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Interaction of N-Methyl-2-pyrrolidone with Aminobenzoic Acids in Solution and in Solid State[1,2]

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The interaction of N-methyl-2-pyrrolidone (NMP) with aminobenzoic acids was studied, observing the effect on the solubility of aminobenzoic acids in ether in comparison with that of N-ethyl-2-pyrrolidone (NEP). *p*-Aminobenzoic acid (PABA) and *p*-aminosalycilic acid (PAS) formed slightly soluble complexes in ether with NMP, while the other aminobenzoic acids formed soluble complexes in ether.

From the solubility data, the stoichiometrical ratio and the stability constant K of the formation of complex were calculated. K value was strongly affected by the orientation of the substituent group and the existence of the hydroxyl group in aminobenzoic acid, as the decreasing order for NMP-aminobenzoic acids complexes was as follows: PABA> anthranilic acid (ANA)>*m*-aminobenzoic acid. K value for NEP complexes decreased in comparison with that for NMP complexes. This may be due to the steric hindrance of ethyl group in NEP.

On the other hand, the complex formation in solid phase was recognized in NMP–PABA, NMP–PAS, and NMP–ANA systems by powder X-ray diffractometry and IR absorption spectroscopy.

The dissolution rate of these solid complexes was studied by stationary disk method, and it was found that the complexes dissolved fast compared with the respective original compounds.

These results suggested that the complex formation with NMP may enhance the bioavailability of drugs.

Keywords——N-methyl-2-pyrrolidone; aminobenzoic acid; interaction; complex; solubility; stoichiometry; stability constant; dissolution rate; X-ray diffractometry; IR spectroscopy

N-Methyl-2-pyrrolidone (NMP) is a molecular unit of polyvinylpyrrolidone (PVP) which is known to form complexes with a variety of compounds and has widely been used in various fields.[4] In this connection, NMP is also expected to form complexes with various drugs.[5]

Furthermore, there is no report concerning the toxicity of NMP. Therefore, NMP may afford some means of increasing the usefulness of drugs.

The present study was attempted to investigate the interaction of NMP and its ethyl analog, N-ethyl-2-pyrrolidone (NEP), with aminobenzoic acids, on the basis of the effect of NMP or NEP on the solubility of aminobenzoic acids in organic solvents. The stoichiometry of complexes and the apparent stability constant of the formation of the complexes are discussed.

Moreover, an investigation was made to obtain the complexes with NMP in solid state. Such complexes were confirmed by powder X-ray diffractometry and infra-red (IR) absorption

1) This paper forms Part V of "Pharmaceutical Interactions in Dosage Forms and Processing." The preceding paper, Part IV: M. Kurozumi, N. Nambu, and T. Nagai, *Chem. Pharm. Bull.* (Tokyo), **23**, 3062 (1975).

2) A part of this work was presented at the 95th Annual Meeting of Pharmaceutical Society of Japan, Nishinomiya, April 1975.

3) Location: *Ebara-2-4-41, Shinagawa-ku, Tokyo 142, Japan.*

4) S. Shimabayashi, *Hyohmen*, **12**, 1 (1973); A.P. Simonelli, S.C. Mehta, and W.I. Higuchi, *J. Pharm. Sci.*, **58**, 538 (1969).

5) K. Kono, T. Nagai, and H. Nogami, *Chem. Pharm. Bull.* (Tokyo), **21**, 366 (1973).

spectrophotometry. And their dissolution profiles in water also studied by a stationary disk method.

Experimental

Materials——*p*-Aminobenzoic acid (PABA), *m*-aminobenzoic acid (MABA), and anthranilic acid (ANA) were used after recrystallization from water. *p*-Aminosalicylic acid (PAS), NMP and NEP of reagent grade were used without further treatment.

Phase Solubility Studies——The given amounts of each substrate and the various amounts of ligands in 10 ml of ether,[6] as shown in Table I, were sealed in vials and incubated for 48 hr at 10°. Then, 1 ml of the

Table I. Amount of Substrate and Ligand in 10 ml of Ether in the Solubility Studies

Substrate	Ligand	Substrate	Ligand
PABA, 0.24 g	NMP, 0—0.18 g	PAS, 0.20 g	NEP, 0—0.20 g
PABA, 0.20 g	NEP, 0—0.14 g	MABA, 0.18 g	NMP, 0—0.10 g
PAS, 0.20 g	NMP, 0—0.18 g	ANA, 2.00 g	NMP, 0—0.16 g

supernatant was sampled out, and ether was evaporated at 50°. After the residue was dissolved in water or ethanol, the concentration was determined spectrophotometrically (according to ultraviolet (UV) absorption method) using a Hitachi 124 spectrophotometer. The stoichiometry and the stability constant were calculated from the solubility diagram.[7]

Preparation of NMP Complexes in Solid State

NMP-PABA Complex——A weighed amount of dried PABA was dissolved in the minimum volume of ether, mixed with the solution of the stoichiometrical amount of NMP in ether, stirred well for 2 hr, and then kept standing at room temperature for 24 hr. The microcrystalline particles formed were filtered out, washed with ether and dried under vacuum.

NMP-PAS Complex——This was prepared according to the same way as NMP–PABA complex.

NMP-ANA Complex——A weighed amount of dried ANA was dissolved in the minimum volume of ether, mixed with the solution of the stoichiometrical amount of NMP in ether, stirred well for 24 hr at room temperature, and then evaporated to dryness. The crust formed was pulverized thoroughly and dried under vacuum.

In case of MABA with NMP, no complex was formed in solid state.

Powder X-Ray Diffraction Studies——Powder X-ray diffractometry was carried out using a Rigaku Denki Geigerflex Model D-2 diffractometer by Ni-filtered Cu–Kα radition.

IR Absorption Spectroscopy——This was done using a Shimadzu Model IR-400 infrared spectrophotometer.

Procedure for the Determination of the Dissolution Rate——The dissolution rate was determined by a stationary disk method, using the apparatus described in the previous paper.[8] Three tenths gram of the sample was compressed in a cylindrical die by a Shimadzu hydraulic press for KBr tablets for IR spectroscopy. The compressed disk was not ejected out of the die, and the die cavity was stoppered. The die wearing the compressed disk was set on the dissolution apparatus so as to make the disk face to the stirrer. Every experiment was done under the following conditions: water as the dissolution medium; at 37°; 300 rpm of rotating velocity of the stirrer; 1.0 cm diameter of the disk of sample compressed under 100 kg/cm^2. One milliliter of the solution was sampled out at appropriate time intervals, and diluted appropriately with the water of the same temperature for spectrophotometric assay. The concentration of samples was determined according to UV absorption method using a Hitachi 124 spectrophotometer.

Result and Discussion

Phase Solubility Diagrams

As shown in Fig. 1 and 2, the solubilities of PABA and PAS were found to increase with the addition of NMP, reaching the respective certain values. Furthermore, the crystalline complexes precipitated at the higher concentrations of NMP. The addition of NEP also made

6) Ether was chosen as the solvent because it seemed most suitable according to the preliminary experiment.
7) T. Higuchi and K.A. Connors, *Advan. Anal. Chem. Instr.*, **4**, 117 (1965).
8) Y. Hamada, N. Nambu, and T. Nagai, *Chem. Pharm. Bull.* (Tokyo), **23**, 1205 (1975).

the solubility of PABA increase, but not that of PAS. The solubility of ANA and MABA also increased with the addition of NMP. From the data in the plateau region of the respective diagrams in Fig. 1 and 2, the stoichiometrical ratios of NMP–PABA and NMP–PAS

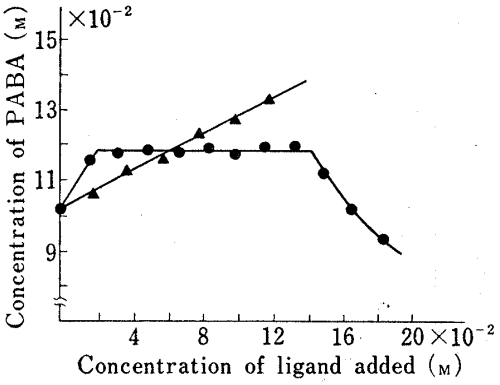

Fig. 1. Solubility of PABA in Ether Solution at 10° as a Function of NMP (●) or NEP (▲) added

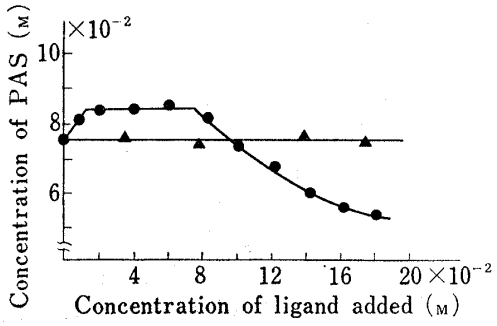

Fig. 2. Solubility of PAS in Ether Solution at 10° as a Function of NMP (●) or NEP (▲) added

complexes were determined to be 1:1 for both of them, and also the stability constants for both systems were calculated. For the other systems, in which the solubility of substrate increased linearly with the increase of the concentration of ligand, the stability constants were calculated assuming the formation of 1:1 complex. The data are summarized in Table II. For the complexes NMP-aminobenzoic acids, the decreasing order of K value was as

Table II. Complex Formation of PABA, PAS, MABA, and ANA with NMP or NEP at 10° in Ether

Substrate	Ligand	Stoichiometry of complex	Stability const. K (M^{-1})
PABA	NMP	1:1	61.64
PAS		1:1	24.99
ANA		—	41.96
MABA		—	11.76
PABA	NEP	—	3.36
PAS		—	—

follows: PABA>ANA>MABA, indicating that the interaction is strongly affected by the orientation of the substituent group of substrate. Moreover, the fact that the NMP–PABA complex gave a very large K value compared with NMP–PAS complex and similarly NEP–PABA complex did compared with NEP–PAS complex indicated that the interaction was markedly lowered by the existence of hydroxyl group in PAS. On the other hand, K values for NEP–PABA and NEP–PAS complexes decreased or were negligible in comparison with those for the NMP complexes. This result is considered due to the steric hindrance of ethyl group in NEP, because the respective carbonyl groups of NMP and NEP, which have relation to the interaction with the amino groups of substrates as will be described later, may hold almost the same electronic situation.

Formation of the Complexes in Solid State

As an example, Fig. 3 shows the powder X-ray diffraction patterns of PABA and the PABA–NMP complex. These patterns are different from each other, and indicated that the interaction of PABA with NMP gave a new solid phase. Moreover, the IR absorption spectra also indicated the existence of interaction in solid phase, as shown in Fig. 5. Regard-

ing the solid complexes of NMP with PAS and ANA, the formations were confirmed in the same way. Moreover, it was recognized that these complexes were stable in solid state when kept in a desiccator.

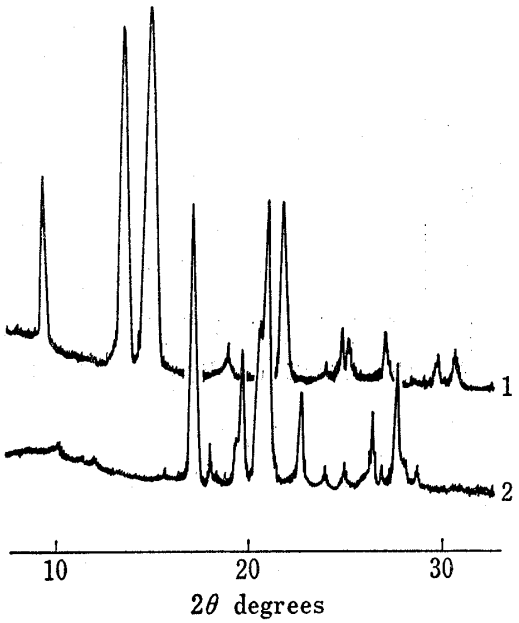

Fig. 3. Powder X-Ray Diffraction Patterns of PABA and NMP–PABA Complex by Cu-Kα Radiation

1: PABA
2: NMP–PABA complex

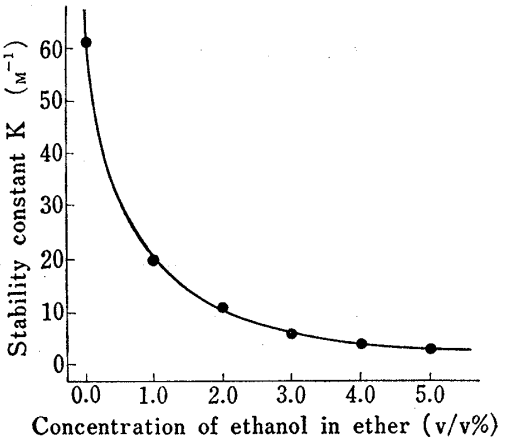

Fig. 4. Relationship between Stability Constant K of NMP–PABA Complex in Various Polarities of Solvents prepared by Mixing Ether and Ethanol

Consideration of the Binding Mechanism of Complex

When the complex formation of NMP–PABA was investigated in various polarities of solvents prepared by mixing ether and ethanol, K value decreased with the increase of the concentration of ethanol in ether (v/v%), as shown in Fig. 4. A similar tendency was observed

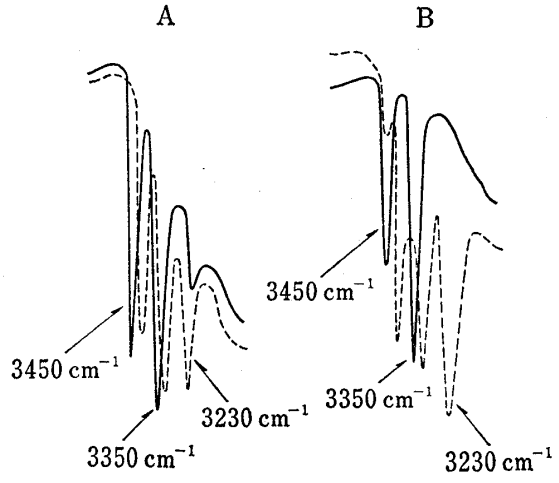

Fig. 5. IR Absorption Spectra of PABA, NMP–PABA Complex, PAS, and NMP–PAS Complex according to KBr Disk Method

A:—; intact PABA, ---; NMP–PABA complex
B:—; intact PAS, ---; NMP–PAS complex

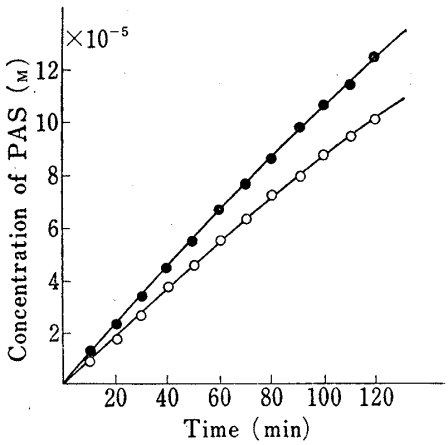

Fig. 6. Initial Dissolution Curves of PAS (○) and NMP–PAS Complex (●) in 250 ml Water at 37° by Stationary Disk Method

with NMP–PAS complex. This result indicated that the hydrogen bonding may be a primary force of the formation of these complexes.[9]

Figure 5 shows the IR absorption spectra of NMP–PABA and NMP–PAS complexes according to KBr disk method. The NH stretching bands of PABA and PAS at 3450 and 3350 cm^{-1} shifted to a lower wavenumber region in the respective complexes with NMP. Moreover, a band due to imino group appeared at 3230 cm^{-1} in both the complexes. These results suggested the hydrogen bonding between amino group of PABA or PAS and carbonyl group of NMP may participate in the formation of the respective complexes. However, the fact that any remarkable change of carbonyl bands of NMP in these complexes was not detected, remains to be explained. Therefore, further examination should be made for a clear explanation of the binding mechanism.

Dissolution Rate of the Complexes in Water in Comparison with Original Compounds

The dissolution rate of complexes was studied by stationary disk method after the formation of complex was confirmed in solid phase by powder X-ray diffractometry and IR absorption spectrophotometry. Figure 6 shows the dissolution profile of NMP–PAS complex. The dissolution rate of NMP–PAS complex was fast compared with that of intact PAS. The similar tendency was observed in the other complexes. On the other hand, the dissolution rates of intact PABA, PAS, and ANA in 1% NMP solution almost coincided with that in water. Namely, the solubilizing effect was not observed for intact PABA, PAS, and ANA in solution of NMP. Therefore, it may be considered that the increase in dissolution rate of these complexes was caused by the interaction of NMP with PABA, PAS and ANA in solid state.

The above results suggested that the complex formation with NMP may enhance the bioavailability of drugs.

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9) M. Otagiri, K. Uekama, K. Ikeda, and S. Onodera, *Chem. Pharm. Bull.* (Tokyo), **23**, 3228 (1975).