Molecular Structure of Rebek's Diacid–Quinoxaline: Confirmation of Two-Point Binding

Robert A. Pascal, Jr.,* and Douglas M. Ho

Department of Chemistry
Princeton University
Princeton, New Jersey 08544

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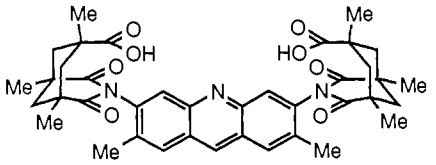
Rebek and co-workers have shown that the diacid **1** is an effective host for a variety of cyclic diamines, notably pyrazine, quinoxaline, phenazine, pyrimidine, quinazoline, and DABCO, and, on the basis of a variety of NMR data, they have proposed that "two-point binding" of these diamines by the convergent carboxyl groups is the likely mode of complexation.[1,2] More recently, Jorgensen et al.[3] have argued, on the basis of the results of a computational study, that two-point binding is disfavored in **1**·pyrazine and that only one strong hydrogen bond is made in typical structures of this complex. They conclude, "The guest floats above the acids groups; the cleft is too small for two point binding, which is also disfavored on entropic grounds." [3] Given the structural similarity of pyrazine, quinoxaline, and phenazine, these calculations call into question the two-point binding motif for these and related aromatic diamines in association with **1**. In this context, we now report the single crystal X-ray structure of a 1:1 complex of Rebek's diacid and quinoxaline (**2**), which unambiguously establishes two-point binding as the mode of complexation.



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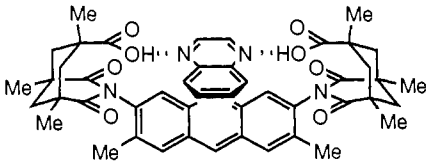

2

Crystals of **2** were obtained by the slow evaporation of an ethanol solution of **1**[4] containing an excess of quinoxaline, and the molecular structure of the complex was determined by X-ray analysis.[5] The crystals are triclinic, space group $P\bar{1}$, $Z = 4$; thus there are two crystallographically independent molecules of the complex **2** in the asymmetric unit which we designate **A** and **B** (Figure 1). *Both **A** and **B** exhibit nearly symmetric, syn,*[3] *two-point binding of quinoxaline*: in complex **A** the hydrogen-bonded N···O distances are 2.761 and 2.790 Å, and in **B** they are 2.661 and 2.691 Å. The O_H···O_H separation in complex **A** is 8.355 Å, and in **B** it is 7.928 Å. The former approaches the 8.4-Å separation specified by Jorgensen et al.[3] for optimal syn two-point binding of pyrazine. It is important to note that the N···N distance in

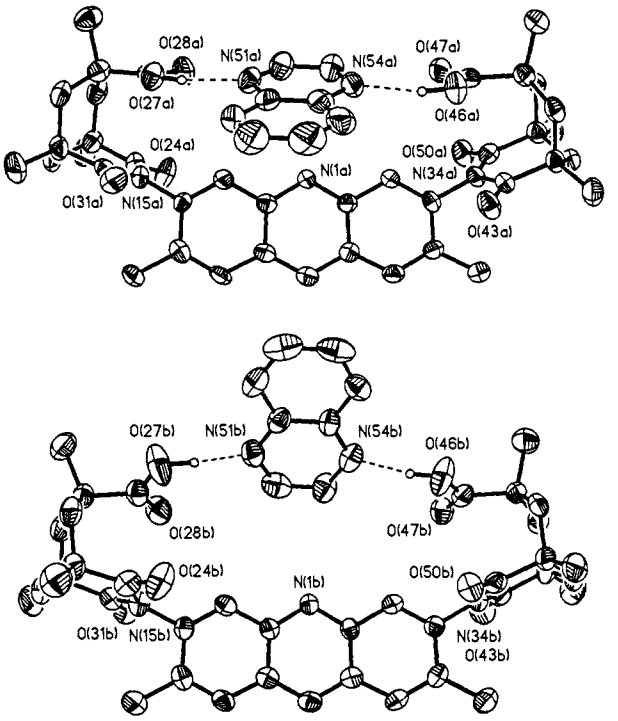

Figure 1. X-ray structures of complexes **A** (top) and **B** (bottom). Both complexes have been oriented so that the mean plane of the acridine nucleus is parallel to the plane of the page. Thermal ellipsoids are drawn at the 50% probability level, and all but the H-bonded hydrogen atoms have been omitted for clarity.

pyrazine, 2.796 Å,[6] is essentially identical to the N···N distances for quinoxaline found in the present study, 2.822 (**A**) and 2.793 Å (**B**), so the observed chelation of quinoxaline is not the result of a more compact structure than pyrazine.[7]

The two complexes differ instructively with respect to the binding geometry. Most significantly, in complex **A** the cleft is large enough to accommodate two essentially collinear 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 contrast, the cleft is 0.43 Å narrower in complex **B**, and the quinoxaline nitrogens lie approximately 0.7 Å above the plane of the carboxyl oxygens.[8] Thus in **B** the cleft is indeed too small for optimal chelation, and the quinoxaline is pushed slightly

(1) (a) Rebek, J., Jr.; Askew, B.; Islam, N.; Killoran, M.; Nemeth, D.; Wolak, R. *J. Am. Chem. Soc.* **1985**, *107*, 6736–6738. (b) Rebek, J., Jr.; Askew, B.; Killoran, M.; Nemeth, D.; Lin, F.-T. *J. Am. Chem. Soc.* **1987**, *109*, 2426–2431.

(2) Rebek, J., Jr. *Acc. Chem. Res.* **1990**, *23*, 399–404, and references cited therein.

(3) Jorgensen, W. L.; Boudon, S.; Nguyen, T. B. *J. Am. Chem. Soc.* **1989**, *111*, 755–757.

(4) Rebek, J., Jr.; Marshall, L.; Wolak, R.; Parris, K.; Killoran, M.; Askew, B.; Nemeth, D.; Islam, N. *J. Am. Chem. Soc.* **1985**, *107*, 7476–7481.

(5) Crystal data for **2**: $C_{39}H_{43}N_3O_8 \cdot C_8H_6N_2 \cdot 0.5C_2H_6O$; 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 from ethanol measuring 0.10 × 0.38 × 0.38 mm was used for intensity measurements, which were made with $4° \le 2\theta \le 50°$ by using graphite-monochromated Mo Kα radiation ($\lambda = 0.710\,73$ 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 methods 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 all other hydrogens were refined with a riding model with idealized geometry. Refinement of 1121 parameters converged at $R(F) = 0.0574$, $R_w(F) = 0.0556$, and $S = 0.98$. Full details are given in the supplementary material.

(6) de With, G.; Harkema, S.; Feil, D. *Acta Crystallogr., Sect. B* **1976**, *32*, 3178–3184.

(7) Nor are the basicities of pyrazine [$pK_a(BH^+) = 0.7$] and quinoxaline [0.6] very different: Albert, A. In *Physical Methods in Heterocyclic Chemistry*; Katritzky, A., Ed.; Academic Press: New York, 1963; Vol. 1, p 21.

(8) The 8.355-Å O_H···O_H separation in **A** is achieved in part by a gentle 10.8° twist of the acridine nucleus, a torsional degree of freedom that was not sampled in the calculations of Jorgensen et al.[3] AM1 calculations[9] indicate that such a twisted geometry is only 0.4 kcal/mol above the nearly planar ground state. Curiously, the acridine nucleus in **B** is slightly arched, a deformation that actually brings the H-bonded oxygens closer together.

(9) Dewar, M. J. S.; Zoebisch, E. G.; Healy, E. F.; Stewart, J. J. P. *J. Am. Chem. Soc.* **1985**, *107*, 3902–3909.

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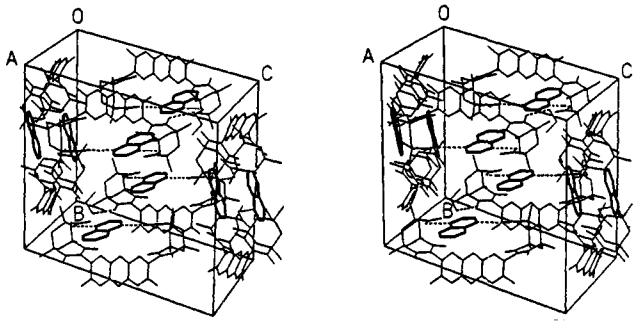

Figure 2. Stereoview of the unit cell of the crystals of complex **2**. Hydrogen atoms have been omitted for clarity.

out of the cleft, but symmetrical two-point binding is maintained. Clearly it is preferable for the complex to form two slightly bent hydrogen bonds rather than a single linear H-bond. The orientation of quinoxaline about the axis of chelation is dramatically different in the two complexes. In complex **A**, the benzene ring of the quinoxaline is inclined toward the acridine nucleus, and the dihedral angle between mean planes of the two aromatic systems is 64.5°. In contrast, the quinoxaline of **B** is swung away from the acridine, and the corresponding angle is 140.9°. In neither complex is there any evidence of the π-stacking interactions between quinoxaline and acridine proposed by Rebek et al.[1b] to account for the enhanced binding of quinoxaline with respect to pyrazine, but there is π-stacking of quinoxalines between paired molecules of complex **B** in the crystal structure (see Figure 2).

Rebek et al. observed a 12-fold ratio of K_{assoc} values for the binding of pyrazine and pyridine by compound **1** in chloroform,[1] but Jorgensen et al. calculated that a K_{assoc} ratio on the order of 400 would be expected "for true two point binding" (of pyrazine).[3] The results presented here suggest that two hydrogen bonds should easily form in the pyrazine complex,[10] so the modest difference in association constants likely reflects other factors, perhaps a slight increase in strain in **1** upon adopting a conformation suitable for two-point binding. Clearly, additional experimental and computational studies will be required to elucidate the subtle differences in binding affinity among the various amines.

In conclusion, the present data confirm the previously proposed[1] two-point binding of quinoxaline by diacid **1** and strongly suggest that related aromatic diamines are chelated by **1** in a similar manner.

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Supplementary Material Available: Full crystallographic data and processing descriptions, final atomic coordinates, bond lengths and angles, torsional angles, anisotropic thermal parameters, and several figures for complex **2** (34 pages). Ordering information is given on any current masthead page.

(10) We cannot, of course, directly determine the structure of **2** in solution; however, the two crystallographically independent complexes **A** and **B** represent two separate determinations of the structure of **2** in different local environments. The fact that *both* **A** and **B** 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.