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UNUSUAL BEHAVIOR OF 3,4:10,11-BIS(2',3'-QUINOLINO)TRICYCLO-[6.3.0.0^{2,6}]UNDECANE UPON ATTEMPTED MONOPROTONATION WITH TRIFLIC ACID

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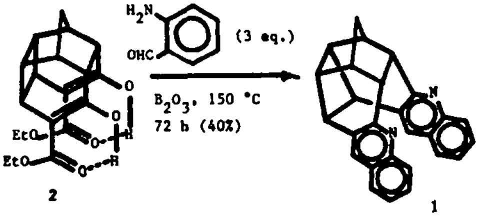
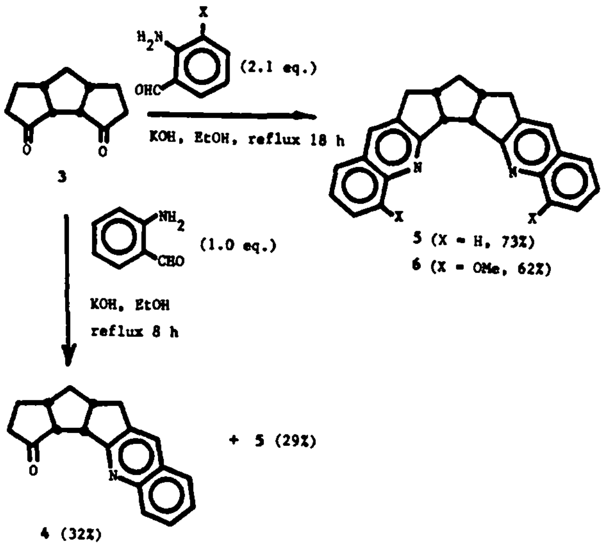
Abstract: The title compound (**5**, 73%) and the corresponding bis(8'-methoxy) derivative (**6**, 62%) were synthesized via base promoted Friedländer condensations of tricyclo[6.3.0.0^{2,6}]undecane-3,11-dione (**3**) with excess ortho-aminobenzaldehyde and with 2-amino-3-methoxybenzaldehyde, respectively. Only diprotonated **5** could be isolated via reaction of the title compound with triflic acid. X-ray crystal structures of **5** and of two polymorphic forms of diprotonated **5** (i.e., **7a** and **7b**) are reported.

As part of a program in the general area of host-guest chemistry that is concerned with the synthesis and chemistry of a potential new class of molecular hosts,[1] we recently reported the synthesis of a novel molecular cleft, **1**, via two sequential Friedländer condensations between pentacyclic bis(ketoester) **2** and ortho-aminobenzaldehyde (Scheme 1).[1b] The corresponding reaction of tricyclo[6.3.0.0^{2,6}]undecane-3,11-dione (**3**)[2] with ortho-aminobenzaldehyde[3] (1.0 equivalents) in the presence of potassium hydroxide in refluxing absolute ethanol for 8 h led directly to the formation of monoadduct (**4**, mp 117-118°C, 32% yield) along with a comparable quantity of the corresponding diadduct (**5**, mp 181-182 °C, 29% yield). Direct synthesis of diadduct **5** was achieved in 73% yield similarly via Friedländer condensation of **3** with ortho-aminobenzaldehyde (2.1 equiv). Finally, Friedländer condensation of **3** with excess 2-amino-3-methoxybenzaldehyde[3] afforded the corresponding bis(8'-methoxy) derivative of **5** (i.e., **6**, mp 246-247 °C, Scheme 2) in 62% yield.

Scheme 1



Scheme 2



The structure of **5** was elucidated via single crystal X-ray structural analysis. A structure diagram of **5** is shown in Figure 1. Bond distances and bond angles in **5** fall well within normal ranges. The quinoline rings are twisted about the central five-membered ring such that N(12)...N(17) = 3.19 A and C(5)...C(24) = 5.75 Å (corresponding values for the second molecule in the asymmetric unit at 2.54 and 6.37 Å, respectively).[4] The X-ray crystal structure of a cationic Rh(I) complex of **4** has been reported recently.[5]

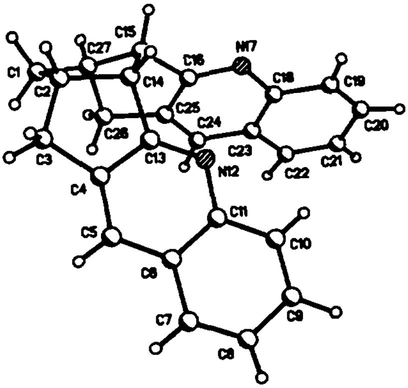


Figure 1. X-ray structure drawing of **5**

Inspection of molecular models suggests that **5** can adopt a conformation in which the two quinoline nitrogen atoms come into close mutual proximity. This suggests that it may be possible for **5** to function as a "proton sponge",[6] thereby reacting with one equivalent of a protic acid to afford a symmetrical monoprotonated species. However, when we attempted to isolate a quaternary ammonium salt from the reaction of **5** with trifluoromethanesulfonic acid (1 equivalent), only the corresponding diprotonated species could be obtained.

Potentiometric titration data was obtained in an effort to gain additional insight into this protonation process. Stepwise protonation of **5** can be represented by the following equilibria:

$B + H^+ \rightleftarrows HB^+$ (equilibrium constant K_1) (1)

$HB^+ + H^+ \rightleftarrows H_2B^+$ (equilibrium constant K_2) (2)

Here, the protonation constants K_1 and K_2 are expressed in molar concentration units. Solutions that contained the free base[7] and excess standardized aqueous perchloric acid solution were titrated with CO_2-free standardized aqueous sodium hydroxide solution.[8] Analysis of the potentiometric titration curves (pH vs. moles NaOH, obtained at 25.0 °C in 80% aqueous methanol solution) was performed by using the computer program PKAS.[9] The following values were thereby obtained: $\log K_1 = 5.36 \pm 0.02$ and $\log K_2 = 4.84 \pm 0.02$. Species distribution calculations obtained by using the program COMICS[10] revealed that monoprotonated **5** (i.e., HB^+) is formed only over a narrow pH range (i.e., ca. pH 4-6), and its concentration never exceeds ca. 45% of the total ligand concentration present in solution. The values of $\log K_1$ and $\log K_2$ observed for **5** are similar to those found for analogous aromatic amine systems (measured in water).[11]

X-ray crystal structures of two polymorphic forms of diprotonated **5** (i.e., **7a**, mp 215-216 °C and **7b**, mp 258-260°C) were obtained. In **7a**, the two N-H moieties are hydrogen bonded to a water molecule. One triflate ion forms a bifurcated hydrogen bond with N-H, while the second triflate ion forms a hydrogen bond with the water molecule. This second triflate ion also forms a second hydrogen bond to an adjacent water molecule. The water molecule participates in forming four hydrogen bonds; two of the bonds involve symmetry related triflates. Compound **7a** contains five hydrogen bonds per formula unit, which form a hydrogen-bonded chain that persists throughout the molecule.

In **7b**, as in **7a**, the two N-H moieties are hydrogen bonded to a water molecule. The two triflate ions form hydrogen bonds to the water molecule through the water hydrogen atoms. There is a discrete unit composed of dication **7b**, a water molecule, and two triflate ions. Unlike **7a**, **7b** is both unstable and hygroscopic. Although the crystal was sealed in glass, decomposition nevertheless occurred during X-ray data collection. Dication **7a** forms four hydrogen bonds per formula unit, and a distinct monomeric cluster exists. Crystal packing diagrams of **7a** and **7b** appear in Figures 2 and 3, respectively.

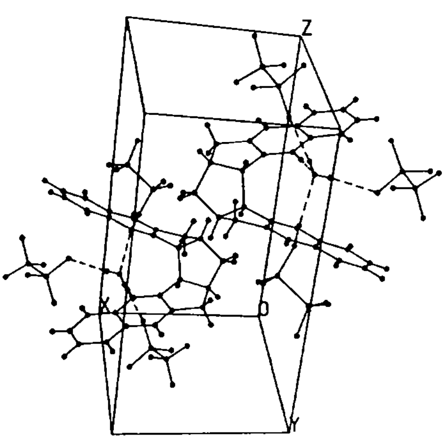


Figure 2. Crystal packing diagram of **7a**

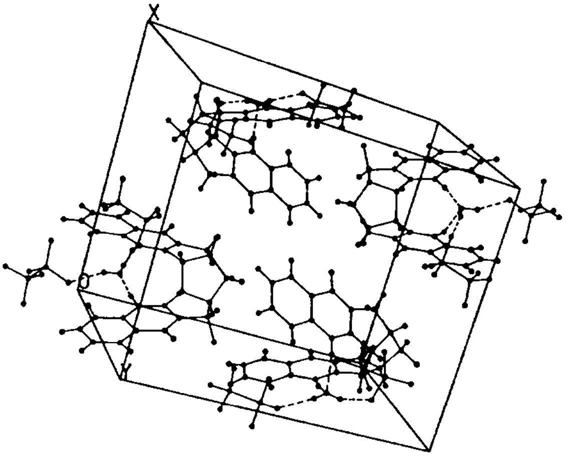


Figure 3. Crystal packing diagram of **7b**

The structures of dications **7a** and **7b** are compared in Figure 4. Here, it is seen that the differences in hydrogen bonding between **7a** and **7b** noted above affect the relative conformations of the dications. Consequently, the two quinoline "arms" are spread further apart in **7a** vis-à-vis **7b** (i.e., the nonbonded distances N...N' and H...H' differ significantly in **7a** and **7b**).

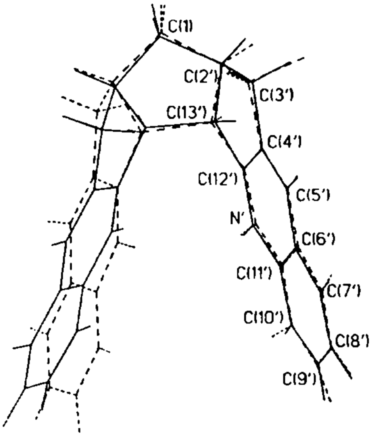


Figure 4. X-ray structure drawings of dications **7a** (solid line) and **7b** (broken line)

Experimental Section

Melting points are uncorrected.

Friedländer Condensation of 3 with *ortho*-Aminobenzaldehyde (1 equiv). A mixture of 3[2] (1.47 g, 8.26 mmol) and *ortho*-aminobenzaldehyde[3] (1.00 g, 8.26 mmol) in absolute ethanol (50 mL) under nitrogen was heated to reflux. To this refluxing solution was added dropwise a solution of potassium hydroxide (85% KOH, 100 mg, 1.52 mmol) in absolute ethanol (20 mL), and the resulting solution was refluxed for 8 h. The reaction mixture was cooled to room temperature and then concentrated in vacuo. Water (25 mL) was added, and the residual aqueous mixture was extracted with methylene chloride (3 x 20 mL). The combined extracts were washed with brine (10 mL), dried (anhydrous sodium sulfate), and filtered. The filtrate was concentrated in vacuo, and the residue was purified via column chromatography on silica gel by using 70% ethyl acetate-hexane mixed solvent as eluent. The first chromatography fractions afforded a colorless solid. Recrystallization of this material from hexane afforded pure 3,4-(2',3'-quinolino)tricyclo[6.3.0.0^{2,6}]undecan-11-one (**4**, 700 mg, 32%) as a colorless microcrystalline solid: mp 117-118 °C; IR (KBr) 3038 (m), 2925 (s), 2893 (s), 1722 (br, vs), 1411 cm^{-1} (s); ^{1}H NMR ($CDCl_3$) δ 0.91 (sextet, *J* = 6.5 Hz, 1 H), 1.30 (quintet, *J* = 6.5 Hz, 1 H), 1.89 (sextet, *J* = 7.0 Hz, 1 H), 2.05-2.12 (m, 2 H), 2.45-2.55 (m, 1 H), 2.84-2.92 (m, 2 H), 3.07-3.27 (m, 3 H), 4.02-4.07 (m, 1 H), 7.41-7.46 (m, 1 H), 7.56-7.62 (m, 1 H), 7.69-7.72 (m, 1 H), 7.88 (br s, 1 H), 7.99-8.04 (m, 1 H); ^{13}C NMR ($CDCl_3$) δ 27.91 (t), 35.94 (t), 38.96 (t), 39.91 (t), 43.61 (d), 44.19 (d), 54.43 (d), 57.20 (d), 125.77 (d), 127.21 (d), 127.40 (s), 128.29 (d), 129.25 (d), 131.54 (d), 134.45 (s), 147.62 (s), 166.14 (s), 219.11 (s); mass spectrum (70 eV), *m/e* (relative intensity) 263 (molecular ion, 100.0), 262 (28.8), 208 (31.2), 207 (38.2), 206 (44.9), 181 (22.7), 180 (67.2), 168 (50.1), 167 (24.2). Anal. Calcd for $C_{18}H_{17}NO$: C, 82.09; H, 6.50. Found: C, 82.12; H, 6.53.

Continued elution of the chromatography column afforded a pale yellow solid (800 mg). Recrystallization of this material from ethyl acetate hexane afforded pure 3,4:10,11-Bis(2',3'-quinolino)tricyclo[6.3.0.0^{2,6}]undecane (**5**) as a yellow solid: mp 181-182 °C (lit.[4] mp not reported); IR (KBr) 3043 (m), 2928 (s), 1620 (m) 1505 (m), 1417 cm^{-1} (s); ^{1}H NMR ($CDCl_3$) δ 1.41 (tripled AB, J_{AB} = 14.1 Hz, *J'* = 5.1 Hz, 1 H), 2.35 (doubled AB, J_{AB} = 17.6

Hz, $\underline{J}'$ = 5.1 Hz, 2 H), 2.60 (tripled $A\underline{B}$, $\underline{J}_{AB}$ = 14.1 Hz, $\underline{J}'$ = 9.3 Hz, 1 H), 3.09 (dd, $\underline{J}_1$ = 16.6 Hz, $\underline{J}_2$ = 8.5 Hz, 2 H), 3.21-3.33 (m, 2 H), 4.21-4.28 (m, 2 H), 7.30-7.57 (complex m, 10 H); ^{13}C NMR ($CDCl_3$) δ 37.19 (t), 39.74 (t), 44.74 (d), 56.03 (d), 125.11 (d), 126.93 (d), 127.28 (s), 127.61 (d), 129.14 (d), 129.92 (d), 135.62 (s), 147.31 (s), 166.90 (s). Anal. Calcd for $C_{25}H_{20}N_2$: C, 86.17; H, 5.79. Found: C, 85.98; H, 5.76.

Friedländer Condensation of 3 with *ortho*-Aminobenzaldehyde (2.1 equiv). A mixture of 3[2] (2.50 g, 14.0 mmol) and *ortho*-aminobenzaldehyde[3] (3.63 g, 30.0 mmol) in absolute ethanol (100 mL) under nitrogen was heated to reflux. To this refluxing solution was added dropwise a solution of potassium hydroxide (85% KOH, 1.68 g, 25.5 mmol) in absolute ethanol (25 mL), and the resulting solution was refluxed for 18 h. The reaction mixture then was cooled to room temperature and then concentrated in vacuo. Water (25 mL) was added, and the residual aqueous mixture was extracted with methylene chloride (3 x 20 mL). The combined extracts were washed with brine (10 mL), dried (anhydrous sodium sulfate), and filtered. The filtrate was concentrated in vacuo, thereby affording a pale yellow solid (4.6 g). This material was purified via column chromatography on silica gel by using 70% ethyl acetate-hexane mixed solvent as eluent. Pure **5** (3.5 g, 73%) was thereby obtained as a yellow solid: mp 181-182 °C. The infrared, proton NMR and carbon-13 NMR spectra of this material were identical in all respects with the corresponding spectra of authentic **5** prepared earlier (vide supra).

3,4:10,11-Bis(8'-methoxy-2',3'-quinolino)tricyclo[6.3.0.0^{2,6}]undecane (6). A mixture of 3[2] (600 mg, 3.37 mmol) and freshly prepared[3] 2-amino-3-methoxybenzaldehyde (1.35 g, 9.00 mmol) in absolute ethanol (30 mL) under nitrogen was heated to reflux. To this refluxing solution was added dropwise a solution of potassium hydroxide (85% KOH, 100 mg, 1.52 mmol) in absolute ethanol (5 mL), and the resulting solution was refluxed for 8 h. Workup of the reaction mixture was performed in the manner described above for the corresponding synthesis of **5**. The reaction product was purified via column chromatography on silica gel by using 4:1 ethyl acetate-hexane mixed solvent as eluent. Pure **6** (850 mg., 62%) was thereby obtained as a pale yellow microcrystalline solid: mp 246-247 °C; IR (KBr) 1600 (s), 1555 (s), 1445 (br, s), 1345 (m), 1265 cm^{-1} (s); ^1H NMR ($CDCl_3$) δ 1.28 ($\underline{A}B$, $\underline{J}_{AB}$ = 10.5 Hz, 1 H), 1.44 ($A\underline{B}$, $\underline{J}_{AB}$ = 10.5 Hz, 1 H), 2.00-2.36 (m, 2 H), 2.82-3.32 (m, 4 H), 3.54 (s, 6 H), 4.02-4.323 (m, 2 H), 6.60-6.82 (m, 2 H), 7.08-7.28 (m, 4 H), 7.51 (s, 2 H); ^{13}C NMR ($CDCl_3$) δ 37.40 (t), 39.61 (d), 44.94 (t), 55.15 (d), 56.13 (q), 105.94 (s), 118.81 (d), 120.50 (s), 124.86 (s), 128.57 (d), 129.68 (d), 136.11 (d), 155.49 (s), 165.70 (s). Anal. Calcd for $C_{27}H_{24}N_2O_2$: C, 79.39; H, 5.92. Found: C, 79.14; H, 5.99.

Potentiometric Titration Measurements. Titrations were performed at 25.0 °C under nitrogen by using a Metrohm 665 digital buret. pH_{obs} measurements were made by using a Metrohm 6.0216.0 combination electrode and Fisher 825 MP pH meter. The pH meter and digital buret were interfaced to a Zenith computer system. The electrode was calibrated via titration of acetic acid with NaOH in 80% aqueous methanol.[8a-c] The observed pH readings were converted to $[H^+]$ by using relationships $[H^+] = (10^{-pH})\gamma_\pm$ and $pH = pH_{obs} - \delta$, where the activity coefficent, $\gamma_\pm$, is calculated by using the extended Debye-Hückel equation and δ is a correction for solvent effects.[8d] Solutions contained the free base (**5**, 0.441-0.690 mM) and $HClO_4$ (2.01-2.74 mM); the titrant was NaOH (9.93-10.46 mM).

X-ray Structure of 5. The structure was solved by direct methods. Final R-factor from full matrix least-squares refinement by using 3742 observed data ($F_o > 3\sigma(F_o)$) was 0.053 ($\underline{w}R$ = 0.062). Crystal Data for **5**: $C_{25}H_{20}N_2$, triclinic, space group $P\overline{1}$ with $a = 12.080$ (1), $b = 12.213$ (1), $c = 15.537$ (2) Å, $\alpha = 106.51(1)$, $\beta = 96.59$ (1), $\gamma = 117.36$ (1)°, $V = 1870.7$ (4) Å^3, Z = 4 (2 molecules per asymmetric unit), $d_{calc} = 1.23$ g-cm^{-3}, and $\mu(CuK\alpha) = 5.23$ cm^{-1}, R = 0.953.[4,12]

X-ray Structures of 7a and 7b. All data were collected on a Nicolet R3m/μ update of a $P2_1$ diffractometer by using graphite monochromated MoKα radiation ($\lambda = 0.71073$ Å). Data were collected by the ω-scan technique by using a variable scan rate. A ψ-scan empirical absorption correction was applied, and the structures were solved by direct methods. The structures were refined by a block-cascade least-squares technique. Hydrogen atoms were located in difference maps and were refined with isotropic thermal parameters. The function minimized was $\Sigma \underline{w}(|F_o| - |F_c|)^2$ with $\underline{w} = [\sigma^2(F_o) + .00050\, F_o^2]^{-1}$. All computer programs were used as supplied by Nicolet for Desktop 20 Microeclipse and Nova 4/C configuration. Atomic scattering factors and anomalous dispersion corrections were taken from International Tables for X-ray Crystallography.[13]

Crystal data for **7a**: $[C_{25}H_{22}N_2]^{+2}[F_3CSO_3^-]_2(H_2O)$, space group $P2_1/C$ with a = 15.199 (3), b = 10.367 (2), c = 18.079 (3) Å, β = 97.01°, V = 2827.4 (7) Å^3, Z = 4, d_{calc} = 1.566 g-cm^{-3}, and μ(MoKα) = 2.66 cm^{-1}, R = 0.0714 for 2298 reflections.[12] Crystal data for **7b**: $[C_{25}H_{22}N_2]^{+2}[F_3CSO_3^-]_2(H_2O)$, space group $P\bar{1}$ with a = 9.037 (1), b = 10.284 (1), c = 15.833 (2) Å, α = 88.40(1), β = 81.61 (1), γ = 76.09 (1)°, V = 1417.4 (3) Å^3, Z = 2, d_{calc} = 1.562 g-cm^{-3}, and μ(MoKα) = 2.66 cm^{-1}, R = 0.0434 for 2957 reflections.[12]

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References & Footnotes

1. (a) Marchand, A. P.; Annapurna, P.; Flippen-Anderson, J. L.; Gilardi, R.; George, C. Tetrahedron Lett. **1988**, 29, 6681. (b) Marchand, A. P.; Annapurna, P.; Watson, W. H.; Nagl. A. J. Chem. Soc., Chem. Commun. **1989**, 281.

2. Mehta, G.; Srikrishna, A.; Reddy, A. V.; Nair, M. S. Tetrahedron **1981**, 37, 4543.

3. ortho-Aminobenzaldehyde and 2-amino-3-methoxybenzaldehyde were prepared via reduction of the corresponding nitrobenzaldehyde with ammoniacal ferrous sulfate. See: Smith, L. I.; Opie, J. W. Org. Syn. **1955**, Coll. Vol. 3, 56.

4. While this study was in progress, another report of the synthesis of **5** and its X-ray crystal structure were communicated. See: Mehta, G.; Prabhakar, C.; Padmaja, N.; Ramakumar, S.; Viswamitra, M. A. Tetrahedron Lett. **1989**, 30, 6895. The unit cell of **5** reported therin is related to that of **5** obtained in the present study by a simple transformation of the triclinic axes.

5. Watson, W. H.; Nagl, A.; Marchand, A. P.; Annapurna, P. Acta Crystallogr., Sect. C: Cryst. Struct. Commun. **1989**, C45, 856.

6. "Proton Sponge"® is a registered trademark of Aldrich Chemical Company for 1,8-bis(dimethylamino)naphthalene. Here, the term "proton sponge" refers to the possibility that **5** may be susceptible to monoprotonation in a manner analogous to the behavior of Proton Sponge . See: Staab, H. A.; Saupe, T. Angew. Chem., Int. Edit. Engl. **1988**, 27, 865.

7. Due to the low solubility of **5** in water, 80% methanol-water (w/w) was used as solvent.

8. (a) Rorabacher, D. B.; Mackellar, W. J.; Shu, F. R.; Bonavita, Sr. M. Anal. Chem. **1971**, 43, 561. (b) Gelsema, W. J.; deLigny, C. L.; Remijnse, A. G.; Blijleven, H. A. Recl. Trav. Chim. Pays-Bas **1966**, 85, 647. (c) Gelsema, W. J.; deLigny, C. L.; Blijleven, H. A. Ibid. **1967**, 86, 852. (d) deLigny, C. L.; Luykx, P. F. M.; Rehback, M.; Weineke, A. A. Ibid. **1960**, 79, 699, 713.

9. Motekaitis, R. J.; Martell, A. E. Can. J. Chem. **1982**, 60, 168.

10. Perrin, D. D.; Sayce, I. G. Talanta **1967**, 14, 833.

11. E.g., quinoline: log K = 4.91; 1,10-phenanthroline: log K - 4.86. Data taken from Smith, R. M.; Martell, A. E. In Critical Stabilty Constants; Plenum: New York, 1974, Vol. 2, pp. 222, 251.

12. Tables of coordinates and bond lengths and bond angles for **5**, **7a**, and **7b** are availble from the Crystallographic Data Centre, Cambridge University, University Chemical Laboratory, Cambridge CB2 1EW, England.

13. International Tables for X-ray Crystallography; Kynoch Press: Birmingham, 1974; Vol. IV. (Present distributor, D. Reidel: Dordrecht).