

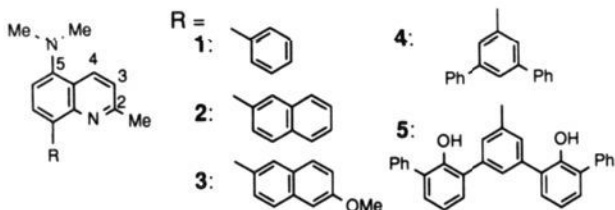
Effects of Ion-Pair Structure on Relative Basicity in Chloroform: Acid-Base Equilibria Controlled by Steric Repulsion, π -Stacking Interactions, and Hydrogen Bonding within an Ion Pair

Kei Manabe,^{1a} Kimio Okamura,^{1b} Tadamasu Date,^{1b} and Kenji Koga^{*,1a}

Faculty of Pharmaceutical Sciences
University of Tokyo
Hongo, Bunkyo-ku, Tokyo 113, Japan
Organic Chemistry Research Laboratory
Tanabe Seiyaku Co., Ltd., 2-2-50
Kawagishi, Toda, Saitama 335, Japan

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Acid-base equilibria in nonaqueous solvents have received much attention.² The strengths of acids and bases in such solvents depend not only on the electronic properties of the acids and bases but also on solvent properties^{2e,3} and ion-pair structure.^{2c} The control of ion-pair structure,⁴ which can make it possible to alter the relative acidity and basicity. Recently, we have reported that a quinoline derivative, having hydroxyl groups, and a phosphonic acid monoester form a contact ion pair of well-defined structure via three hydrogen-bonding interactions.⁵ In the course of developing this salt-formation system, we have synthesized compounds 1-5, which have two kinds of basic nitrogens (i.e., ring N and 5-NMe₂), and studied the effects of ion-pair structure on the relative basicity of the ring N and the NMe₂ group. Here we report that the preference of the protonation sites of these compounds is controlled by "intra-ion-pair interactions", which include steric repulsion, electron-donor/acceptor (EDA) type π -stacking interactions, and hydrogen bonding.



We studied salt formation between 1-5 and acids by ¹H NMR spectroscopy⁶ at -60 °C. The acids used were D-(+)-camphor-sulfonic acid (CSA), *p*-toluenesulfonic acid (TsOH), and picric acid (PA). In a CDCl₃ solution of a 1:1 mixture of each base and acid, two sets of signals were observed. We conclude that one corresponds to the salt (RN) protonated at the ring N and the other corresponds to the salt (DM) protonated at the NMe₂ group. These assignments were made on the basis of salt-formation induced shifts ($\Delta\delta = \delta(\text{observed}) - \delta(\text{free base})$) of 2-Me and 5-NMe₂; RN shows a large $\Delta\delta$ of 2-Me (0.58-0.31 ppm)⁷ and a small $\Delta\delta$ of 5-NMe₂ (0.10-0.06), and DM shows a small $\Delta\delta$ of 2-Me (0.05-0.02) and a large $\Delta\delta$ of 5-NMe₂ (0.76-

Table I. Ratios of Ring N Protonation and 5-NMe₂ Protonation (RN:DM)^a in CDCl₃ at -60 °C^b

	1	2	3	4	5
CSA	6:4	4:6	4:6	1:9	10:0
TsOH	9:1	8:2	8:2	5:5	10:0
PA	10:0	10:0	10:0	10:0	

^a Determined by the integration of 5-NMe₂ signals. ^b Each 0.75 mM.

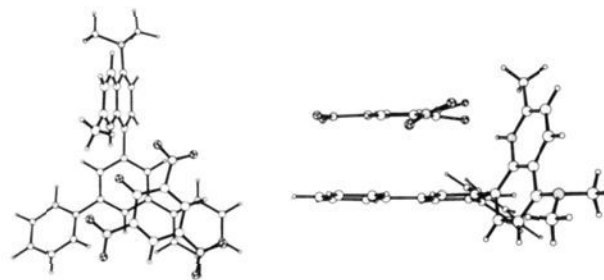
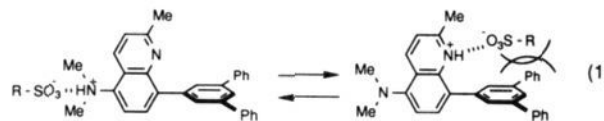


Figure 1. Two views of the X-ray structure of 4-PA.

0.61).⁸ We assume that each salt exists as a contact ion pair in which a hydrogen bond (N⁺H...O⁻) is formed.

Table I lists the ratios of RN and DM. They show the following features:

(1) In the salt formation of 1-4 with the sulfonic acids, increasing the size of the substituents on the quinoline rings increases the proportions of DM. These results indicate the importance of the steric factor for the equilibrium position (eq 1); the steric repulsion between the substituents and the sulfonates mainly affects the relative basicity of the nitrogens in these cases.



(2) In the salt formation of 1-4 with PA, only RN was observed. Furthermore, the ratio of the binding constants^{9,10} of 1-4 with PA was determined to be 1:3:66:88 by the competitive salt-formation experiments (-60 °C) in which 1:1:1 mixtures of 1-3, 4, and PA were used. These results indicate that EDA type π -stacking interactions¹¹ between the aromatic substituents and π -deficient picrate as well as steric factors play an important role for the stability of the salt. The X-ray structure of 4-PA (Figure 1)¹² confirmed the presence of π -stacking interactions. The picrate and one biphenyl unit of 4 adopt a stacked geometry; the distances between the picrate plane and the carbon atoms which form the single bond in the biphenyl unit are 3.42 and 3.43 Å, and the two benzene rings of the biphenyl unit are almost in-plane, with a

(8) When CSA was used, DM showed two diastereotopic methyl groups for 5-NMe₂ (0.13-0.14 ppm apart from each other) while RN showed only one methyl signal for 5-NMe₂.

(9) The binding constant of 4 with PA at 30 °C was found to be 1.3×10^4 M⁻¹ by an NMR titration. We assume that few free ions, if any, exist because of the low polarity of chloroform. See: Reichardt, C. *Solvents and Solvent Effects in Organic Chemistry*, 2nd ed.; VCH: Weinheim, 1988.

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(6) Tetramethylsilane (TMS) was used as an internal standard.

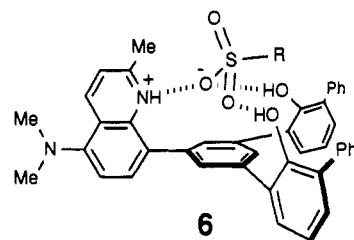
(7) For the related compound⁵ in which a hydrogen atom was substituted for the NMe₂ group of 4, only one kind of salt was observed upon the addition of 1 equiv of TsOH ($\Delta\delta$ of 2-Me: 0.60 ppm).

dihedral angle of 1° . The phenoxide oxygen and the quinolinium N^+H form a hydrogen bond ($N\cdots O$ distance 2.80 Å).

(3) In the case of **5** with the sulfonic acids, only RN was observed. On the basis of the X-ray structure of the related compound,⁵ we conclude that the ion-pair structure **6**, which is stabilized by three hydrogen bonds, causes the preference for the ring N protonation. The observation that the OH protons of **5** shifted downfield by 1.78–1.85 ppm upon the addition of the acids supports the presence of hydrogen bonding.

It is concluded that the interactions within an ion pair significantly affect the relative basicity of two nitrogens in a molecule. The results described here can contribute to the understanding of acid–base equilibria in solvents of low polarity

(12) **4**·PA crystallized in the monoclinic space group $P2_1/c$ ($Z = 4$) with unit cell parameters $a = 11.011(3)$ Å, $b = 13.307(2)$ Å, $c = 21.458(2)$ Å, $\beta = 98.75(1)^\circ$, and $D_{\text{calcd}} = 1.376$ g/cm³. A total of 4682 reflections were observed using graphite-monochromated Cu $K\alpha$ radiation (2θ value in the range 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 0.086



as well as to the development of artificial receptors for anionic substrates.

Supplementary Material Available: Listings of experimental details for the syntheses of **1–5** and details of the X-ray analysis, plots of atom labels, and tables of atomic coordinates, equivalent isotropic thermal parameters, bond lengths, and bond angles for **4**·PA (20 pages); table of observed and calculated structure factors for **4**·PA (20 pages). Ordering information is given on any current masthead page.