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Molecular Complex Formation between N-Vinyl-2-pyrrolidone and Ajmaline[1)]

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The influence of d_6-benzene on the nuclear magnetic resonance (NMR) spectra of N-vinyl-2-pyrrolidone (VP) was investigated. It was found that the orientation of amide group in VP to benzene was different from that in dimethylformamide (DMF) or methylpyrrolidone (MP) owing to repulsion of π-electron between vinyl group in VP and benzene ring. Subsequently the complex formation between DMF, MP, or VP and aromatic ring in ajmaline was also confirmed, in which the individual amide group in DMF, MP, or VP was oriented against aromatic ring in ajmaline as well as against benzene.

In addition, it was recognized that polyvinylpyrrolidone (PVP) formed the complex with benzene in a slightly different orientation from that of VP with benzene because of the steric hindrance of PVP. It became apparent, however, that the resulting orientation was similar to that between VP and benzene when the chain length of PVP was relatively shorter. With increasing molecular weight of PVP, pyrrolidone ring would be considered to tend to lie at a certain angle to the plane of the benzene ring.

Moreover, the complex formation of DMF, MP, or VP with ajmaline was regarded to be weaker than that with benzene from the association constant (Kn). Consequently, on the basis of the Kn value of PVP with benzene, the possibility of interaction between PVP and ajmaline was discussed.

Keywords——polyvinylpyrrolidone; N-vinyl-2-pyrrolidone; N-methyl-2-pyrrolidone; N,N-dimethylformamide; ajmaline; nuclear magnetic resonance (NMR) spectra; solvent effect; molecular complex; coprecipitate; association constant

Polyvinylpyrrolidone (PVP) is known to interact with various drugs, and to enhance the dissolution rate of water insoluble drugs from its coprecipitates by forming the solid solution.[3)] However, the mechanism of these interactions has not yet been clarified.

In the previous paper,[4)] the hydrogen bond formation between PVP and ajmaline was proposed. But it was suggested that the hydrogen bond was not the only decisive factor for these interactions in chloroform on the basis of the increased dissolution characteristics of diacetylajmaline-PVP coprecipitate, in which the hydrogen bond sites of ajmaline were protected.

Molyneux *et al.*[5)] described the importance of interaction between various aromatic compounds and polar groups in PVP, and Eliassaf *et al.*[6)] reported that the phenyl ring of aromatic cosolute is close to the backbone of PVP and acidic groups pointing toward the water molecules in aqueous PVP solution. From these points of view, it was suggested that the interaction between polar groups in PVP and aromatic ring in ajmaline could not be excluded.

In this paper, the investigation for complex formation between N-vinyl-2-pyrrolidone (VP), monomer units of PVP, and benzene or ajmaline was carried out by using nuclear magnetic resonance (NMR) spectra. As the results, the complex formation between VP and benzene or aromatic ring in ajmaline was ascertained, though these orientations were different from those between N-methyl-2-pyrrolidone (MP) or N,N-dimethylformamide (DMF) and

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3) M. Mayersohn and M. Gibaldi, *J. Pharm. Sci.*, **55**, 1323 (1966).
4) H. Matsumaru, S. Tsuchiya and T. Hosono, *Chem. Pharm. Bull.* (Tokyo), **25**, 2504 (1977).
5) P. Molyneux and H.P. Frank, *J. Am. Chem. Soc.*, **83**, 3169 (1961).
6) J. Eliassaf, F. Eriksson and F.R. Eirich, *J. Polym. Sci.*, **47**, 193 (1960).

benzene or ajmaline. Moreover, it was found that PVP formed the complex with benzene in a slightly different manner of orientation from that of VP and benzene. On the basis of these results, the possibility of interaction between PVP and aromatic ring in ajmaline was discussed.

Experimental

Materials——DMF, MP, VP, PVP K-15, and ajmaline employed in this study were commercial grade. To obtain PVP of lower molecular weights, acetone fractionations were performed.[7] The mean molecular weights of the fractions were evaluated to be about 930 (PVP-I), 1700 (PVP-II), and 2000 (PVP-III) by viscosity at 30°.

Determination of NMR Spectra——The NMR spectra were obtained by a JNM-PS-100 spectrometer. The specimens dissolved in spectral grade deuterochloroform ($CDCl_3$) and/or deuterobenzene (C_6D_6) which contained 1% tetramethylsilane (TMS) as an internal reference. In the case of PVP specimens, a drop of deuterowater (D_2O) was added to conceal the signal caused by a trace of water contained in PVP. The chemical shifts of the broad signals in PVP were regarded as one-half of the value of line width. These chemical shifts are accurate to at least ±0.1 Hz.

Results

1) Solvent Effects of Benzene on VP, MP, and DMF

The influence of d_6-benzene on the chemical shifts for each of the protons of 0.225 M VP in $CDCl_3$ is shown in Fig. 1. With an increase of the concentration of d_6-benzene added to $CDCl_3$, all the signals of protons in VP molecule shifted gradually. In 0.98 mol fractions of d_6-benzene, the signal of 2.12 ppm of δ in $CDCl_3$ which derived from 4-H shifted most largely by 1.0 ppm. The signals of 5-H, 3-H, and terminal vinyl protons in VP shifted to upfield

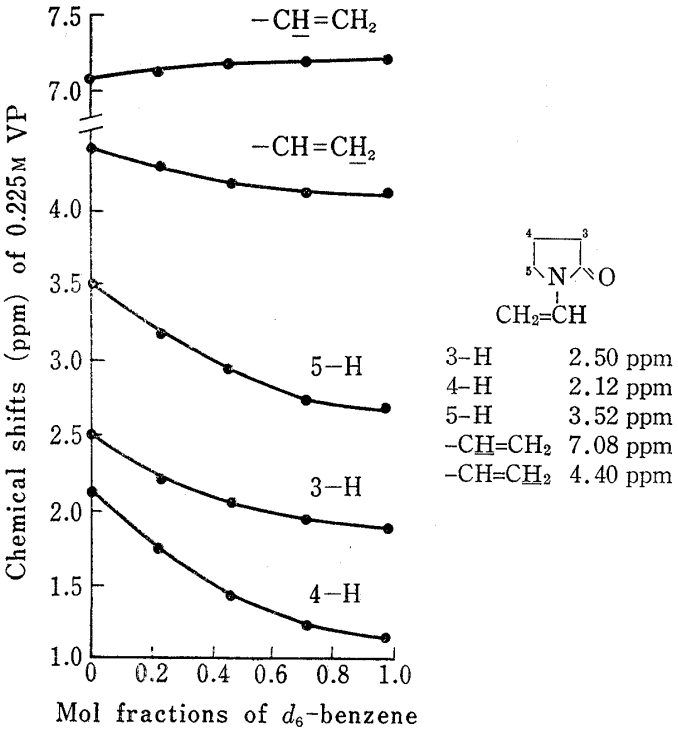

Fig. 1. Solvent Shifts (Δ) of VP Protons in $CDCl_3$ Solution induced by Various Mol Fractions of d_6-Benzene (0, 0.23, 0.47, 0.72, and 0.98 mol fractions)

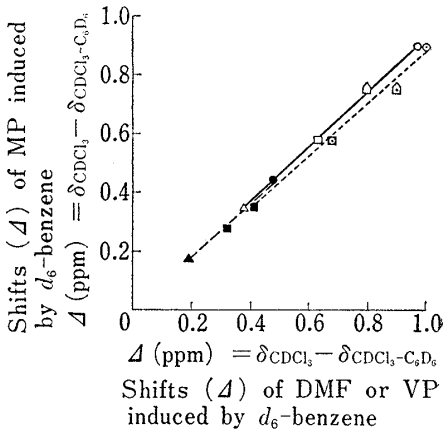

Fig. 2. Relationships of Solvent Shifts (Δ) between DMF or VP and MP on Addition of Various Concentrations of d_6-Benzene

The solid or broken line represents the plots between *trans*-CH_3 in DMF and 5-H in MP or between *cis*-CH_3 in DMF and 1-CH_3 in MP, respectively. The plots between 4-H in VP and 5-H in MP are shown in dotted line. The triangle, square, pentagon, and circle stand for the added concentration of d_6-benzene; 2.78, 5.56, 8.34, and 11.12 M respectively.

7) B. Jirgensons, *J. Polym. Sci.*, **8**, 519 (1951).

by 0.85, 0.61, and 0.30 ppm, respectively. But only the signal of vinyl proton adjacent to nitrogen atom shifted to downfield by 0.12 ppm. Subsequently, the influence of d_6-benzene on DMF or MP was investigated in the same manner. The signals of MP were shifted to upfield in the order of 5-, 4-, 3-H, 1-CH_3, and in the case of DMF the order was as follows; *trans*-, *cis*-CH_3, formyl proton. These solvent shifts (Δ) seemed to be responsible for some complex formation between VP, MP, or DMF and benzene.

Therefore, in order to investigate the strength and orientation of these complexes, the solvent shifts of 5-H and 1-CH_3 groups were plotted against those of *trans*- and *cis*-CH_3 groups in DMF, respectively, as shown in Fig. 2 (solid and broken lines). On the other hand, from the fact that 4-H was more largely influenced by d_6-benzene than 5-H in VP, it appeared that the orientation of VP was different from that of MP against benzene. Accordingly, to compare the strength of interaction between VP or MP and benzene, the solvent shifts of

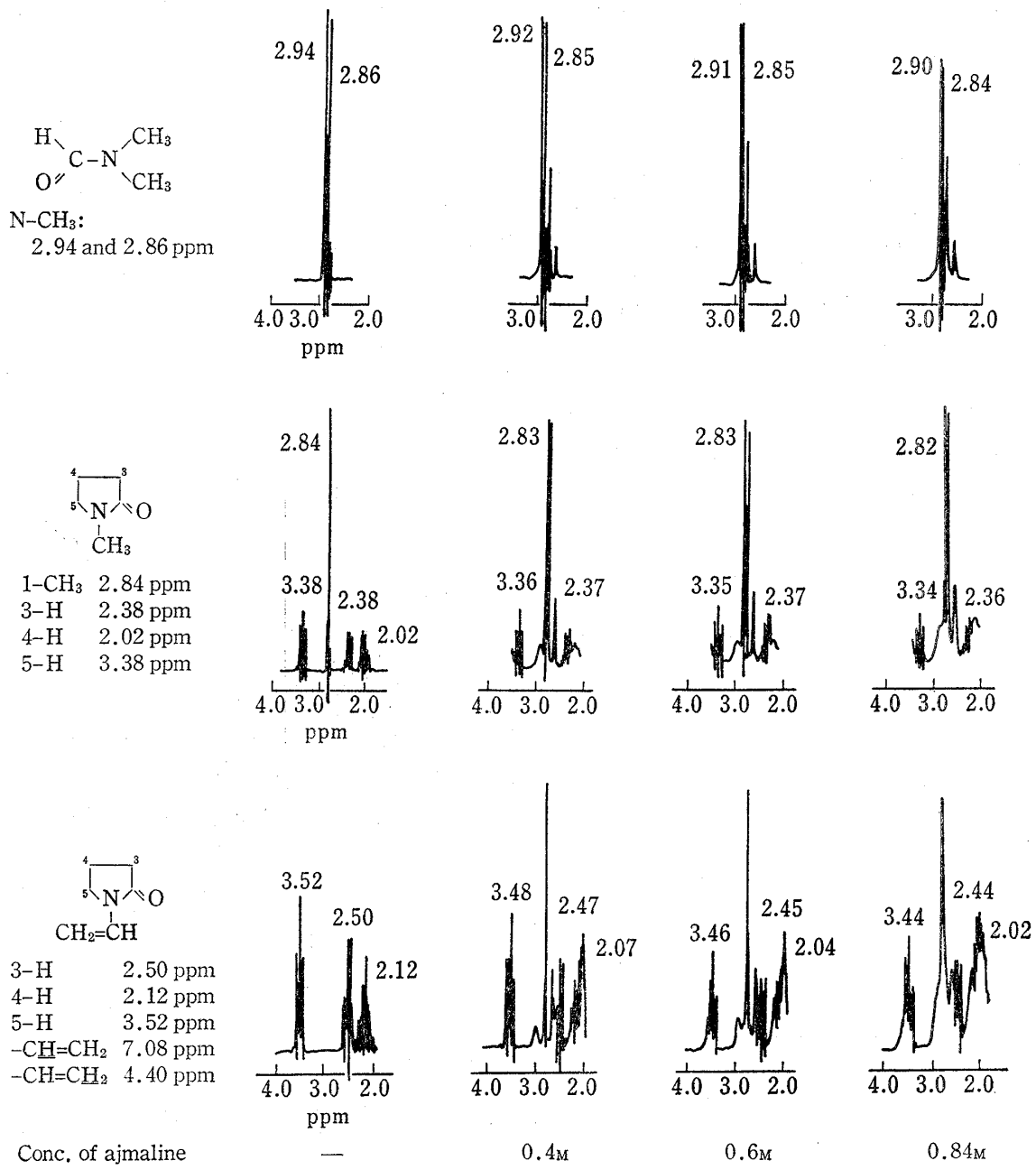

Fig. 3. Changes of Chemical Shifts of *cis*- and *trans*-CH_3 in DMF, 1-CH_3, 3-H, and 5-H in MP, 3-H, 4-H, and 5-H in VP induced by Ajmaline

5-H in MP were plotted against 4-H in VP (dotted line). These straight lines gave similar slopes of about 1.

2) Interaction between Ajmaline and VP, MP, or DMF

The influence of ajmaline on the NMR spectra of 0.34 M DMF, 0.25 M MP, or 0.225 M VP in $CDCl_3$ by varying its concentration (0, 0.4, 0.6, and 0.84 M) was determined, and these spectra are illustrated in Fig. 3. The signals of two methyl groups in DMF shifted by 0.04 and 0.02 ppm, respectively, by the addition of 0.84 M ajmaline. In MP, the signal of 5-H shifted to 3.34 ppm from 3.38 ppm by 0.84 M ajmaline, and both the signals of 1-CH_3 group and 3-H were shifted by 0.02 ppm. But the signal of 4-H was not observed because of its overlap with that of ajmaline. Further, the signal of 4-H in VP shifted to 2.02 ppm from 2.12 ppm by the addition of the same concentration of ajmaline, and those of 5-H and 3-H also shifted by 0.08 ppm and by 0.06 ppm, respectively. The shift of the vinyl proton adjacent to nitrogen atom in VP was not detected for the same reason as with 4-H in MP, and the signal of terminal vinyl protons was not changed by the addition of ajmaline.

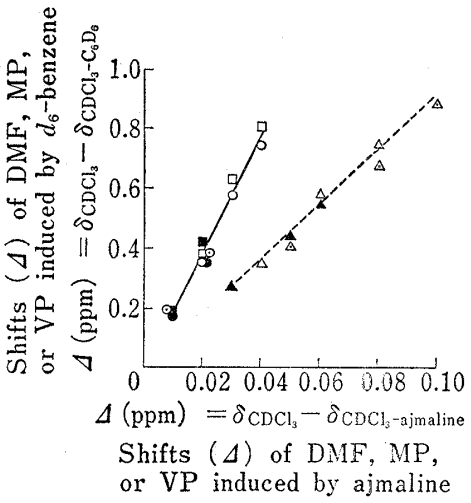

Fig. 4. Relationships of Shifts (Δ) of *trans*- or *cis*-CH_3 in DMF, 1-CH_3, 3-H, or 5-H in MP, and 3-H, 4-H, or 5-H in VP induced by d_6-Benzene against Those induced by Ajmaline

□: *trans*-CH_3 in DMF ■: *cis*-CH_3 in DMF
⊙: 1-CH_3 in MP ▲: 3-H in VP
●: 3-H in MP ◬: 4-H in VP
○: 5-H in MP △: 5-H iu VP

In order to investigate the orientation of these compounds containing amide group for benzene or ajmaline, the shifts of two methyl groups in DMF, 3-, 5-H, and 1-CH_3 group in MP, 3-, 4-, and 5-H in VP by d_6-benzene ($\Delta = \delta_{CDCl_3} - \delta_{CDCl_3\text{-}C_6D_6}$) were plotted against those by ajmaline ($\Delta = \delta_{CDCl_3} - \delta_{CDCl_3\text{-ajmaline}}$), as shown in Fig. 4. One of the straight lines with the steeper slope was obtained from the plots of DMF and MP (solid line), and the other was given from VP (dotted line).

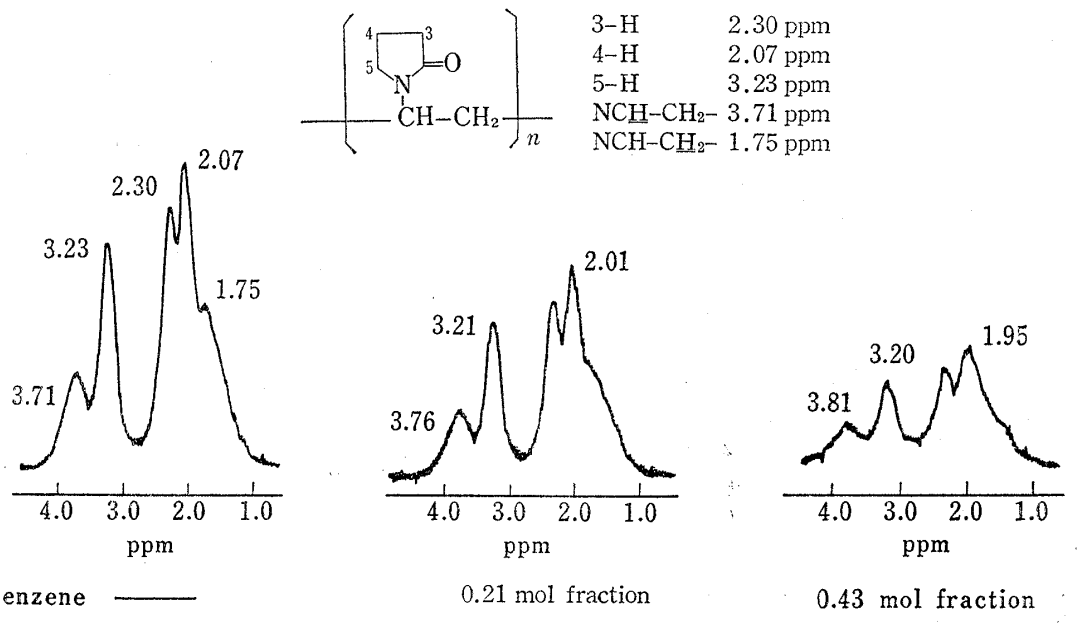

Fig. 5. Solvent Shifts (Δ) of PVP Protons in $CDCl_3$ Solution induced by d_6-Benzene

3) Solvent Effect of Benzene on PVP

The influence of d_6-benzene on the NMR spectra of PVP in $CDCl_3$ was studied (Fig. 5). By the addition of 0.43 mol fractions of d_6-benzene, 3-H in PVP was hardly influenced, and the signals of 5-H and 4-H shifted to upfield by 0.03 ppm and 0.12 ppm, respectively. But the signal of methine protons adjacent to nitrogen atom shifted reversely to downfield by 0.1 ppm.

These results were compared with the solvent shifts of VP by 0.43 mol fractions of d_6-benzene (Fig. 1). Considering the ratio (5.7) of the solvent shifts of 4-H (Δ=0.68) in VP to those of 4-H in PVP, it was obvious that the ratios of upfield shifts of 3-H (Δ=0.44) or 5-H (Δ=0.59) in VP to those of 3-H or 5-H in PVP were very high, and the ratio of downfield shifts of vinyl proton adjacent to nitrogen atom (Δ=−0.07) in VP to that of the corresponding proton in PVP was by far smaller. Therefore, the interaction between PVP of lower molecular weights and benzene was investigated for the purpose of considering the role of chain length of PVP. The solvent shifts ($\Delta=\delta_{CDCl_3}-\delta_{CDCl_3\text{-}C_6D_6}$[8]) of a series of shorter chain length of PVP are summarized in Table I. With an increase in chain length of PVP, the shifts of 3-H and 5-H in PVP decreased gradually, but the signal of 4-H was hardly changed in spite of the chain length. The downfield shifts of methine protons adjacent to nitrogen atom increased with the chain length.

TABLE I. Solvent Shifts (Δ) and Their Ratios (R) against 3-H in PVP of Lower Molecular Weights or PVP K-15 induced by d_6-Benzene

Protons in PVP	(VP) (M.W. 111)		PVP (I) $[\eta]$=0.034 M.W. 930		PVP (II) $[\eta]$=0.049 M.W. 1700		PVP (III) $[\eta]$=0.053 M.W. 2000		PVP (K-15) $[\eta]$=0.112 M.W. 7500
	Δ	R	Δ	R	Δ	R	Δ	R	Δ
3-H	(0.44	1.0)	0.05	1.0	0.02	1.0	0.01	1.0	0
4-H	(0.68	1.5)	0.11	2.2	0.11	5.5	0.11	11.0	0.12
5-H	(0.59	1.3)	0.09	1.8	0.07	3.5	0.05	5.0	0.03
-NCH-CH_2-	(−0.07	−0.2)	−0.01	−0.2	−0.03	−1.5	−0.06	−6.0	−0.10

Each values are Δ (ppm)$=\delta_{CDCl_3}-\delta_{C_6D_6}$ (0.43 mol fractions).

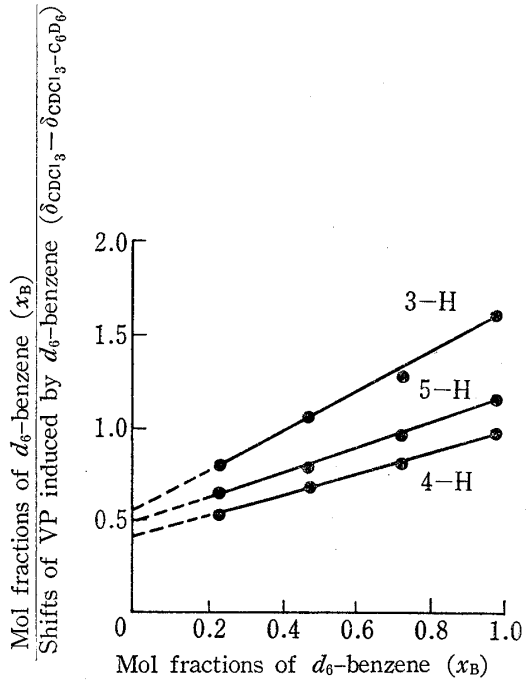

Fig. 6. Plots according to Reported Formula by Tyrrell from Solvent Shifts (Δ) of 3-, 4-, and 5-H in VP induced by d_6-Benzene

4) Determination of Association Constant

The association constant between VP and d_6-benzene was initially obtained by using the following formula reported by Tyrrell[9] which assumed a 1:1 complex formation;

$$x_B/(\delta_A-\delta_1) = x_B/(\delta_A-\delta_{AB}) + 1/Kn(\delta_A-\delta_{AB})$$

where x_B is the mol fractions of d_6-benzene, δ_A and δ_1 are the chemical shifts of VP in pure

8) The concentration of d_6-benzene in this case was taken 0.43 mol fractions.
9) J. Tyrrell, *Can. J. Chem.*, **43**, 783 (1965).

$CDCl_3$ (δ_{CDCl_3}) and in the mixed solvent ($\delta_{CDCl_3-C_6D_6}$), respectively, and chemical shifts of VP, when the complex formation is complete, is denoted by δ_{AB}. Every plot of the signals in VP indicated satisfactorily straight lines as shown in Fig. 6. This result shows that VP and benzene form the 1:1 complex. The average association constant (Kn) was calculated from the intercepts and slopes of these lines. In a similar manner, the Kn values between DMF or MP and benzene, or between DMF, MP, or VP and ajmaline were determined and are summarized in Table II. In the case of PVP and benzene, the Kn value was obtained on the grounds that one benzene molecule interacted with 5.7 monomer units of PVP, which was the ratio of solvent shifts of 4-H in VP to those in PVP.

Table II. Association Constants (Kn: mol fraction^{-1}) between DMF, MP, VP, or PVP and d_6-Benzene or Ajmaline

	DMF	MP	VP	PVP (K-15)
d_6-Benzene	1.20±0.20	1.38±0.20	1.53±0.30	1.41
Ajmaline	0.50±0.03	0.51±0.03	0.63±0.09	—

Discussion

Taking into account the results obtained from previous study[4] together with various reports[5,6] about the interaction between PVP and aromatic compounds, the aromatic ring in ajmaline was noted as an interaction site against PVP.

In the present study, the influence of d_6-benzene, which was employed as a substitute for aromatic ring in ajmaline, on VP, MP, or DMF having the amide group was initially studied. As shown in Fig. 2, the solvent shifts (Δ) of 5-H or 1-CH_3 group in MP were parallel to those of *trans*- or *cis*-CH_3 group in DMF by d_6-benzene in both cases. From these results, it seemed that amide group in MP was oriented against benzene in a similar manner as amide group in DMF. In the case of VP, however, it was revealed that 4-H rather than 5-H was oriented over benzene ring owing to repulsion of π-electrons between vinyl group in VP and benzene ring. In respect to the interaction strength, it was suggested that VP would be influenced by d_6-benzene no less strongly than MP or DMF (Fig. 2).

Subsequently, concerning the interaction of DMF, MP, or VP with ajmaline, it would be considered that the carbonyl group in DMF, MP, or VP influences the nitrogen atom at N(1)-position adjacent to aromatic ring in ajmaline. However, the influence of DMF or MP on the N-methyl group in ajmaline was not at all detected in this study, and the N-methyl group in methylindoline was not also influenced by PVP or 2-pyrrolidone in previous paper.[4] Accordingly, from the linear relationships shown in Fig. 4, it was concluded that the individual amide group in DMF, MP, or VP was oriented against aromatic ring in ajmaline as well as against benzene. Simultaneously it was ascertained that the influence of ajmaline on VP was stronger than that of ajmaline on DMF or MP, because the slope of straight line in VP was not so large as in DMF or MP. The approach of amide group in VP to the aromatic ring in ajmaline might be attributed to some attraction between vinyl group in VP and N-methyl group in ajmaline.

Further, the interaction of PVP and benzene was examined in a narrow range of concentration of PVP for the reason of the limited solubility of PVP in benzene. Consequently, it was found that the tendency of the solvent shifts of signals in PVP by d_6-benzene (Fig. 5) did not agree to that of the corresponding signals in VP (Fig. 1) or in MP either. Therefore, the interaction of benzene and PVP of lower molecular weights was investigated. From the ratio (R), shown in Table I, of solvent shifts of other protons to those of 3-H in PVP of lower molecular weights, it became apparent that the orientation between PVP and benzene tended to be similar to that between VP and benzene rather than between MP and benzene, because

of the enhancement of unsaturation in PVP with the number of terminal vinyl group, when the chain length of PVP was relatively shorter. It would be considered that, with an increase of molecular weight of PVP, the stacking of pyrrolidone ring to benzene ring did not remove from each other horizontally or vertically, but that pyrrolidone ring tended to lie at a certain angle to the plane of the benzene, keeping some distance between 4-H and benzene ring and increasing the distance between 3-H or 5-H and benzene. As the result, it would seem that the methine protons adjacent to nitrogen atom in PVP came to be located in the plane of another benzene ring.

Hatton *et al.*[10] reported that one methyl group moves to upfield much farther than the other, when DMF is diluted with benzene, and they presented the concept termed the collision complex about such solvent shifts. This was explained as follows; two methyl groups are non-equivalent since free rotation is not possible round the double bond in the resonance form, and the oxygen atom with a partially negative charge is situated as far from the center of benzene ring as possible, but the positively charged nitrogen atom is apt to come close to the region of high π-electron density in aromatic ring. So methyl group lying over the benzene ring would be strongly shielded. Moriarty *et al.*[11] also reported the collision complex formation between MP and benzene in conformational studies on N-methyl lactams. From these points of view, the shifts of VP or PVP induced by d_6-benzene and those of DMF, MP, or VP by ajmaline in this study seemed to be essentially analogous to the shifts attributable to the collision complex formation.

Moreover, the difference in the association constants of DMF, MP, VP, or PVP with d_6-benzene was not significant (Table II), but the Kn values of DMF, MP, or VP with ajmaline were smaller than those with benzene ($p<0.01$). In addition, ajmaline yields a larger Kn value with VP than with DMF or MP ($p<0.05$).

It had been expected that the influence of ajmaline on PVP would be demonstrated, but both the signals of 4-H and the methine protons adjacent to nitrogen atom in PVP were overlapped on the signals of ajmaline. Unfortunately, the expected slight influence by ajmaline on 5-H in PVP was too small to be detected. From the values of Kn between DMF, MP, or VP and ajmaline, however, there is reasonable possibility for considering the formation of molecular complex between PVP and ajmaline, which has a smaller Kn value than that of PVP and benzene.

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10) J.V. Hatton and R.E. Richards, *Mol. Phys.*, **5**, 153 (1961).
11) R.M. Moriarty and J.M. Kliegman, *Tetrahedron Lett.*, **1966**, 891.