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Effect of Conformation of Molecules on Molecular Interaction. II.[1] Nicotinamides and Pyridine Esters

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In a series of solubility studies of pyridine derivatives with 8-methoxycaffeine in aqueous solution, an extent of molecular interaction of N,N-dimethylnicotinamide (I) was found to be much less than those of unsubstituted and N-monomethylnicotinamide. Degree of complexation of 3-acetoxypyridine (II) was revealed to be much less than that of methyl nicotinate. Reduced complexing tendencies of I and II were attributed to nonplanar structures of these compounds in solution.

In an earlier study Nakano and Higuchi[3] found that aromatic N,N-dimethylamides interact with theophylline and riboflavin to much less extent than N-unsubstituted and N-monosubstituted amides. They attributed this reduction to unfavorable conformation of aromatic N,N-dimethylamides for molecular interaction.

In a present study we have examined biologically important nicotinamides in order to obtain more information in different series of compounds and extended it to an ester type substituent in pyridine compounds. While coplanar structure of ester group with pyridine ring is possible in methyl nicotinate (methyl ester of nicotinic acid), an ester group in 3-acetoxypyridine (pyridyl ester of acetic acid) cannot lie on the same plane as pyridine ring as can be shown by a scale molecular model. In the latter circumstance the rotation of the substituent group about the pyridine-oxygen bond is expected,[3] preventing it from molecular interaction with added complexing agents. A possible proof for these considerations are attempted.

Experimental

Materials——Reagents used were all from commercial sources. Nicotinamide (recrystallized from benzene, mp 129°), N-methylnicotinamide (recrystallized from benzene, mp 104°), caffeine (recrystallized from water, mp 237°), 8-methoxycaffeine (recrystallized from methanol, mp 179°), N,N-dimethylnicotinamide (vaccum distilled, bp 155° (10 mmHg)), methyl nicotinate (vacuum distilled, bp 70° (3 mmHg)), and 3-acetoxypyridine (3-pyridyl acetate, vacuum distilled, bp 92° (9 mmHg)).

Solubility Studies——Solubility of 8-methoxycaffeine in distilled water (pH around 5.8, 25°) was determined by the same procedure as that described previously[3,4]. Spectrophotometric determination of 8-methoxycaffeine was made at 281 mμ. Small absorbance due to the presence of known amount of pyridine derivatives was substracted from the total absorbance.

Proton Magnetic Resonance Studies——Proton magnetic resonance (pmr) spectra of caffeine (10^{-2}M) in water with and without nicotinamides were recorded on Varian A-60A spectrometer at the temperature of the probe (38°). Methyl signal of tertiary butyl alcohol was used as an internal reference.

pK_a Measurement——A dissociation constant of a conjugated acid of 3-acetoxypyridine was measured by the standard spectrophotometric method.[5] pH was adjusted either with hydrochloric acid or with sodium bicarbonate, and pH values were determined for the solution just after the absorption spectra were taken.

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[1] Part I: M. Nakano and T. Higuchi, *J. Pharm. Sci.*, **57**, 183 (1968).

[2] Location: *Yoshida, Sakyo-ku, Kyoto.*

[3] M. Nakano and T. Higuchi, *J. Pharm. Sci.*, **57**, 183 (1968).

[4] T. Higuchi and D.A. Zuck, *J. Am. Pharm. Assoc.*, Sci. Ed., **42**, 132 (1953).

[5] A. Albert and E.P. Serjeant, "Ionization Constants of Acids and Bases, A Laboratory Manual," Methuen & Co., Ltd., London, 1962, pp. 69—92.

Results

Solubility diagrams of 8-methoxycaffeine in the presence of nicotinamides are recorded in Fig. 1.

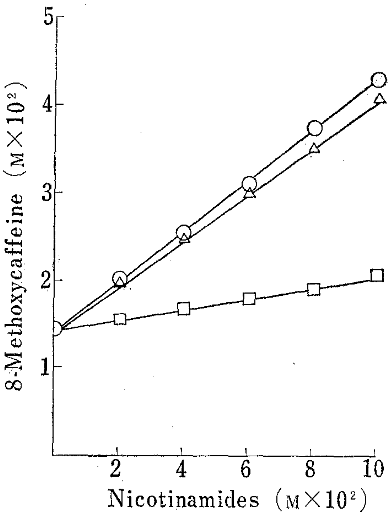

Fig. 1. Solubility of 8-Methoxycaffeine in the Presence of Nicotinamide (○), N-Methylnicotinamide (△), and N,N-Dimethylnicotinamide (□)

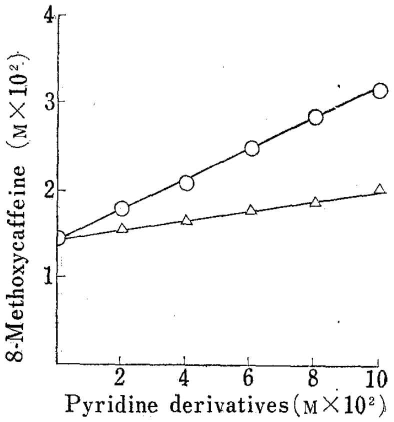

Fig. 2. Solubility of 8-Methoxycaffeine in the Presence of Methyl Nicotinate (○) and 3-Acetoxypyridine (△)

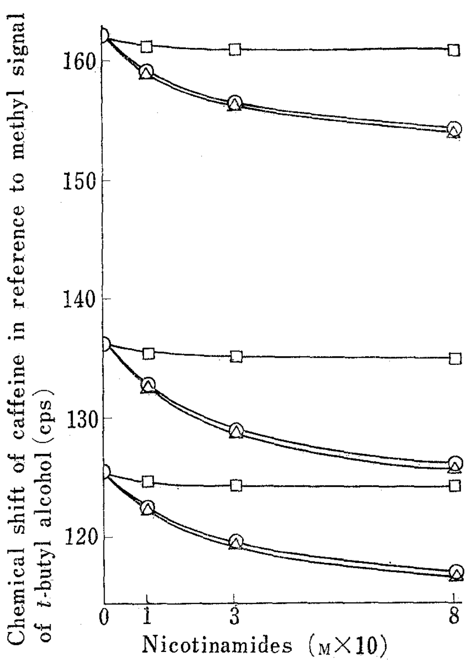

Fig. 3. Chemical Shift of Methyl Groups in Caffeine in the Presence of Increasing Amounts of Nicotinamides at 38° in Water

Key: ○; Nicotinamide, △; N-Methylnicotinamide, □; N,N-Dimethylnicotinamide. From the Bottom, Methyl at 1, Methyl at 3, and Methyl at 7 of Caffeine, respectively.

Table I. Stability Constants for Complexes of 8-Methoxycaffeine with Pyridine Derivatives in Water at 25°

Compound	Stability Constant (M^{-1})
Nicotinamide	28
N-Methylnicotinamide	25
N,N-Dimethylnicotinamide	5
Methyl Nicotinate	14
3-Acetoxypyridine	4

Those in the presence of methyl nicotinate or 3-acetoxypyridine are shown in Fig. 2.

Stability constants computed by the phase solubility technique[6] are presented in Table I.

The positions of three methyl signals of caffeine molecule in the presence of three nicotinamides in water are recorded in Fig. 3.

An approximate pK_a of a conjugated acid of 3-acetoxypyridine was estimated to be 3.1 at 25°.

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[6] T. Higuchi and K.A. Connors, in "Advances in Analytical Chemistry and Instrumentation," Vol. 4, C.N. Reilley, ed., Interscience Publishers, Inc., New York, N.Y., 1965, pp. 144—148.

Discussion

Although N,N-dialkylnicotinamides have been tested as solubilizers for some drugs[7] in water because of much solubility of the amides in water, the outcome does not seem to be very hopeful. This failure can be readily understood from the results shown in Fig. 1 and Table I. Namely much reduction in complexing ability was observed in N,N-dimethylnicotinamide. The reason for this reduction can be rationalized by the nonplanar structure of the compound in solution because a planar structure is not possible in such a compound as this.[3] By the same reason N,N-diethylnicotinamide (nikethamide) is poor complexing agent.[8] The solubility studies were substantiated by pmr study (Fig. 3), where N,N-dimethylnicotinamide shifted the methyl signals of caffeine molecule to much less extent than less substituted amides. Although N-methylbenzamides were shown to be a little stronger complexing agents than unsubstituted benzamides in the interaction with theophylline,[3] complexation of N-methylnicotinamide with 8-methoxycaffeine resulted in small reduction in stability constant in comparison with unsubstituted nicotinamide.

A poor solubilizing power of 3-acetoxypyridine in comparison with methyl nicotinate may also be understood by the same reasoning, nonplanar structure of the former.

Imidazole is known to catalize the hydrolysis of *p*-nitrophenyl acetate,[9,10] while hydrolysis of methyl cinnamate[11,12] was shown to be slowed down in the presence of imidazole. This difference may be rationalized by the present theory; while there is little complexation between *p*-nitrophenyl acetate and imidazole because of nonplanar structure of the former, methyl cinnamate forms complex with imidazole, which is nonreactive to hydroxide ion attack.

Since it is known that ionization of complexing agent affects much an extent of complex formation,[13] pH of the solution and pK_a's of the pyridine derivatives were checked. At around pH 5.8, where solubility studies and pmr determinations were undertaken, all employed compounds are more than 99.7% in nonprotonated form.

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[7] for example, P. Lechart and A. Boime, Fr. Patent 1306607 (Oct. 19, 1962).

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[12] J.A. Mollica, Jr. and K.A. Connors, *J. Am. Chem. Soc.*, **89**, 308 (1967).

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