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2 + 2 Salt Formation Induced by Hydrogen Bonding

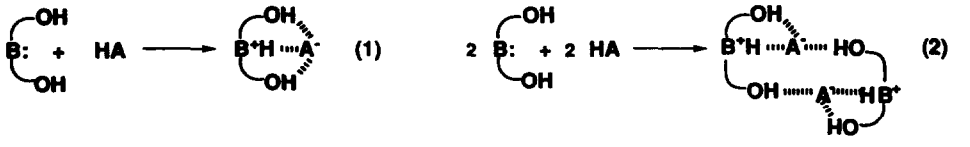
Kei Manabe,*[a] Kimio Okamura,[b] Tadamasa Date,[b] and Kenji Koga*[a]

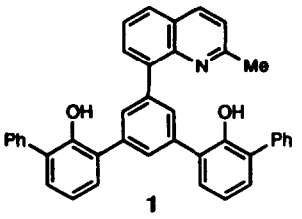
[a]Faculty of Pharmaceutical Sciences, University of Tokyo, Hongo, Bunkyo-ku, Tokyo 113, Japan

[b]Organic Chemistry Research Laboratory, Tanabe Seiyaku Co., Ltd., 2-2-50, Kawagishi, Toda, Saitama 335, Japan

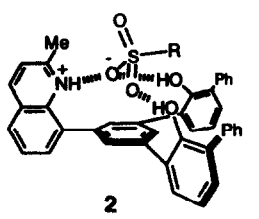
Abstract: A pyridine derivative (3) and TsOH form a 2 + 2 salt with six hydrogen bonds in the solid state, although there are equilibria between some aggregation states induced by hydrogen bonding in solution.

Molecular assembly of synthetic compounds has received considerable attention from the viewpoint of generating nanometer-scale structures.[1] In the control of aggregate structures, hydrogen bondong plays an important role. Some excellent works have shown that three or more molecules can form well-defined aggregates controlled by hydrogen bonding in the solid state[2] as well as in solution.[3] Recently we have reported that quinoline derivatives, exemplified by **1**, form 1 + 1 salts with sulfonic acids in chloroform with three hydrogen bonds (eq 1).[4] The structure of the 1 + 1 salts is assumed to be like **2** on the basis of the X-ray analysis of the related salt and ^{1}H NMR studies.[4a, 5] In the course of developing this system, we have tried to realize salt-assembly system in which several components associate with each other via hydrogen bonding. Here we describe that in the solid state a pyridine derivative (**3**),[6] in contrast with quinoline derivative **1**, forms a 2 + 2 salt with *p*-toluenesulfonic acid (TsOH) as shown in eq 2, and that in solution there are equilibria between some aggregation states induced by hydrogen bonding.

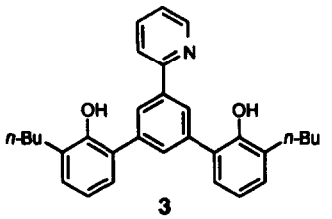




1

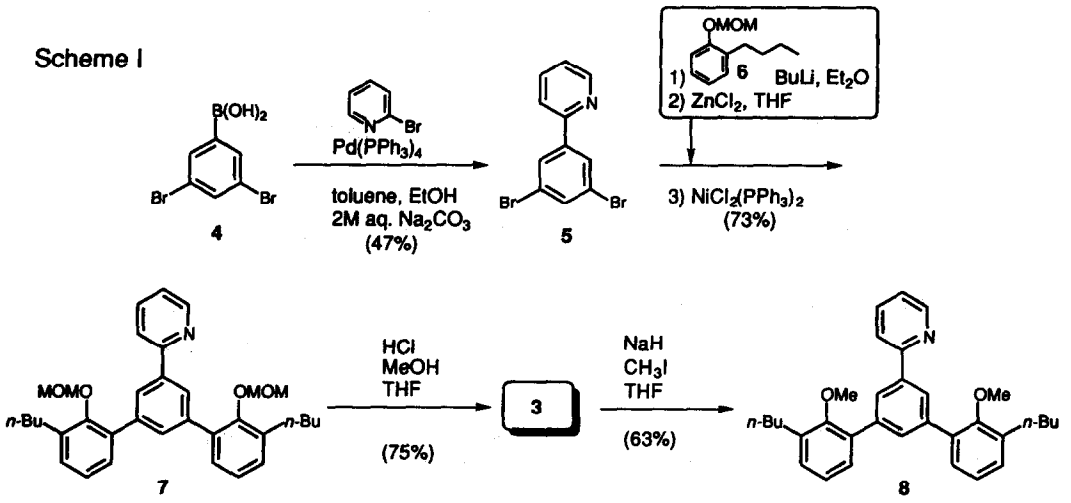


2



3

Scheme I



Pyridine derivative **3** was synthesized as shown in Scheme I. MOM ether **6**[7] was lithiated, transmetalated and subjected to the nickel-catalyzed coupling reaction[8] with **5**, which was prepared from boronic acid **4**[9] and 2-bromopyridine under Suzuki conditions,[10] to give **7**. Deprotection of the MOM groups yielded **3**.[11] The reference compound (**8**) in which the OH groups of **3** were converted to methoxy groups was obtained by methylation of **3**.

Recrystallization of the salt between **3** and TsOH from benzene gave colorless prisms. The X-ray structure[12] of the salt (Figure 1) shows the importance of hydrogen bonding for salt aggregation. Two sulfonate molecules and two protonated **3** molecules form a 2 + 2 salt with six hydrogen bonds as shown in eq 2. Furthermore, two pyridinium rings are stacked with each other at an interplanar distance of ca. 3.5 Å. The π-stacking interaction between the pyridinium rings serves to stabilize the 2 + 2 salt structure. This salt structure is very different from the structure of quinolinium salt **2**.

It is difficult to determine the solution structure of the salt (**3**•TsOH). On the basis of ^{1}H NMR studies described below, however, we conclude that the OH groups of **3** play a significant role in salt aggregation in solution. Addition of 1 equiv of TsOH to a 10 mM solution of **3** or **8** in $CDCl_3$ caused ^{1}H NMR signal changes. For example, the α-proton of the pyridine ring of reference compound **8** showed a salt-formation-induced shift {$\Delta\delta$ = δ(observed) – δ(free **3** or **8**)} of 0.58 ppm.[13] This downfield-shift value remains constant upon dilution to 1.8 mM. Therefore, we assume that salt **8**•TsOH exists as a 1 + 1 salt under these conditions. On the other hand, $\Delta\delta$ values of salt **3**•TsOH depend on the concentration of the salt probably due to aggregation induced by the OH groups. For 1.8 mM, 10 mM and 20 mM solutions, $\Delta\delta$ values were found to be 0.36, 0.24 and 0.18, respectively; increasing the concentration decreases the downfield-shift values. This decrease of $\Delta\delta$ is consistent with the equilibrium shift from the 1 + 1 salt to the 2 + 2 salt in which the stacked geometry of the pyridinium rings (Figure 1) causes upfield shift of the α-proton due to an anisotropic effect. At the present stage, however, we have no evidence for the existence of the 2 + 2 salt in solution. Anyway, the OH groups of **3** paticipate in the aggregation processes of **3**•TsOH.

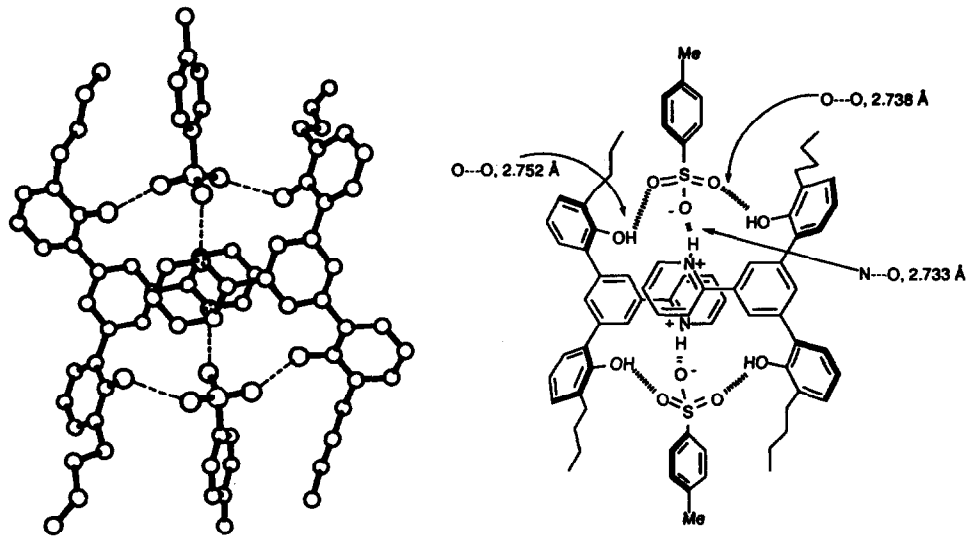


Figure 1. X-ray structure of salt 3•TsOH and hydrogen-bond distances.

The salt aggregation seems to be remarkable in a less polar solvent. For example, addition of 1 equiv of TsOH to a benzene-d_6 solution of **3** resulted in *upfield shift* of the α-proton of the pyridine ring ($\Delta\delta = -0.24$). This result indicates that downfield shift induced by protonation to the pyridine nitrogen is cancelled out by upfield shift induced by the anisotropic effect in the aggregates.

The presence of hydrogen bonds between the OH groups of **3** and the sulfonate anion in solution was confirmed by the following results. (1) The ^{1}H NMR signal of the OH protons of **3** (δ 5.35 in $CDCl_3$, 10 mM) became too broad to be observed upon addition of 1 equiv of TsOH. (2) The infrared absorption band of the νOH (3560 cm^{-1} in $CHCl_3$, 20 mM) became weak, and a broad band of 3260–3340 cm^{-1} appeared, upon additon of TsOH.

It should be noted that there are striking differences between pyridine derivative **3** and quinoline derivative **1** not only concerning the salt structure but concerning a kinetic process. For a 2:1 mixture of **1** and TsOH in $CDCl_3$, the exchange process between free **1** and salt-formed **1** is slow on the ^{1}H NMR time scale at 30 °C.[5] Therefore, two sets of signals (free **1** and salt-formed **1**) are observed. For a 2:1 mixture of **3** and TsOH, however, the exchange between free **3** and salt-formed **3** is fast on the NMR time scale even at –60 °C.

In conclusion, pyridine derivative **3** and TsOH form a 2 + 2 salt induced by hydrogen bonding in the solid state. This 2 + 2 salt may exist even in solution, although there are equilibria between some aggregates. The results described here show that salt aggregation can be controlled by hydrogen bonding, and that small structural changes of bases (*e.g.*, quinoline ring → pyridine ring) can also affect salt structures and acid–base equilibria in solvents of low polarity.

REFERENCES AND NOTES

1 Whitesides, G. M.; Mathias, J. P.; Seto, C. T. *Science* **1991**, *254*, 1312.

2 (a) Etter, M. C. *Acc. Chem. Res.* **1990**, *23*, 120. (b) Zerkowski, J. A.; Seto, C. T.; Wierda, D. A.; Whitesides, G. M. *J. Am. Chem. Soc.* **1990**, *112*, 9025. (c) Zerkowski, J. A.; Seto, C. T.; Whitesides, G. M. *J. Am. Chem. Soc.* **1992**, *114*, 5473. (d) Simard, M.; Su, D.; Wuest, J. D. *J. Am. Chem. Soc.* **1991**, *113*, 4696. (e) Geib, S. J.; Hirst, S. C.; Vicent, C.; Hamilton, A. D. *J. Chem. Soc., Chem. Commun.* **1991**, 1283. (f) Garcia-Tellado, F.; Geib, S. J.; Goswami, S.; Hamilton, A. D. *J. Am. Chem. Soc.* **1991**, *113*, 9265. (g) Geib, S. J.; Vicent, C.; Fan, E.; Hamilton, A. D. *Angew. Chem., Int. Ed. Engl.* **1993**, *32*, 119.

3 (a) Seto, C. T.; Whitesides, G. M.; *J. Am. Chem. Soc.* **1990**, *112*, 6409. (b) Seto, C. T.; Whitesides, G. M.; *J. Am. Chem. Soc.* **1991**, *113*, 712. (c) Zimmerman, S. C.; Duerr, B. F. *J. Org. Chem.* **1992**, *57*, 2215. (d) Yang, J.; Fan, E.; Geib, S. J.; Hamilton, A. D. *J. Am. Chem. Soc.* **1993**, *115*, 5314.

4 (a) Manabe, K.; Okamura, K.; Date, T.; Koga, K. *J. Am. Chem. Soc.* **1992**, *114*, 6940. (b) Manabe, K.; Okamura, K.; Date, T.; Koga, K. *J. Am. Chem. Soc.* **1993**, *115*, 5324.

5 Manabe, K.; Okamura, K.; Date, T.; Koga, K. *J. Org. Chem.* in press.

6 Hydrogen-bonding effects on salt formation of another pyridine derivative have been reported: Motomura, T.; Aoyama, Y. *J. Org. Chem.* **1991**, *56*, 7224.

7 Townsend, C. A.; Bloom, L. M. *Tetrahedron Lett.* **1981**, *22*, 3923.

8 (a) Negishi, E.; King, A. O.; Okukado, N. *J. Org. Chem.* **1977**, *42*, 1821. (b) Minato, A.; Tamao, K.; Hayashi, T.; Suzuki, K.; Kumada, M. *Tetrahedron Lett.* **1981**, *22*, 5319.

9 Kim, Y. H.; Webster, O. W. *J. Am. Chem. Soc.* **1990**, *112*, 4592.

10 Miyaura, N.; Yanagi, T.; Suzuki, A. *Synth. Commun.* **1981**, *11*, 513.

11 Analytical data for **3**: mp 150–151°C; ^{1}H NMR ($CDCl_3$, TMS, 270 MHz) δ 0.96 (6H, t, J = 7.3 Hz), 1.42 (4H, tq, J = 7.6 Hz and 7.3 Hz), 1.65 (4H, tt, J = 7.6 Hz and 7.6 Hz), 2.69 (4H, t, J = 7.6 Hz), 5.35 (2H, brs), 6.94 (2H, t, J = 7.6 Hz), 7.16 (2H, d, J = 7.3 Hz), 7.19 (2H, dd, J = 7.6 Hz and 1.7 Hz), 7.28 (1H, t, J = 5.0 Hz), 7.65 (1H, t, J = 1.7 Hz), 7.78 (2H, d, J = 5.0 Hz), 7.79 (1H, s), 8.12 (2H, d, J = 1.7 Hz), 8.70 (1H, d, J = 5.0 Hz); ^{13}C NMR ($CDCl_3$, TMS, 67.8 MHz) δ 14.0, 22.7, 30.1, 32.0, 120.4, 120.9, 122.7, 127.1, 127.4, 127.9, 129.5, 130.0, 130.6, 136.9, 139.2, 141.3, 149.9, 150.4, 156.6; IR (KBr) 3400, 2950, 2920, 2850, 1590, 1465, 1440, 1410, 1375, 1235, 1215 cm^{-1}; IR (chloroform) 3560, 2960, 2930, 1590, 1460, 1410, 1325, 1195, 1110 cm^{-1}; MS *m/z* 451 (M^+), 436 (M^+-Me), 422 (M^+-Et). Anal. Calcd for $C_{31}H_{33}NO_2$: C, 82.45; H, 7.36; N, 3.10. Found: C, 82.16; H, 7.38; N, 3.09.

12 **3**•TsOH crystallized in the triclinic space group $P\bar{1}$ (z = 2) with unit cell parameters a = 12.247(2) Å, b = 15.265(3) Å, c = 9.193(1) Å, α = 100.87(1)°, β = 103.44(1)°, γ = 90.30(2)°, and D_{calcd} = 1.26 g/cm^3. A total of 4869 reflections were observed using graphite-monochromated Cu Kα radiation (2θ values in the range of 0–120°). The structure was solved by direct methods using the computer program SIR 85 and the difference Fourier method. The final R value is 0.083.

13 We assume that complete salt formation between **3** or **8** and TsOH occurs because of strong acidity of TsOH, and that the salt exists as a contact ion pair because of low polarity of $CDCl_3$.

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