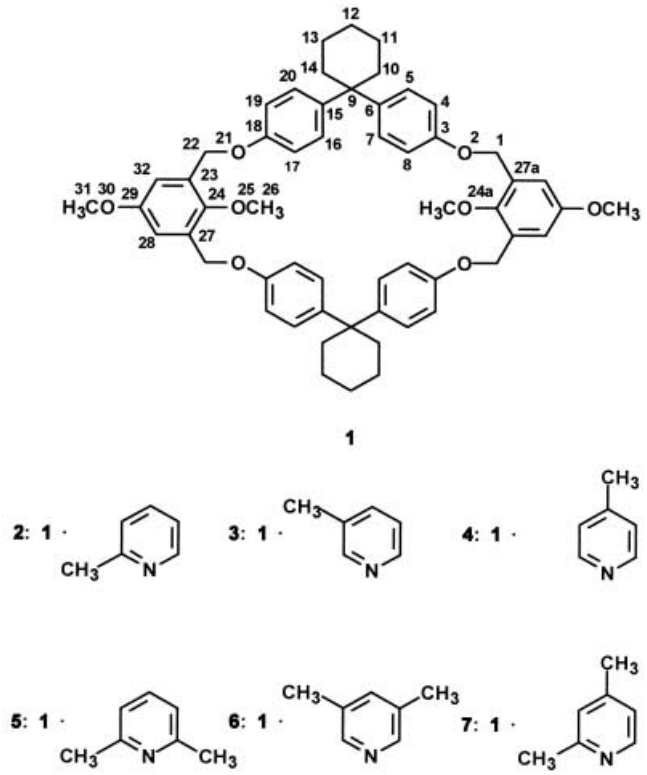

Scheme 1. Atom numbering of the host molecule **1** and inclusion compounds **2**–**7**.

Results and Discussion

Inclusion properties: The inclusion compounds **2**–**4** and **5**–**7** (Scheme 1) were obtained by dissolving the host **1** in the liquid guest, and crystals of suitable quality could be obtained by slow evaporation at room temperature.

Thermal analyses were carried out to study the macroscopic properties of these compounds and details are given in Table 1. For the picoline isomers, the thermal gravimetry/differential scanning calorimetry (TG—DSC) results indicate that all three compounds exhibit a one-step desolvation reaction, and the endotherm peaks at around 119–131 °C are associated with this process. The endotherms observed above 240 °C are the result of a phase change in the host and a subsequent melting in case of **2** and **3**.[13, 14] The behavior is even more complex for **4**. Here, another polymorphic phase can be postulated which melts at 240 °C, recrystallizes to the same polymorph as in **2** and **3**, and is finally subject to the set of phase changes and melting mentioned above. Based on the experimentally observed loss of weight, a host-to-guest ratio of 1:2 can be assumed in all cases.

For the lutidine isomers, experimental host-to-guest ratios based on mass loss were 1:2 for **5** and **6**, and 1:4 for **7**. DSC results also show that similar to the picoline series, the same type of polymorphism is found for **5** and **6**. An interesting finding was that no phase change could be detected before melting in the case of **7**.

Table 1. Thermal analysis results for **2**–**7**.

Compound		**2**	**3**	**4**	**5**	**6**	**7**
host–guest ratio[a]		1:2	1:2	1:2	1:2	1:2	1:4
TG results	calculated mass loss [%]	17.8	17.8	17.8	19.9	19.9	33.2
	experimental mass loss [%]	17.4	17.6	17.6	22.0	19.9	31.7
DSC results	peak A (desolvation) T_{on} [°C]	126	131	119	135	118	127
	peak B (melting and recrystallization) T_{on} [°C]	–	–	240	–	–	–
	peak B (phase change) T_{on} [°C]	254	253	256	258	255	–
	peak C (melting) T_{on} [°C]	262	262	264	264	265	265

[a] Host–guest ratios deduced based on TG–DSC results are in agreement with elemental analyses of compounds **2**–**7**.

Crystal structures and competition experiments: To investigate the building principles of the new inclusion compounds, the six crystal structures of **2**–**7** have been studied in this work. Crystal data and structural refinement are given in Table 2.

Investigations of the picoline series: The space groups adopted in the inclusion compounds of the picoline series are $P2_1/n$ with $Z=2$ for **2** and **3**, and $C2/c$ with $Z=4$ for **4**. In contrast to what might be expected for macrocyclic hosts such as **1**, no cavitates were observed in any of the three structures. In fact the conformation of the host molecule as described by the eight torsion angles of the asymmetric unit (Table 3), is such that the two opposite methoxy groups point towards the center of the cyclophane, leaving insufficient space for the encapsulation of a guest (Figure 1a). This behavior is difficult to explain based only on close-packing arguments, as a different conformation of the host has been observed in the inclusion compound with toluene.[12] Structural differences must be related to the guest and can be assigned to the double-proton-acceptor role of the picoline nitrogen in **2**–**4**. Details of the hydrogen bonding parameters for **2**–**4** are given in Table 4 and are in the same range as those previously discussed.[6a, 15] For **2** and **3**, lattice constants are very similar and they belong to the same clathrate group.

As exemplified in Figure 2a for **2**, six host molecules build up an intermolecular cavity. This cavity is filled with two picoline molecules that are in van der Waals contact with each other. While the same packing in both structures **2** and **3** is observed (Figure 2b), there are minor differences in the weak C–H···N– hydrogen bonding interactions (Figures 3a and 3b). In both cases a C–H···N– hydrogen bond is found between the picoline nitrogen atom and an aromatic hydrogen atom of the dimethoxy-substituted hydroquinone ring with d([guest]N···[host]H) = 2.57 Å for **2** and 2.79 Å for **3**.

In **2**, the second slightly weaker interaction involves a hydrogen atom on the exocyclic methoxy group with a contact distance of 2.94 Å. In contrast, a hydrogen atom of the methylene bridge in the cyclophane host is involved in this interaction (d(N···H) = 2.89 Å) in **3**. Lattice constants for **4** indicate that this compound belongs to a different class of clathrates than **2** and **3**. Also, in this structure the nitrogen atom of 4-picoline acts as a double proton accept-

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Table 2. Crystal data, data collection, and refinement parameters of inclusion compounds **2**–**7**.

Compound	**2**	**3**	**4**	**5**	**6**	**7**
empirical formula	$C_{56}H_{60}O_8 \cdot 2C_6H_7N$	$C_{56}H_{60}O_8 \cdot 2C_6H_7N$	$C_{56}H_{60}O_8 \cdot 2C_6H_7N$	$C_{56}H_{60}O_8 \cdot 2C_7H_9N$	$C_{56}H_{60}O_8 \cdot 2C_7H_9N$	$C_{56}H_{60}O_8 \cdot 4C_7H_9N$
M_r [g mol^{-1}]	1047.29	1047.29	1047.29	1075.34	1075.34	1289.65
crystal dimensions [mm]	$0.37 \times 0.5 \times 0.43$	$0.43 \times 0.5 \times 0.5$	$0.34 \times 0.34 \times 0.34$	$0.34 \times 0.34 \times 0.40$	$0.45 \times 0.34 \times 0.22$	$0.30 \times 0.30 \times 0.10$
T [K]	293 (2)	293 (2)	293 (2)	292 (2)	178 (2)	183 (2)
radiation used	$Mo_{K\alpha}$	$Mo_{K\alpha}$	$Mo_{K\alpha}$	$Mo_{K\alpha}$	$Cu_{K\alpha}$	$Cu_{K\alpha}$
crystal system	monoclinic	monoclinic	monoclinic	monoclinic	triclinic	triclinic
space group	$P2_1/n$	$P2_1/n$	$C2/c$	$P2_1/n$	$P\bar{1}$	$P\bar{1}$
a [Å]	9.949 (2)	9.906 (2)	17.810 (7)	9.934 (3)	9.870 (1)	11.182 (3)
b [Å]	16.079 (2)	16.638 (3)	10.820 (2)	16.074 (4)	17.133 (2)	12.862 (2)
c [Å]	18.144 (4)	17.750 (3)	30.540 (9)	18.229 (7)	17.438 (1)	13.919 (9)
α [°]	90	90	90	90	89.48 (1)	90.05 (2)
β [°]	93.19 (2)	95.87 (1)	72.55 (2)	93.35 (4)	85.16 (1)	112.54 (3)
γ [°]	90	90	90	90	86.19 (1)	100.56 (2)
V [Å^3]	2898.0 (9)	2910.1 (9)	5614 (3)	2906 (2)	2931.5 (5)	1812 (1)
Z (formula)	2	2	4	2	2	1
ρ_{calcd} [g cm^{-3}]	1.200	1.195	1.239	1.229	1.218	1.182
μ [cm^{-1}]	0.78	0.77	0.80	0.79	6.22	5.93
$F(000)$	1120	1120	2240	1152	1152	692
θ range scanned [°]	1–25	1–25	1–25	1.5–25	2.5–75	3.5–75
range of indices h, k, l	± 11, 19, 21	± 11, 19, 15	± 21, 12, 36	± 11, 19, 21	12, ± 21, ± 21	± 13, ± 16, 17
reflections collected	5255	4679	5042	5264	12064	7203
independent reflections	5088	4509	4941	5095	10639	5276
No. of parameters refined	309	358	357	366	721	422
$R_1[I > 2\sigma(I)]$	0.0945	0.0401	0.0528	0.0532	0.0528	0.0558
wR_2 (F^2)	0.2484	0.1122	0.1315	0.1318	0.1443	0.1461
S (goodness-of-fit)	1.387	0.921	0.950	0.931	1.056	1.049
$\Delta\rho_{max}$ [e Å^{-3}]	0.888	0.152	0.208	0.197	0.162	0.135
$\Delta\rho_{min}$ [e Å^{-3}]	−0.575	−0.189	−0.225	−0.220	−0.238	−0.257

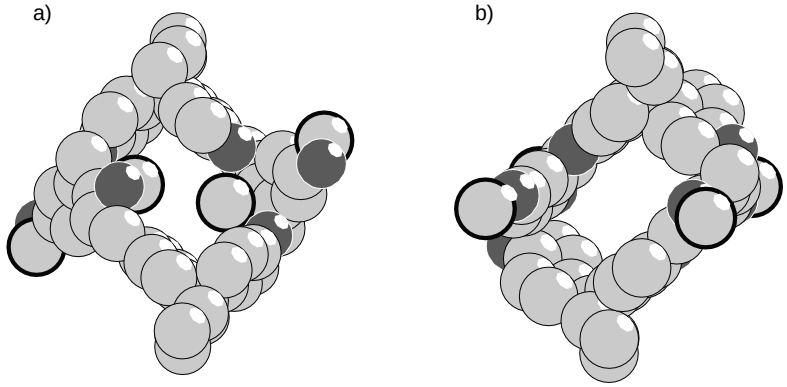

Figure 1. a) Van der Waals representation of the host molecule in **3** showing the methoxy groups pointing towards the center of the cyclophane. b) Van der Waals representation of the host molecule in **7** showing the methoxy groups pointing outwards from the center of the cyclophane; carbon atoms of the methoxy groups are presented in dark black borders.

Table 3. Torsion angles [°] of **1** in **2**–**7**.[a]

Compound	**2**	**3**	**4**	**5**	**6**	**7**
C(24)-C(23)-C(22)-O(21)	76.7 (6)	82.9 (3)	−80.0 (4)	75.8 (4)	−92.9 (2)	−179.4 (2)
C(23)-C(22)-O(21)-C(18)	−167.5 (5)	−173.2 (2)	169.7 (3)	−157.3 (3)	161.2 (1)	−178.9 (2)
C(22)-O(21)-C(18)-C(19)	−12.4 (8)	−2.1 (3)	12.9 (5)	−11.4 (5)	−1.7 (2)	1.5 (3)
C(20)-C(15)-C(9)-C(6)	−108.9 (6)	−104.9 (3)	−109.1 (4)	61.3 (3)	79.6 (2)	−82.0 (2)
C(15)-C(9)-C(6)-C(7)	−60.3 (6)	−62.1 (3)	59.5 (4)	−65.2 (3)	−59.5 (2)	−6.1 (2)
C(4)-C(3)-O(2)-C(1)	−8.4 (8)	−17.2 (3)	−22.6 (5)	−13.2 (3)	−8.5 (2)	176.0 (2)
C(3)-O(2)-C(1)-C(27)	−157.4 (5)	157.7 (2)	151.8 (3)	169.5 (2)	164.1 (1)	73.6 (2)
O(2)-C(1)-C(27)-C(24)	74.4 (6)	79.6 (2)	81.5 (4)	75.9 (2)	76.2 (2)	132.6 (1)

[a] Atoms defining the torsion angles are numbered according to Scheme 1.

or. However, the major difference is the fact that two host molecules are involved in this double hydrogen bonding (Figure 4). One interaction involves a hydrogen atom of an endocyclic methyl group of the first host molecule, while the second one is based on an interaction with a hydrogen atom of the exocyclic methyl group of the neighboring host molecule. The stability of the host–guest complex is further improved by a third weak hydrogen bond not observed in the other two structures. Here, a weak C–H···O– hydrogen bond can be postulated between the hydrogen atom of the picoline 4-methyl group and the methoxy oxygen atom of the host molecule with d[guest]H···O[host] = 2.65 Å.

The differences in the packing are quite evident in Figure 5. In the intramolecular cavities, only one guest molecule can be incorporated. Layers of host–guest associates are

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Table 4. Weak hydrogen-bonding parameters in **2**–**7**.

Compound	Donor (DH)	Acceptor (A)	H···A [Å]	D–H···A [°]
2	C32H32A	N1G1	2.57	164.8
	C31H31A	N1G1	2.94	125.6
3	C28H28A	N1G1	2.79	153.6
	C1H1A	N1G1	2.89	158.0
4	C26AH26A	N1G1	2.95	104.3
	C31BH31B	N1G1	2.79	153.5
	C7G1H7GA	O25A	2.65	164.2
5	C32H32A	N1G1	2.79	168.2
	C31H31A	N1G1	2.89	129.1
6	C28H28A	N1G1	2.86	153.2
	C1H1B	N1G1	2.79	160.1
	C8G1H8G6	O25A	2.73	155.8
	C7G1H7G5	O25A′	2.71	129.7
	C32H32A	N1G2	2.74	156.4
	C22H22B	N1G2	2.86	159.1
	C8G2H8G1	O25	2.73	155.9
7	C31H31A	N1G1	2.63	167.5
	C5G2H5G2	O25	2.77	136.8

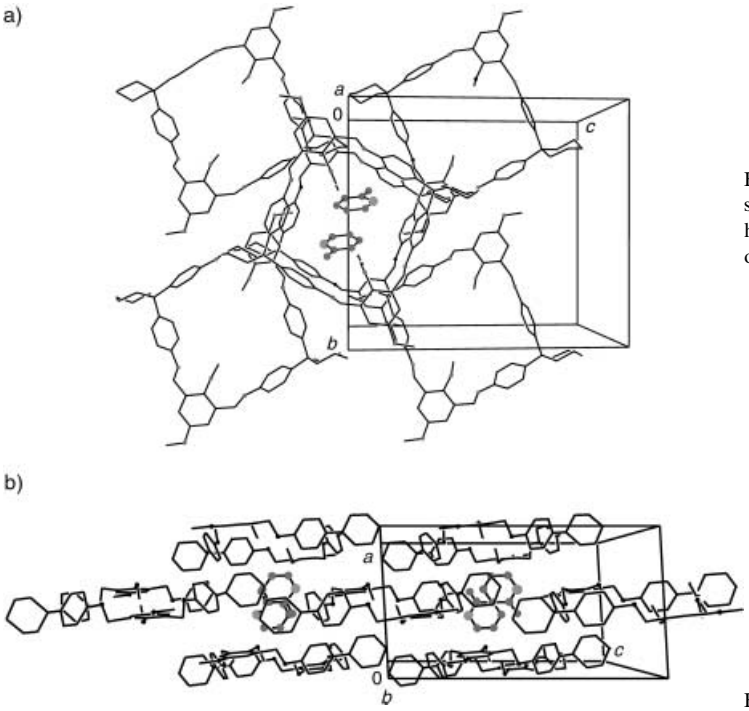

Figure 2. a) Intermolecular cavity for two 2-picoline guest molecules in **2** built by six host molecules; b) packing structure of **2** along *b* axis; all hydrogen atoms are omitted.

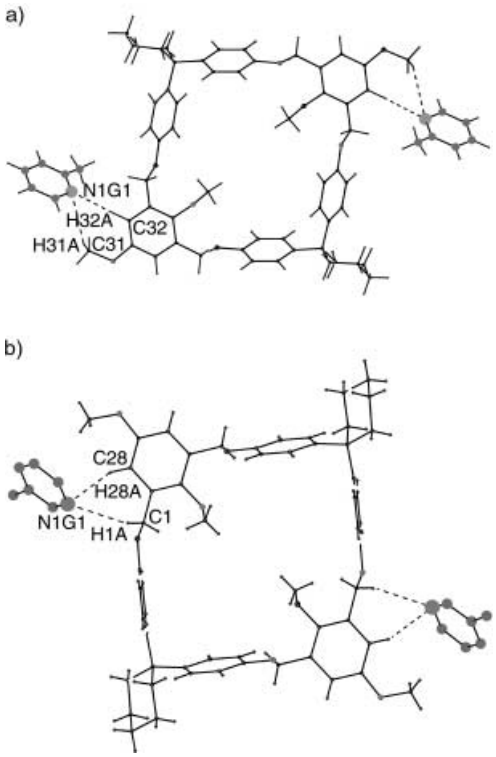

Figure 3. Host–guest associates (1:2) and C–H···N– hydrogen bonding scheme between the nitrogen atom of the picolines and C–H bonds of the host molecule found in a) **2**; and b) **3**; hydrogen atoms of 3-picoline are omitted in b).

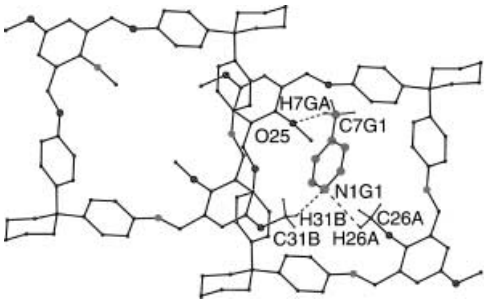

Figure 4. Hydrogen bonding scheme for **4** showing the different interactions of one 4-picoline guest molecule with two host molecules; all hydrogen atoms are omitted, except those involved in weak host–guest interactions.

oriented parallel to *c* which are linked together only by van der Waals interactions. The above-mentioned third hydrogen bonding interaction between the picoline nitrogen atom and the adjacent host molecule is able to further stabilize the observed layer structure.

The structural similarities and differences found in **2**–**4** prompted us to perform binary and ternary competition experiments to determine the enclathration selectivity of the host for the picoline isomers (Figure 6). Each two-component experiment shows the mol fraction (X) of a given host in the initial solution versus the mol fraction (Y) of that guest included by the host. The diagonal line represents zero selectivity. In the case of 3-picoline versus 2-picoline, virtually no selectivity can be found (Figure 6a). The structural differences between these compounds are so minor that no effect results. This is also the case in the two other binary systems (Figures 6b and 6c). Interestingly, the selectivities are strongly concentration dependent so that the inclusion of 4-picoline is strongly favored if its mol fraction (X) is greater than 0.4 in Figure 6b and 0.3 in Figure 6c, but is strongly disfavored if the mol fraction is below 0.21 and 0.3, respectively. It should be mentioned here that it would only be possible for the host molecule to incorporate 4-picoline in all cases. Based on that finding, we assume that kinetic factors during the crystallization process primarily determine the selectivity when isomers whose inclusion compounds belong to different classes of

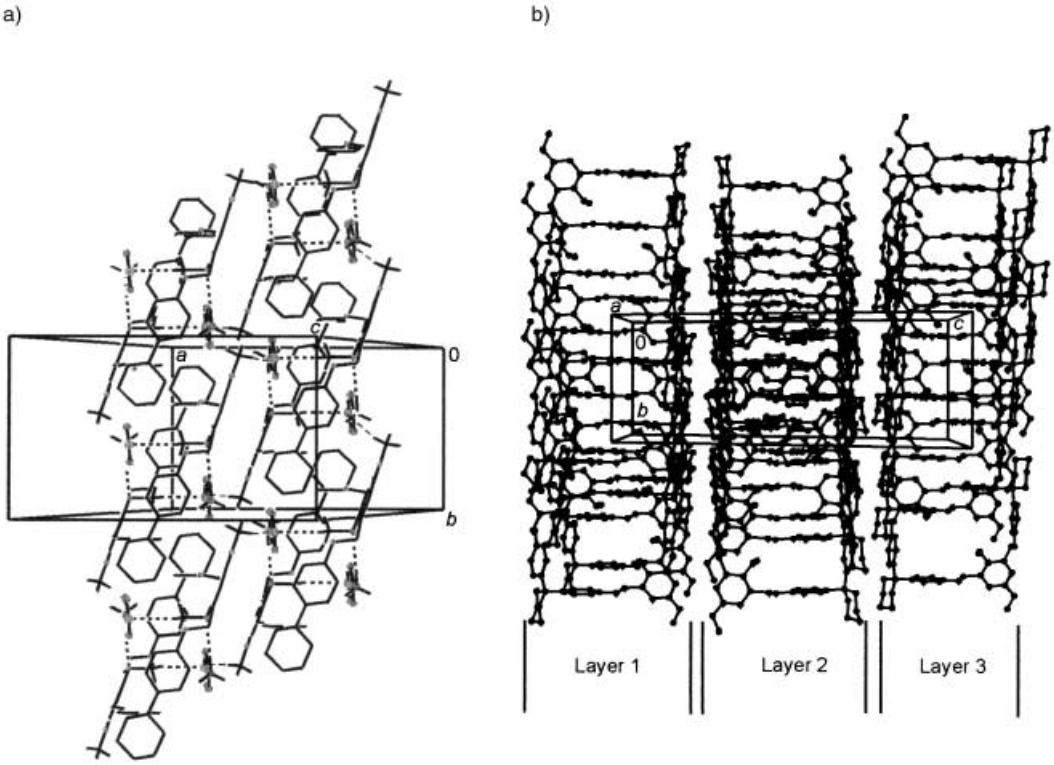

Figure 5. a) Projection along the *c* axis for **4**; all hydrogen atoms are omitted, except those involved in hydrogen bonding; b) general view of the layers built up by host molecules in **4**; guest molecules are omitted.

clathrates are involved. This assumption is strengthened by the concentration-dependent selectivities observed in the ternary mixture experiments (Figure 6 d). We selected starting mixtures represented by the circle, and the resulting mixtures in the inclusion compounds move into the direction indicated by the two arrows. Here, 4-picoline is strongly favored when its mol fraction is higher than 0.35 – 0.39. A moderate preference for 3-picoline can be found when X(4-picoline) is below 0.3.

To get a better understanding of the selectivities, and to investigate if thermodynamic aspects also play an important role, lattice energy calculations were performed for **2**, **3**, and **4** using the atom – atom potential method. By employing the program HEENY,[16] we determined the van der Waals energies using a force field given by Equation (1), in which r is the interatomic distance, and the coefficients a, b, c, and d are those given by Giglio[17] and improved by Pertsin and Kitaigorodskii.[18]

$$U(r) = a\exp(-br)/r^d - c/r^6 \quad (1)$$

Representative host – guest pairs were selected and appropriate summations of all host – host, host – guest, and guest – guest interactions were carried out; the following lattice energies were obtained: **2**: -132.1; **3**: -130.3; **4**: -160.7 kJ mol^{-1}. This outcome shows that stabilities of the inclusion complexes increase in the order $\mathbf{3} \approx \mathbf{2} < \mathbf{4}$. This is partly in agreement with the observation that 4-picoline is strongly favored in many of the binary and ternary mixture competition experiments. However, the lattice energies of **2** and **3** are close, and the moderate preference of **3** in parts of the ternary mixture experiments therefore can only be due to kinetic effects.

Investigations of the lutidine series: Results obtained for the picoline series led to similar experiments applying the lutidine isomers under two different aspects. First, the concentration-dependent selectivities observed so far were both remarkable and unexpected, and a more general proof of that behavior would be advantageous. Second, the preferred 4-picoline in the preliminary experiments was the only isomer showing an inherent C_2 symmetry. Two of the lutidine isomers (2,6- and 3,5-lutidine) also have C_2 symmetry but lack a methyl group in the 4-position relative to the nitrogen atom. This is true for the third isomer 2,4-lutidine. These investigations should also determine which of the two effects is more important.

Space groups adopted in **5** are $P2_1/n$ with $Z = 2$ and $P\bar{1}$ for **6** and **7** with $Z = 2$ and $Z = 1$, respectively. The conformation of the host molecule in **5** and **6** is similar to those described for the picoline series (Table 3, Figure 1 a). As already found in the TG – DSC results, compound **7** behaves somewhat differently. In **7**, there are significant differences in the torsion angles that yield a conformation in which the methoxy groups point outwards. As a result, a rectangular cavity is formed (Figure 1 b). For **5**, structural similarities to **2** and **3** occur (Figure 7). The lutidine nitrogen atom functions as a double proton acceptor with C–H $\cdots$ N– hydrogen bonding towards an aromatic hydrogen of the host with d([guest]N $\cdots$ [host]H) = 2.79 Å and a hydrogen atom on the exocyclic methoxy group with a contact distance of 2.89 Å (see also Table 4). In summary, the inclusion compound of **1** with 2,6-lutidine belongs to the same clathrate group as **2** and **3**.

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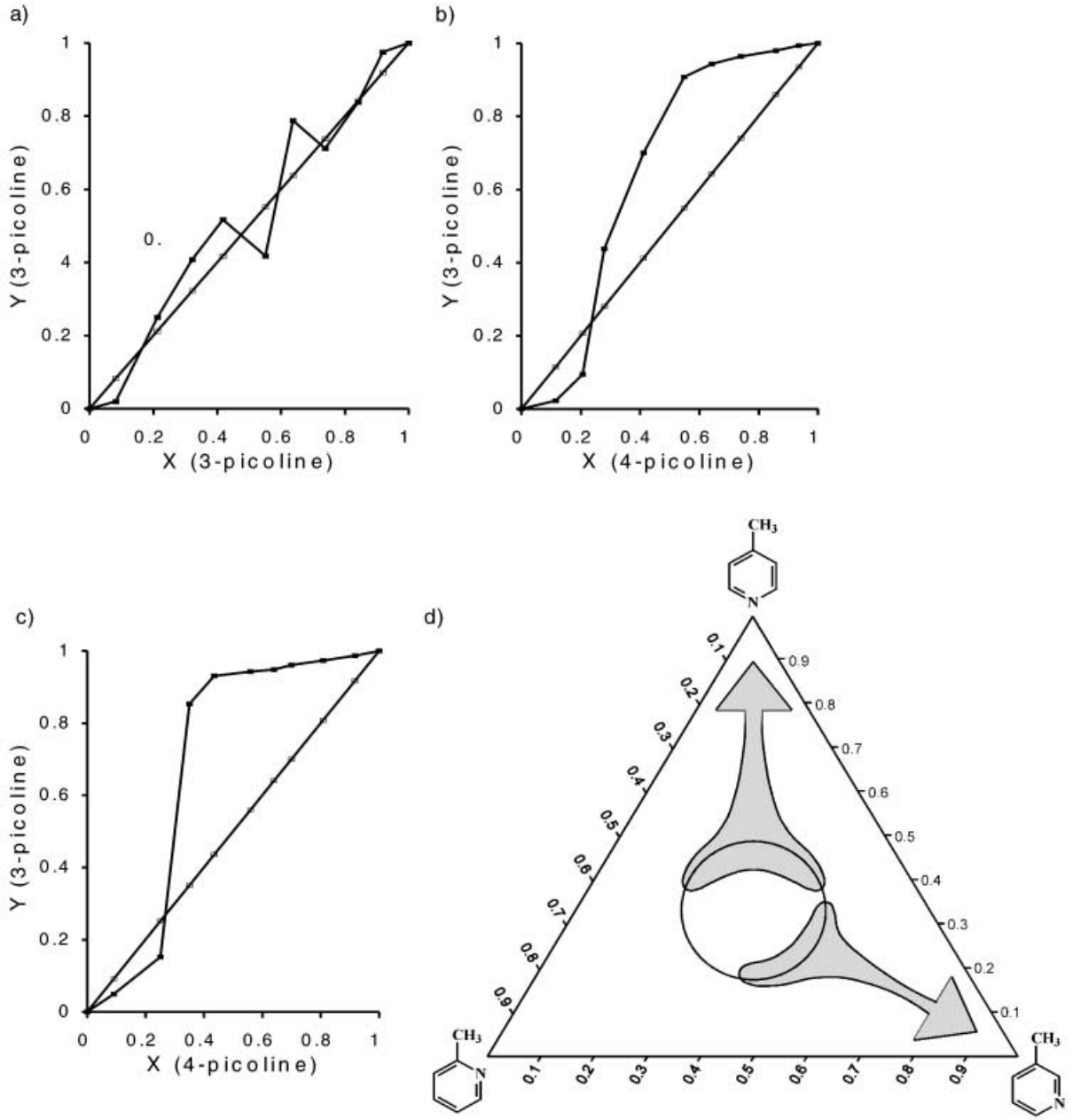

Figure 6. Results of the competition experiments: a) 3-picoline versus 2-picoline; b) 2-picoline versus 4-picoline; c) 3-picoline versus 4-picoline; d) three-component competition in the picoline series; mixtures applied in d) are represented by the circle in the middle, and the resulting mixtures in the inclusion compounds move into the direction of the isomer indicated by the arrow.

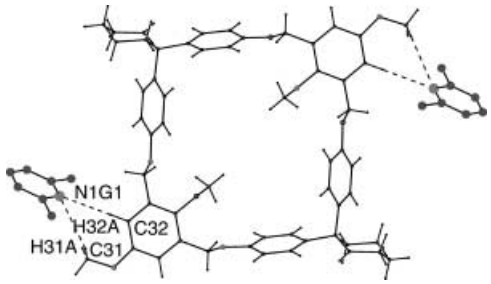

Figure 7. C–H···N– hydrogen bonding scheme and 1:2 host–guest associates found in **5**; hydrogen atoms of 2,6-lutidine are omitted.

The structure of **6** is more complex (Figure 8). Two different types of host–guest associates can be observed which are only differentiated by host–guest interactions. Both types of associates have a similar structural motif. Two guest molecules of the same type fit into a cavity formed by six host molecules. In both associates, the lutidine molecules build up the set of two C–H···N– hydrogen bonds already observed in structures **2**, **3**, and **5** (Figure 8a, data given in Table 4). Differences in the two host–guest associates are related to the stabilization by weak hydrogen bonds which are formed between the lutidine I methyl hydrogen atoms and a methoxy oxygen atom as acceptor on associate type II and between the lutidine II methyl hydrogen atoms and a methoxy oxygen atom on associate type I, respectively (Figure 8b). In the case of lutidine I, two contacts of this type can be found, while lutidine II builds up only one of these interactions.

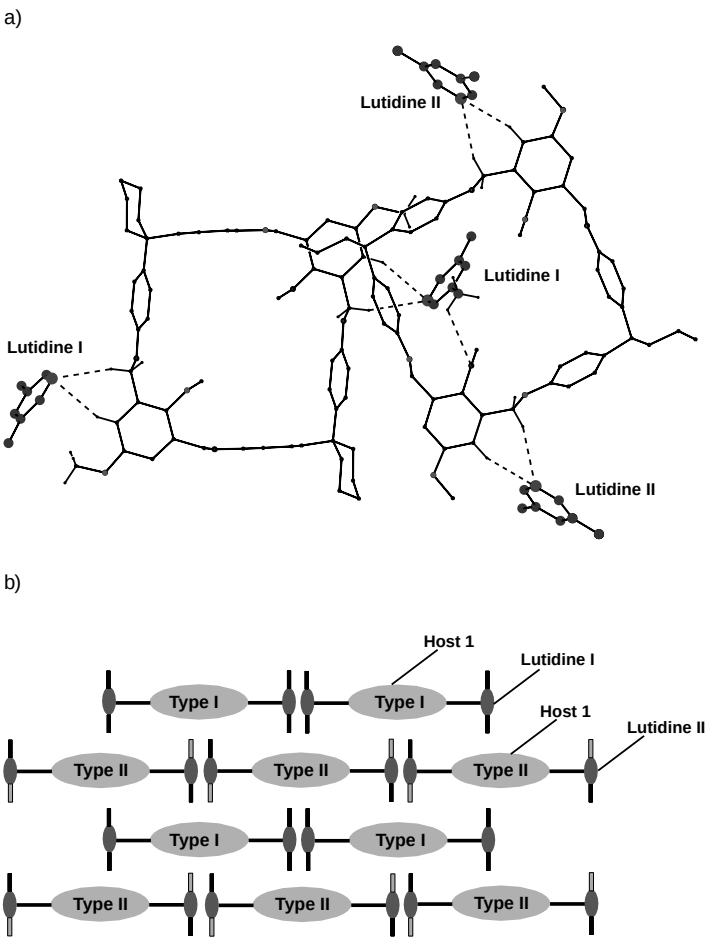

Figure 8. a) Hydrogen bonding scheme and set of two host–guest associates found in **6**; only hydrogen atoms involved in weak host–guest interactions are presented; b) schematic presentation of the packing of the two types of host–guest associates (type I and II) and their inter-associate C–H···O– hydrogen bonding motif; lutidine methyl groups (represented by dark sticks) form weak contacts to the adjacent host molecule; those represented by light sticks do not.

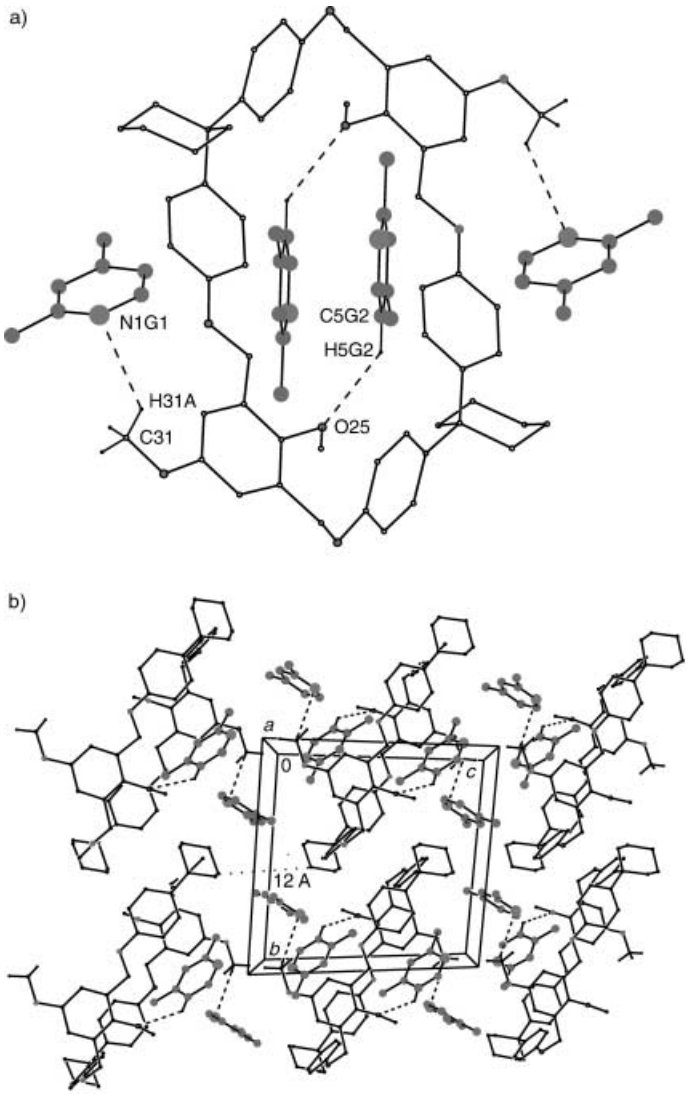

Figure 9. a) Hydrogen bonding scheme between the four 2,4-lutidine guests and the corresponding host molecule in **7**; all hydrogen atoms are omitted, except those involved in hydrogen bonding; b) projection of **7** along [100]; all hydrogen atoms are omitted.

As mentioned before, the conformation of the host in **7** is different and although cavitates of sufficient space are formed, none of the 2,4-lutidines are encapsulated. In fact, tubulates are observed as exemplified in Figure 9b. Guest molecules are arranged along [100] in channels of approximately 12 Å width. While many interactions appear to be at the transition between simple van der Waals contacts and weak C–H···N– or C–H···O– hydrogen bonds, two contacts seem to be important for the structural outcome of the inclusion compound. Both the C–H···N– contact of N1G1 to hydrogen H31A on the exocyclic methoxy group with a comparatively short contact distance of 2.63 Å, and a C–H···O– contact of H5G2 of another 2,4-lutidine to O25 with d[guest]H···O[host] = 2.77 Å, could be the reason for the fact that the two methoxy groups point outside the cavity (Figure 9a).

Based on our experience in the picoline series, concentration-dependent selectivities should be observed in all binary and ternary competition experiments; this is indeed also the case for the lutidine series (Figure 10). As shown in Figure 10a, there is a dramatic change in guest selectivity in the case of 2,6-lutidine versus 3,5-lutidine. While 2,6-lutidine is favored if its mol fraction is greater than 0.4, an almost exclusive (>97%) incorporation of 3,5-lutidine is observed if its mol fraction rises above 0.6. This is surely one of the most prominent examples of the fact that host selectivities can be strongly influenced by slight changes in reaction conditions. The binary experiments in Figures 10b and 10c and the ternary experiment in Figure 10d indicate that 2,4-lutidine is favored in all cases if mol fractions are above 0.30–0.35 in the binary experiments and 0.25 in the ternary experiment. Although preferences are not as pronounced as in the example discussed above, highly enriched inclusion compounds with purities >90% can be reached when a slight excess of 2,4-lutidine ($X > 0.5$) is present in the mother liquor.

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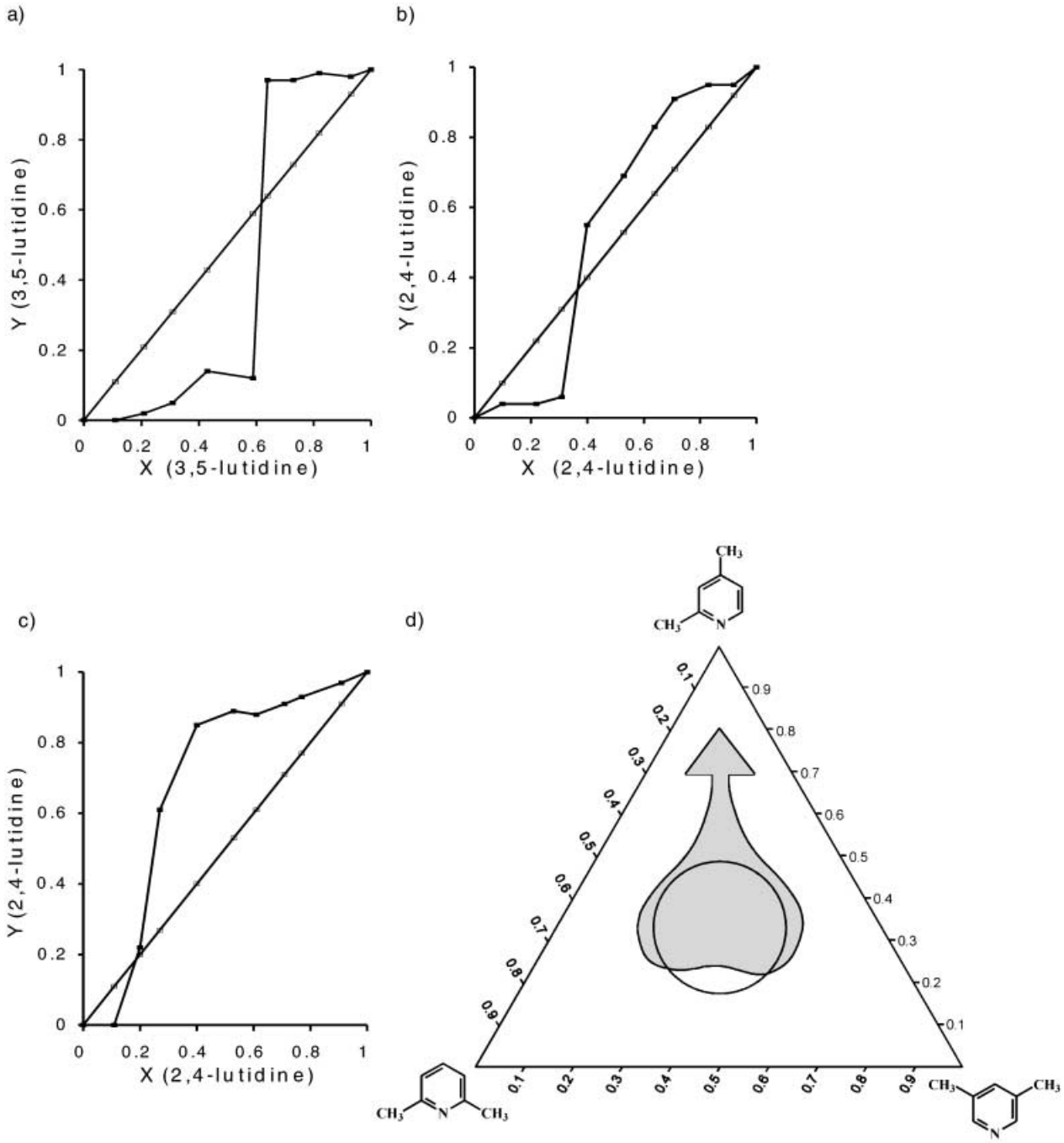

Figure 10. Results of the competition experiments: a) 2,6-lutidine versus 3,5-lutidine; b) 2,6-lutidine versus 2,4-lutidine; c) 2,4-lutidine versus 3,5-lutidine; d) three-component competition in the lutidine series; mixtures applied in d) are represented by the circle in the middle, and the resulting mixtures in the inclusion compounds move into the direction of the isomer indicated by the arrow.

Conclusion

The crystal structures of the host molecule **1** with the three isomers of picoline and lutidine were elucidated. In the subsequent competition experiments, concentration-dependent selectivities could be observed in those cases in which the inclusion complexes had been assigned to different adduct classes. Preferences for the picoline and lutidine isomer with the methyl group in the 4-position relative to the nitrogen atom were evident and can be microscopically explained by a set of favorable hydrogen bonding schemes in combination with the endo- or exocyclic methoxy groups of the host molecules. Crystal structure data and results of the thermal analyses are in agreement with each other. Both host–guest ratios in the different inclusion complexes and the observation of phase changes in the thermal analyses are in agreement with the crystal structures determined. Although we are not able to unequivocally assign the phase changes to the crystal structures observed, there are some indications that the latter may be due to a conformational change before melting in the host molecule in all complexes apart from **7**. Here, the only example of an open conformation of the host molecule was

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found. This assumption has also been supported by results previously described.[12] The present work also illustrates that one should be cautious when selectivities of crystalline inclusion compounds are deduced from guest competition experiments.

Experimental Section

General methods: Host compound **1** was synthesized as described earlier.[12] Single crystals of suitable quality for X-ray crystallographic studies of the inclusion compounds **2**–**7** were obtained by dissolving **1** in the appropriate picoline or lutidine isomer and subsequent slow evaporation at room temperature. Finely powdered specimens obtained from continuously stirred solutions were used for the thermal analyses. Thermal gravimetry (TG) and differential scanning calorimetry (DSC) were performed on a Perkin–Elmer PC7 series system. Here, samples were crushed, blotted dry, and placed in open platinum crucibles for TG, and in crimped but vented aluminum crucibles for DSC. Sample weight in each case was 1.3–3 mg. The temperature range was typically 30–300 °C at a heating rate of 20 °C min^{-1}. The samples were purged by a stream of nitrogen flowing at 40 cm^3 min^{-1}.

X-ray crystallographic studies: X-ray diffraction data were measured on a CAD4 diffractometer, and during the data collection three reference reflections were monitored periodically to check crystal stability. The data reduction included correction for Lorentzian and polarization effects. All structures were solved by direct methods using SHELX-86[19] and refined by employing full-matrix least-squares with SHELX-93.[20]

CCDC 177085–177090 contain the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/conts/retrieving.html (or from the Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: (+44) 1223-336033; or deposit@ccdc.cam.uk).

Competition experiments: Competition experiments were carried out between pairs of guests as follows: A series of eleven vials was made up with mixtures of two guests such that the mole fraction of a given guest varied from 0 to 1. The host was added to the mixture and allowed to dissolve by gently warming. The total guest–host ratio was kept at 20:1 in each case; this ensured even the exclusive inclusion of the minor isomer. The mixture was allowed to cool and concentrate slowly. After 2–3 days, the resulting crystalline inclusion compounds were filtered, dried, and dissolved in methanol. The resulting solutions were analyzed by gas chromatography together with the mother liquor from which the crystals had been obtained. This type of experiment was extended to investigate the simultaneous competition by all three isomers. Initial compositions of the three isomers were judiciously selected to sample the three guest components. The crystalline inclusion compounds obtained and the mother liquors were analyzed as before.

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