Pergamon

Tetrahedron Vol. 50, No. 29, pp. 8559-8568, 1994

0040-4020/94 $7.00+0.00

0040-4020(94)00479-X

Molecular Structures of Host-Guest Complexes with Rebek's Diacid

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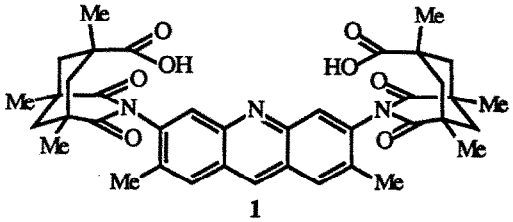
Abstract: The crystal and molecular structures of 1:1 complexes of Rebek's diacid (1) with pyrazine (2) and quinoxaline (3) have been determined by single crystal X-ray diffraction. The unit cells of the crystalline 1:2 and 1:3 each contain two crystallographically independent molecules of their respective complexes; all four complexes exhibit nearly symmetric, syn, two-point binding of the diamine guests by the convergent carboxyl groups of 1. These data confirm the original structural proposal of Rebek et al. (J. Am. Chem. Soc. 1987, 109, 2426-2431), and stand in contrast to the central conclusion (one-point binding) of Jorgensen et al.'s computational study of the complex of Rebek's diacid and pyrazine (J. Am. Chem. Soc. 1989, 111, 755-757). In addition, the X-ray structure of Rebek's diacid hydrochloride (1:HCl) has been determined. In this complex, compound 1 is protonated on the acridine nitrogen, and the chloride counterion participates in a "three-point binding", T-shaped, hydrogen-bonded network within the diacid cleft.

Rebek and co-workers have shown that the diacid **1** is an effective host for a variety of amines in chloroform solution, most notably the cyclic diamines pyrazine (**2**, $K_a = 1.4 \times 10^3\ M^{-1}$), quinoxaline (**3**, 2.3×10^4), and phenazine (**4**, 2.2×10^3).[1,2] They have proposed, primarily on the basis of NMR data, that "two-point binding" of these and other diamines by the convergent carboxyl groups of **1** is the likely mode of complexation.[1,2] However, this structural proposal has been controversial: in 1989, Jorgensen et al. argued, on the basis of Monte Carlo simulations of the complex **1:2** in chloroform solution, that two-point binding (as illustrated below) is disfavored, and that instead only one strong hydrogen bond is made in typical structures of the complex.[3]



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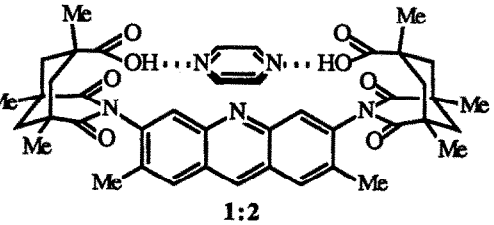

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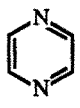

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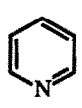

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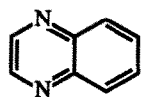

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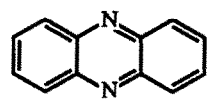

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Indeed, the relative magnitudes of the association constants for monoamines and diamines reported by Rebek et al. are not easily rationalized by a simple two-point binding model. For example, they observed a 12-fold ratio of the K_a's for the binding of pyrazine and the monoamine pyridine (**5**, $K_a = 1.2 \times 10^2$ M^{-1}).[1] Since pyridine can make only one strong hydrogen bond with **1**, one might expect the addition of a second hydrogen bond in the pyrazine complex to yield more than a 12-fold increase in the association constant. In fact, the calculations of Jorgensen et al. which favor one-point binding of pyrazine reproduced the 12-fold ratio of K_a's for pyrazine and pyridine, and they calculated that a K_a ratio on the order of 400 would be expected if complex **1:2** were to display "true two point binding".[3] On the other hand, the observed K_a ratio for quinoxaline and pyridine is 192, a plausible ratio for two-point vs. one-point binding of the amines, but how can one account for the 15-fold increase in binding of **3** with respect to **2**, when the two diamines have extremely similar geometries and basicities?[4,5] Rebek et al. argued that this increase in binding was due to favorable π-stacking interactions in the quinoxaline complex,[1b] and Jorgensen et al. did not address this issue.[3]

At the very least, direct, reliable structural data are required to begin to resolve these difficulties.[6] We now report the single crystal X-ray structures of the complexes of Rebek's diacid with pyrazine and quinoxaline, which unambiguously establish two-point binding as the mode of complexation. In addition, we report the X-ray structure of the the hydrochloride of **1**, a unique "three-point binding" complex of chloride ion which, by means of comparison with the diamine complexes, highlights the conformational flexibility of **1**.[7]

RESULTS

Crystals

In our initial experiments, we attempted to crystallize compound **1** from common organic solvents containing equimolar and excess amounts of the diamines **2** and **3**. From the outset, small, poorly diffracting crystals of 1:1 complexes (as judged by NMR) of **1** and quinoxaline were obtained from simple alcohols, but it was only after many trials that a suitable specimen for structure determination was obtained from ethanol containing a five-fold excess of **3**. The crystals proved to be triclinic, space group $P\bar{1}$, $Z = 4$; thus they contain two crystallographically independent molecules of the complex **1:3** in the asymmetric unit, as well as one molecule of ethanol.[8] It is noteworthy that the unit cell parameters derived from the earlier, less good crystals from ethanol are identical within experimental error to those of the final sample; there is no evidence that the earlier samples were of a different crystal form.

We were unable to obtain satisfactory crystals of a pyrazine complex with **1** from ordinary solvents; ultimately, however, large single crystals of **1:2** were formed by the evaporation of solutions of **1** in liquid pyrazine (mp 58 °C) at 70 °C. At room temperature the crystals decomposed within a few hours by loss of pyrazine, but at 235 K they were indefinitely stable. These crystals also proved to be triclinic, space group $P\bar{1}$, $Z = 4$, and they contained not only two independent molecules of the complex **1:2**, but also five additional molecules of uncomplexed pyrazine in the asymmetric unit.[8]

In addition to the diamine complexes, the hydrochloride of **1** crystallized readily from acetonitrile. These crystals are monoclinic, space group $P2_1/c$, $Z = 4$, and they contain one molecule of **1:HCl** and one molecule of acetonitrile in the asymmetric unit.[8]

Structures of the diamine complexes

As a result of the large asymmetric units in the crystals of **1:2** and **1:3**, the solution and refinement of the crystal structures yielded the geometries of four crystallographically independent complexes of diamines with Rebek's diacid. The two pyrazine complexes we designate **1:2A** and **1:2B** (Figure 1), and the two quinoxaline complexes **1:3A** and **1:3B** (Figure 2). All four complexes exhibit nearly symmetric, syn,[3] two-point binding of their respective diamines, and thus these data strongly support the original structural proposal of Rebek et al.[1]

The two pyrazine complexes have very similar geometries. In complex **1:2A** the hydrogen-bonded N···O distances are 2.740 (7) and 2.776 (7) Å, and in **1:2B** they are 2.757 (7) and 2.767 (7) Å. The OH···OH separation in complex **1:2A** is 8.25 Å, and in **1:2B** it is 8.28 Å. The latter values are only slightly less than the 8.4 Å separation specified by Jorgensen et al.[3] for optimal syn two-point binding of pyrazine. Thus the cleft in each host is large enough to accommodate two essentially collinear hydrogen bonds between the host and guest, and none of the pyrazine nitrogens lies more than 0.20 Å from the mean plane defined by the four carboxylic acid oxygens in each of their respective hosts. Notably, the N···N distances in the chelated pyrazines in **1:2A** and **1:2B**, 2.785 (8) and 2.798 (7) Å, respectively, are essentially identical to the N···N distance observed in crystalline pyrazine, 2.796 Å.[4]

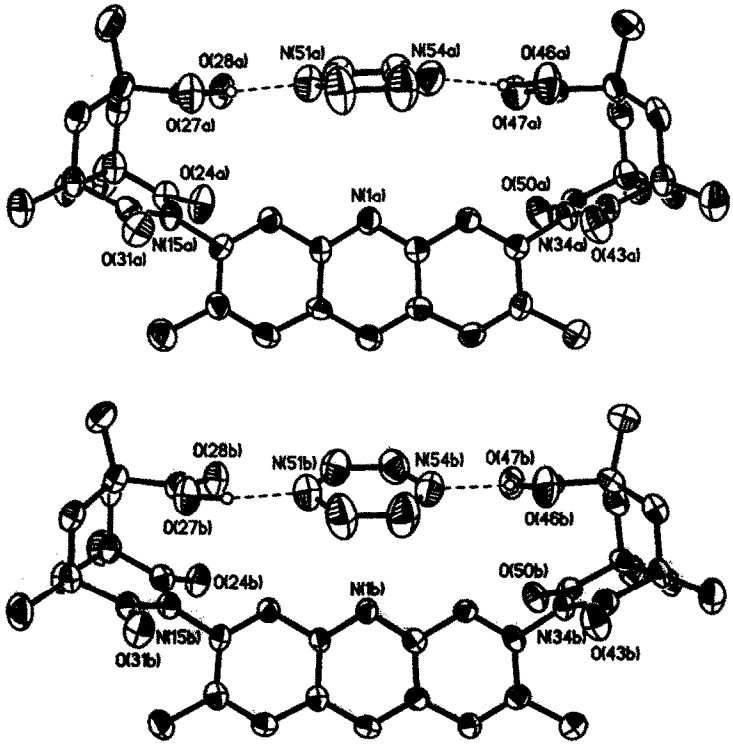


Fig. 1. The X-ray structures of complexes **1:2A** (above) and **1:2B** (below). Thermal ellipsoids are drawn at the 50% probability level.

The quinoxaline complex **1:3A** strongly resembles the pyrazine complexes, but the complex **1:3B** is substantially and instructively different. In **1:3A** the hydrogen-bonded N···O distances are 2.761 (7) and 2.790 (7) Å, and the OH···OH separation is 8.36 Å. Thus this cleft also permits a nearly collinear set of hydrogen bonds between the host and guest, and the quinoxaline nitrogens are no more than 0.06 Å from the mean plane of the carboxyl oxygens. In complex **1:3B**, however, the OH···OH separation is only 7.93 Å, which appears to be too small for optimal chelation. The quinoxaline is pushed slightly out of the cleft, so that the quinoxaline nitrogens lie approximately 0.7 Å above the plane of the carboxyl oxygens. Nevertheless, symmetric two-point binding is maintained with the formation of two slightly bent hydrogen bonds. The N···O distances in **1:3B** are 2.691 (7) and 2.661 (7) Å.

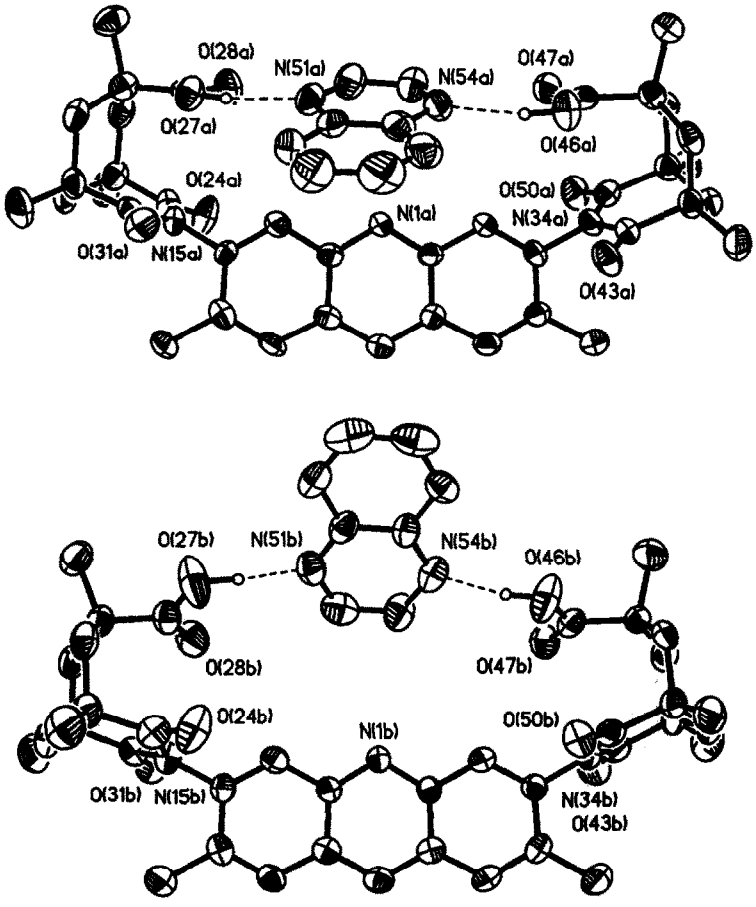


Fig. 2. The X-ray structures of complexes **1:3A** (above) and **1:3B** (below).

The orientation of the guests about the axes of chelation in complexes **1:2A**, **1:2B**, and **1:3A** are roughly similar, with the "outside" edge of each diamine tilted by varying degrees toward the acridine nucleus. In **1:3B**, however, the benzene ring of the quinoxaline is swung away from the acridine. In the absence of a clear orientational preference in the four X-ray structures, it is probable that the diamines enjoy considerable rotational freedom about the axis of chelation in solution. In this regard, while Rebek et al.[1b] proposed that π-stacking interactions between quinoxaline and acridine would account for the enhanced binding of **3** with respect to **2**, in neither **1:3A** nor **1:3B** is there any evidence of such interactions. There is, however, π-stacking of quinoxalines between molecules of complex **1:3B** paired about an inversion center in the crystal structure, and interestingly both **1:2A** and **1:2B** exhibit π-stacking of the chelated pyrazines between pairs of complexes related by inversion symmetry.

Structure of Rebek's diacid hydrochloride

The structure of **1:HCl** (Figure 3) is in striking contrast to those of the diamine complexes. As expected, compound **1** is protonated on the acridine nitrogen, but the surprising result is the T-shaped, three-point binding of the chloride counterion within the diacid cleft. The hydrogen bonding network is nearly symmetric, with O···Cl distances of 3.134 (7) and 3.139 (7) Å, and an N···Cl distance of 3.101 (7) Å. Interestingly, the chloride ion participates in no other hydrogen bonds in the crystal, and the chief intermolecular chloride contacts are to the hydrophobic back surfaces of the Kemp's triacid moieties. We are unaware of any similar hydrogen-bonding geometry for a chloride ion. In contrast to the diamine complexes, the carboxylic acids in **1:HCl** adopt an anti[3] orientation for chloride chelation. Furthermore, the OH···OH separation is only 6.21 Å, a full 2 Å shorter than the average separation observed in the diamine complexes.

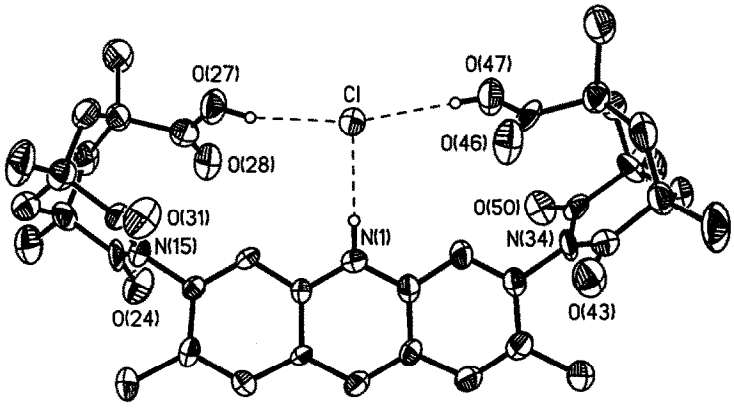


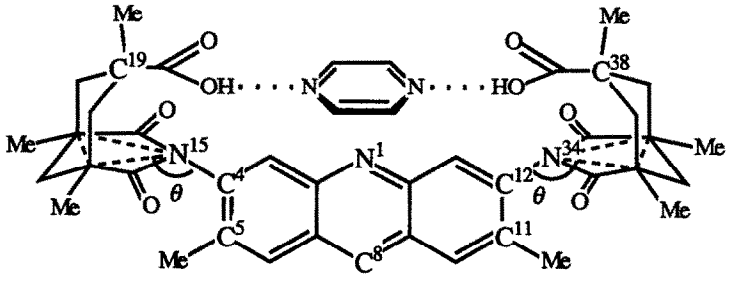
Fig. 3. The X-ray structure of **1:HCl**.

DISCUSSION

The crystal structures of the pyrazine and quinoxaline complexes of Rebek's diacid strongly support the original proposal of two-point binding in these and related diamine complexes of **1**.[1,2] We cannot, of course, directly determine the structure of these complexes in solution; however, the crystallographically independent complexes **1:2A**, **1:2B**, **1:3A**, and **1:3B** represent four separate determinations of the structure of Rebek's diacid-diamine complexes in different local environments. The fact that all four exhibit two-point binding, while possessing significantly different conformations and hydrogen-bonding geometries, is the best evidence that two-point binding will be the preferred mode of complexation in other environments as well.

Why then do the Monte Carlo simulations of Jorgensen et al.[3] fail to show two-point binding in **1:2**? Jorgensen et al. found that the cleft of **1** was unable to open wide enough to accomodate the two-point binding of the guest; however, their calculation appears to have been too highly constrained. The geometry of **1** employed in the simulation had been fully optimized by molecular mechanics in the absence of a guest, but in the Monte Carlo simulation, only six torsional degrees of freedom were allowed: rotations about the two imide-acridine N–C bonds, the two carboxyl C–C bonds, and the two carboxyl C–OH bonds.[3] These degrees of freedom are lateral motions which permit only limited opening of the cleft.

Table I. Bending Distortions in Complexes of Rebek's Diacid **1**.



Complex	Imide Bending[a] $(180° - \theta)^b$	Acridine Flex[a] $(180° - \angle N^{15}N^1C^8N^{34})$	Acridine Twist[a] $(\angle C^4C^5C^{11}C^{12})$
1:2A	5.1 (0.4)°, 3.1 (0.4)°	8.5 (0.1)° [c]	0.5 (0.4)°
1:2B	4.1 (0.4)°, 2.9 (0.4)°	5.4 (0.1)° [c]	1.8 (0.4)°
1:3A	4.1 (0.6)°, 5.6 (0.6)°	4.0 (0.1)° [c]	10.7 (0.5)°
1:3B	3.0 (0.6)°, 4.8 (0.6)°	9.3 (0.2)° [d]	7.3 (0.5)°
1:HCl	-5.6 (0.8)°, -3.4 (0.7)°	2.6 (0.2)°	9.5 (0.7)°

[a] Estimated standard deviations are given in parentheses (note 9). [b] θ is the angle formed by the imide-acridine C–N bond with the plane defined by the three atoms linked by the dashed lines. [c] N^{15} and N^{34} flex away from the diamine guest. [d] N^{15} and N^{34} flex toward the diamine guest.

Inspection of the crystal structures indicates that several bending degrees of freedom are important for the widening of the cleft in the pyrazine and quinoxaline complexes and for the narrowing of the cleft in **1:HCl** (see Table I). Paramount among these distortions is the bending at the junction of the acridine and the Kemp's triacid moieties, largely due to pyramidalization of the imide nitrogens. This is most clearly seen in the superposition of the Rebek's diacids of complex **1:3A** (which has the widest cleft) and **1:HCl** (the most narrow) in Figure 4. In the former, the imide nitrogens are pyramidalized downwards, and in the latter, upwards. From the data in Table I, it may be seen that the average downward bending of the imide is about 4° in the diamine complexes, and the upward bending in the hydrochloride complex is also about 4°. However, because of the long lever arm between the imide nitrogen and the carboxyl group, an overall 8° change in pyramidalization can account for an almost 1 Å change in the width of the cleft. The tricyclic acridine nuclei in the complexes also exhibit significant flexing and twisting distortions (Table I). The effect of flexure on the OH···OH separation is easily seen in the view of complex **1:2A** in Figure 5. The OH···OH separation in this complex is 8.25 Å, but the acid carbonyl O···O separation is only 7.20 Å. In each of the complexes, it is some combination of the imide bending, acridine flexure and twist, and rotations about the imide-acridine C–N bonds which permits opening of the Rebek's diacid clefts, although not every complex exhibits all of these distortions to a significant degree (see Table I).[10]

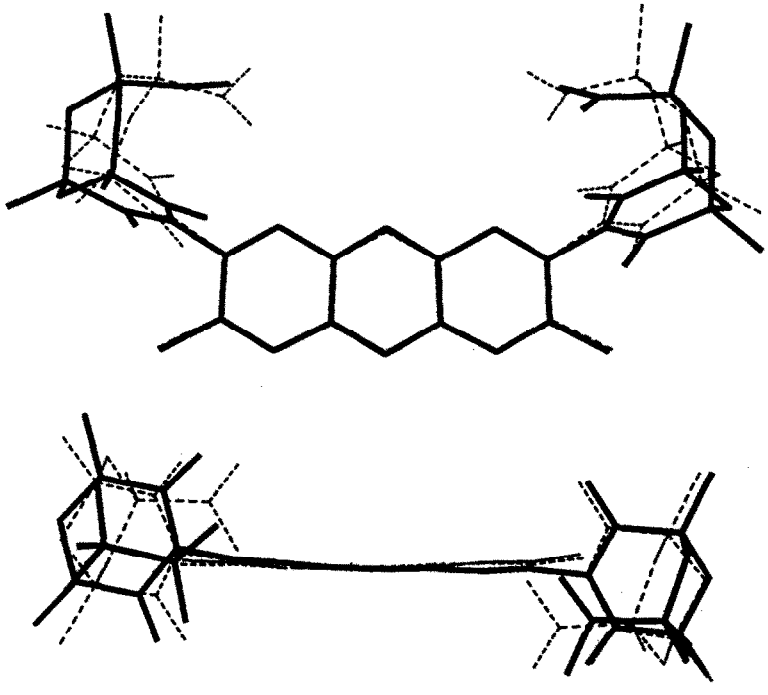


Fig. 4. Side and top views of the superimposed structures of the Rebek's diacids in complexes **1:3A** (bold lines) and **1:HCl** (dashed line).

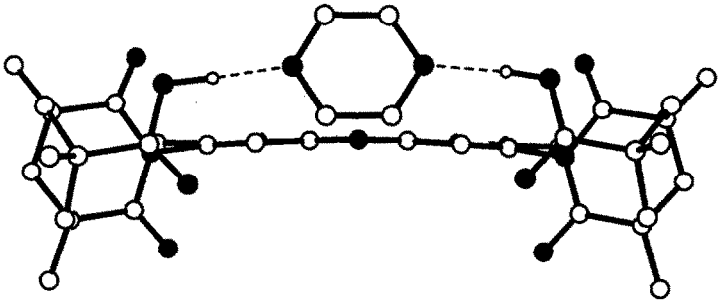


Fig. 5. Top view of complex **1:2A** which illustrates the flexure of the acridine nucleus and the difference between the OH···OH and acid carbonyl O···O separations.

In conclusion, the present structural studies amply display the ability of Rebek's diacid to form two-point hydrogen-bonded complexes with aromatic diamines. In addition, they demonstrate that this molecule is quite flexible, and that small changes in critical framework bond angles may be amplified into substantial displacements at the diamine binding site. By implication, computational studies on such delicate systems must be as free as possible of artificial constraints which may bias the results in an unanticipated fashion. However, while these crystal structures provide firm support for the two-point binding geometry, they do not explain the observed difference in the affinity of Rebek's diacid for pyrazine and quinoxaline in solution, and further experimental or computational studies will be required to elucidate this subtle selectivity.

EXPERIMENTAL SECTION

Crystallization and X-ray structure of 1:2. Compound **1** was prepared by the method of Rebek et al.[11] Single crystals of **1:2** were obtained by the concentration of solutions of **1** in liquid **2** at 70 °C. In a typical experiment, ~3 mg of **1** were dissolved in ~0.3 mL of hot pyrazine, and the solution was rapidly filtered, through a small piece of tissue paper stuffed into a Pasteur pipette, into a 13 × 100 mm test tube. The tube was placed in a oil bath at 70 °C, and the pyrazine solvent slowly evaporated and solidified on the walls of the tube. After 2-3 h, crystals were observed in the remaining solution, and the mixture was drawn into a warm Pasteur pipette and immediately spread onto a piece of filter paper. After the liquid pyrazine solidified, orange crystals of the complex **1:2** were selected from the mass of solid pyrazine.

Crystal data: $C_{39}H_{43}N_3O_8 \cdot C_4H_4N_2 \cdot 2.5C_4H_4N_2$; triclinic, space group $P\bar{1}$; $a = 13.859$ (2) Å, $b = 17.613$ (3) Å, $c = 21.989$ (3) Å, $\alpha = 93.72$ (1)°, $\beta = 89.76$ (1)°, $\gamma = 109.84$ (1)°, $V = 5038$ (1) Å^3, $Z = 4$, $D_{calcd} = 1.269$ g/cm^3. A prism measuring 0.12 × 0.20 × 0.55 mm was used for intensity measurements, which were made with 4°

$\leq 2\theta \leq 50°$ by using graphite monochromated Mo Kα radiation ($\lambda = 0.71073$ Å) at 235 K on a Siemens P4 diffractometer. A total of 17,821 unique reflections were measured, of which 7193 were considered to be observed [$|F_o| > 3\sigma(F_o)$]. The structure was solved by molecular replacement and refined by full-matrix least-squares using the SHELXTL PLUS software. In the final cycles of refinement, all non-hydrogen atoms (except for those of a disordered pyrazine solvent molecule) were refined with anisotropic displacement coefficients, the four carboxyl hydrogens were refined with isotropic displacement coefficients, and a riding model with idealized geometry was used for all other hydrogens. Due to disorder, the nitrogen atoms in one of the pyrazine solvent molecules was not identified, and this pyrazine was modelled with two C_6 hexagons, which were refined as rigid bodies with isotropic displacement coefficients. Refinement of 1261 parameters converged at $R(F) = 0.0554$, $wR(F) = 0.0558$, and $S = 0.99$.

X-ray structure of ***1*****:3.** Crystals of **1:3** were obtained by the slow evaporation of solutions of **1** in ethanol containing a five-fold excess of **3**. Crystal data: $C_{39}H_{43}N_3O_8 \cdot C_8H_6N_2 \cdot 0.5C_2H_6O$; triclinic, space group $P\bar{1}$; $a = 12.680$ (2) Å, $b = 17.987$ (2) Å, $c = 19.792$ (3) Å, $\alpha = 77.41$ (1)°, $\beta = 86.22$ (1)°, $\gamma = 78.55$ (1)°, $V = 4317$ (1) Å^3, $Z = 4$, $D_{calcd} = 1.285$ g/cm^3. A yellow prism measuring $0.10 \times 0.38 \times 0.38$ mm was used for intensity measurements, which were made with $4° \leq 2\theta \leq 50°$ by using graphite monochromated Mo Kα radiation ($\lambda = 0.71073$ Å) at 235 K on a Siemens P4 diffractometer. A total of 15,292 unique reflections were measured, of which 5775 were considered to be observed [$|F_o| > 3\sigma(F_o)$]. The structure was solved by molecular replacement and refined by full-matrix least-squares using the SHELXTL PLUS software. In the final cycles of refinement, all non-hydrogen atoms were refined with anisotropic displacement coefficients, the four carboxyl hydrogens were refined with isotropic displacement coefficients, and a riding model with idealized geometry was used for all other hydrogens. Refinement of 1121 parameters converged at $R(F) = 0.0574$, $wR(F) = 0.0556$, and $S = 0.98$.

X-ray structure of ***1*****:HCl.** Crystals of **1:HCl** were obtained from acetonitrile. Crystal data: $C_{39}H_{43}N_3O_8 \cdot HCl \cdot C_2H_3N$; monoclinic, space group $P2_1/c$; $a = 12.026$ (2) Å, $b = 14.274$ (3) Å, $c = 25.380$ (4) Å, $\beta = 114.22$ (1)°, $V = 3974$ (1) Å^3, $Z = 4$, $D_{calcd} = 1.269$ g/cm^3. A yellow prism measuring $0.10 \times 0.10 \times 0.18$ mm was used for intensity measurements, which were made with $4° \leq 2\theta \leq 50°$ by using graphite monochromated Mo Kα radiation ($\lambda = 0.71073$ Å) at 296 K on a Siemens P4 diffractometer. A total of 7044 unique reflections were measured, of which 2520 were considered to be observed [$|F_o| > 2\sigma(F_o)$]. The structure was solved by direct methods and refined by full-matrix least-squares using the SHELXTL PLUS software. In the final cycles of refinement, all non-hydrogen atoms were refined with anisotropic displacement coefficients, and a riding model with idealized geometry was used for all but the three acidic hydrogens. These were taken from the difference-Fourier map and idealized along the observed N-H and O-H vectors to 0.90 Å and 0.85 Å, respectively. The methyl H atoms of the acetonitrile solvent molecule were not observed and were not included. Refinement of 487 parameters converged at $R(F) = 0.0789$, $wR(F) = 0.0617$, and $S = 0.92$.

Acknowledgment. This work was supported by National Science Foundation Grant CHE-9106903 and National Institutes of Health Grant AI24146.

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5. The basicities of pyrazine [pK_a (BH^+) = 0.7] and quinoxaline [0.6] are very similar: Albert, A. in *Physical Methods in Heterocyclic Chemistry*; Katritzky, A., Ed.; Academic Press: New York, 1963; Vol. 1, p 21.
6. The desirability of X-ray structures was emphasized by Rebek et al. in their original publication on these complexes,[1a] but satisfactory crystals of the complexes are difficult to obtain.
7. A portion of this work (the structure of **1:3**) has been published previously as a preliminary communication: Pascal, R. A., Jr.; Ho, D. M. *J. Am. Chem. Soc.* **1993**, *115*, 8507-8508.
8. The crystal parameters and a summary of the data collection and structure solution are given in the Experimental Section.
9. Estimated standard deviations for these angles were calculated with the aid of the program PLATON-93: see Spek, A. L. *Acta Crystallogr., Sect. A* **1990**, *46*, C34.
10. Bending distortions of the bicyclic "Kemp's triacid" units might also affect the size of the cleft, and the degree to which these units are bent "open" or "closed" is reflected in the distances N^{15}–C^{19} and N^{34}–C^{38} (see the structure in Table I). In **1:HCl** these distances are 3.38 and 3.34 Å, in the complexes **1:2** they range from 3.30 to 3.34 Å, and in the complexes **1:3** from 3.28 to 3.48 Å. However, these small distortions do not appear to influence significantly the OH···OH separations.
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(*Received in USA* 7 *March* 1994; *accepted* 20 *May* 1994)