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THERMODYNAMIC AND SPECTROSCOPIC PROPERTIES OF 2-PYRROLIDINONES. 3.* NMR SPECTROSCOPIC STUDIES ON 2-PYRROLIDINONE IN DIFFERENT SOLVENTS

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ABSTRACT

^{1}H, ^{13}C, ^{15}N and ^{17}O NMR chemical shifts, $^{1}J_{NH}$ and $^{1}J_{CH}$ coupling constants and line widths ($\Delta\nu_{1/2}$) of the ^{14}N and ^{17}O resonance lines were determined for 2-pyrrolidinone neat and for several 2-pyrrolidinone–solvent systems. The ^{17}O NMR chemical shift of 2-pyrrolidinone was clearly most sensitive to the solvent effects, but changes with the solvent were also observable in the ^{13}C (C=O) and ^{15}N NMR chemical shifts, the $^{1}J_{NH}$ coupling constants and especially the line widths of the ^{14}N and ^{17}O resonance lines. In general, the results reflected a hydrogen bonding effect between the oxygen atom of 2-pyrrolidinone and the proton-donating solvents and a weak molecular interaction of the NH proton of 2-pyrrolidinone with the proton-accepting solvents. The results are compared with the NMR data for the corresponding binary mixtures of 1-ethyl-2-pyrrolidinone.

INTRODUCTION

Lactams have attracted special interest among chemists since they include important antibiotics such as penicillin. The molecular interactions in lactam mixtures are relevant to the pharmacological and other prospective uses of these compounds and also to a fuller understanding of their chemical properties.

In earlier studies on the polarity, complex formation and important spectroscopic properties of several carboxamides, sulphonamides and sulphinamides,[1–7] we confirmed the usefulness of multinuclear NMR spectroscopy as a tool for investigating the molecular interactions between the solute–solute and solute–solvent molecules. Quadrupolar nuclei such as ^{17}O and ^{14}N are particularly sensitive probes of their environments.

Systematic investigations of the hydrogen bonding of *N*-substituted 2-pyrrolidinones, 1-methyl-2-pyrrolidinone and 1-phenyl-2-pyrrolidinone and its derivatives substituted in the benzene ring with various proton donors have been made in our laboratory.[8,9] In this work we extended our studies to 2-pyrrolidinone, neat and in various solvents, using NMR spectroscopy to obtain detailed information on its interactions in solvent systems.

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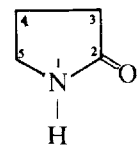


2-Pyrrolidinone (**1**)

The 2-pyrrolidinone molecule (**1**) contains two different types of interacting groups, a carbonyl group possessing electron-donor properties and an NH group possessing electron-acceptor properties. Hydrogen bond formation with proton donors occurs through the carbonyl oxygen atom, since in the IR spectrum the carbonyl band of the complexed lactam appears as a shoulder on the low-frequency side of the carbonyl band of the uncomplexed lactam.[8] Information about the weak acidic properties of the NH groups is obtained from near-infrared spectroscopic studies.[9] Marked self-association of 2-pyrrolidinone has been demonstrated both in precise near-infrared spectroscopic studies and in dielectric measurements.[10,11] The solute–solute interaction between the 2-pyrrolidinone molecules should therefore also be observable in binary and ternary solution mixtures.

EXPERIMENTAL

2-Pyrrolidinone (purum, Fluka, Buchs, Switzerland) was distilled above CaO and stored over Type 4A molecular sieves. Acetone (analytical-reagent grade, E. Merck, Darmstadt, FRG) was first refluxed with $KMnO_4$ and, after cooling, Na_2CO_3 was added. It was then left to stand for 2 h, distilled and preserved over Type 4A molecular sieves.[13] Dimethyl sulphoxide (purum, Fluka) was distilled above CaH_2 and preserved over Type 4A molecular sieves.[13] 1,4-Dioxane (analytical-reagent grade, E. Merck) was refluxed for 12 h with dilute HCl under a nitrogen atmosphere, dried with K_2CO_3 and then refluxed twice with sodium and distilled from above sodium.[14] Dichloromethane (spectroscopic grade, E. Merck), nitromethane (puriss, Fluka) and carbon tetrachloride (IR spectroscopic grade, Fluka) were dried and preserved over Type 4A molecular sieves. Chloroform (Uvasol, E. Merck) was used as received. Benzyl alcohol (puriss, Fluka) was distilled from above CaO and preserved over Type 4A molecular sieves.[13] 2-Propanol (reinst, E. Merck) was refluxed with CaO for 2 h, distilled and preserved over Type 4A molecular sieves.[13] 2,2,2-Trifluoroethanol (puriss, Fluka) was distilled from above K_2CO_3 and preserved over Type 4A molecular sieves.[7] Water was distilled and deionized.

Samples were prepared in a 1 : 1 molar ratio in the various solvents. All the NMR experiments were performed on materials of isotopically natural abundance in the observed nucleus. Measurements were made on Jeol JNM FX-100 and Jeol FX-200 NMR spectrometers with noise decoupling. An external ^{7}Li lock was used to stabilize the field frequency ratio.

The ^{14}N, ^{13}C, ^{15}N, ^{17}O and ^{1}H NMR spectra were obtained at operating frequencies of 7·14, 25·00, 10·04, 13·46 and 199·50 MHz, spectral widths of 20, 6, 6, 10 and 3 kHz, pulse widths of 56, 7, 10, 30 and 8 μs and pulse repetitions of 0·1, 2·5, 8, 0·05 and 5 s, respectively. The chemical shifts of the ^{13}C and ^{1}H nuclei are reported relative to internal tetramethylsilane, those of the ^{17}O nucleus relative to external water and those of the ^{15}N nucleus relative to internal nitromethane doped with $Cr(acac)_3$. All the NMR spectra were recorded at 301 ± 2 K as especially the ^{17}O NMR chemical shifts are sensitive to temperature.

RESULTS AND DISCUSSION

Table 1 shows the ^{15}N, ^{17}O and NH proton NMR chemical shifts and the $^1J_{NH}$ coupling constants and the line widths ($\Delta\nu_{1/2}$) of the ^{17}O and ^{14}N resonance lines of 2-pyrrolidinone neat and in various solvents. The ^{13}C NMR chemical shifts and the $^1J_{CH}$ coupling constants are presented in Table 2, ^1H NMR chemical shifts in Table 3 and the concentration dependences of the ^{15}N NMR chemical shifts and the line widths ($\Delta\nu_{1/2}$) of the ^{14}N resonance lines in Table 4.

Table 1. ^{15}N, ^{17}O and ^1H(NH) NMR chemical shifts and $^1J_{NH}$ coupling constants and line widths ($\Delta\nu_{1/2}$) of ^{17}O and ^{14}N resonance lines of 2-pyrrolidinone neat and in various solvents at 301 K

Solvent	$-\delta^{15}N$ (ppm)	$\delta^{17}O$ (ppm)	δ^1H(NH) (ppm)	$^1J_{NH}$ (Hz)	$\Delta\nu_{1/2}(^{17}O)$ (Hz)	$\Delta\nu_{1/2}(^{14}N)$ (Hz)
Neat	262·2	282	7·94	92·2	330; 265[a]	1174
Acetone	264·1	289	7·80	92·4	138	396
Nitromethane	264·9	282	7·70	92·4	158	417
Dimethyl sulphoxide	263·4	291	7·70	92·5	253; 172[a]	559
1,4-Dioxane	263·8	288	7·78	92·4	344; 430[b]	435
Carbon tetrachloride	261·7	284	8·20	92·9	660[b]	659
Dichloromethane	262·6	283	7·93	92·3	172	430
Chloroform	261·8	273	8·02	91·7	487; 516[b]	485
Benzyl alcohol	260·4	274	7·78	93·0	875[b]	417
2-Propanol	262·2	275	7·93	92·8	258	545
Water	260·1	271	7·77	92·7	379	796
2,2,2-Trifluoroethanol	260·9	268	7·70	93·1	273	664

[a] At 313 K.
[b] At 296 K.

Table 2. ^{13}C chemical shifts and carbon–proton coupling constants of 2-pyrrolidinone neat and in various solvents at 301 K

	$\delta^{13}C$ (ppm)				$^1J_{CH}$ (Hz)		
Solvent	C-2	C-3	C-4	C-5	C-3	C-4	C-5
Neat	179·4 (179·4[a])	30·6 (30·3[a])	21·3 (20·8[a])	42·7 (42·4[a])	133·8	133·5	142·0
Acetone	179·3	30·6	21·4	42·6	133·9	134·0	142·7
Nitromethane	180·2	30·8	21·5	43·1	133·8	133·1	142·1
Dimethyl sulphoxide	178·2	30·2	20·8	41·9	132·1	132·1	142·1
1,4-Dioxane	179·4	30·5	21·3	42·6	133·3	133·3	141·8
Carbon tetrachloride	178·6	30·1	20·7	42·2	133·3	133·1	141·4
Dichloromethane	179·5	30·7	21·2	42·7	132·3	134·3	141·6
Chloroform	179·4	30·4	20·9	42·5	133·3	133·5	142·1
Benzyl alcohol	179·8	30·3	20·7	42·4	135·3	134·5	141·4
2-Propanol	179·5	30·6	21·1	42·7	134·5	135·3	142·1
Water	180·6	30·8	21·2	43·1	134·4	133·5	142·6
2,2,2-Trifluoroethanol	181·7	31·1	21·6	43·6	132·6	134·8	142·1

[a] from Ref. 17.

Table 3. ^{1}H NMR chemical shifts (ppm) for 2-pyrrolidinone neat and in various solvents at 301 K

Solvent	H-3	H-4	H-5
Neat	2·17	2·05	3·30
Acetone	2·12	2·06	3·31
Nitromethane	2·17	2·07	3·33
Dimethyl sulphoxide	2·11	2·02	3·26
1,4-Dioxane	2·14	2·03	3·29
Carbon tetrachloride	2·14	2·08	3·36
Dichloromethane	2·18	2·06	3·33
Chloroform	2·25	2·10	3·36
2-Propanol	2·19	2·06	3·32
Water	2·25	2·09	3·36
2,2,2-Trifluoroethanol	2·26	2·10	3·37

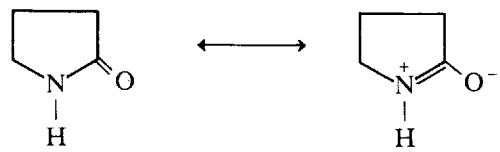
Table 4. Concentration dependence of ^{15}N NMR chemical shifts and line widths of the ^{14}N resonance lines of 2-pyrrolidinone in various mixtures at 301 K

Solvent	X_{amide}	$-\delta^{15}N$ (ppm)	$\Delta\nu_{1/2}(^{14}N)$ (Hz)
Acetone	0·3072	265·1	
	0·4995	264·1	
	0·7051	263·6	
	0·8038	263·3	
	1·0000	262·7	
Dimethyl sulphoxide	0·3038	263·8	
	0·4987	263·5	
	0·6956	263·1	
	0·8030	263·0	
	1·0000	262·7	
Carbon tetrachloride	0·1664		525
	0·5025		659
	0·7926		1069
	1·0000		1174

The ^{13}C NMR results are in good agreement with those of Fronza *et al.*[15] and Marchal *et al.*[16] for lactam. The ^{13}C NMR chemical shift of the carbonyl carbon of neat 2-pyrrolidinone is 179·4 ppm (Table 2),[17] which means that this carbon is slightly less shielded than in 1-ethyl-2-pyrrolidinone (173·3 ppm) and 1-methyl-2-pyrrolidinone (173·9 ppm).[1] The effect of the proton-donating solvent on the chemical shift of this carbon is also smaller for the 2-pyrrolidinone–2,2,2-trifluoroethanol mixture (2·3 ppm towards higher frequencies) than for the corresponding 1-methyl-2-pyrrolidinone (3·2 ppm) and 1-ethyl-2-pyrrolidinone (2·7 ppm) mixtures. Together these results show that the electron density of the carbonyl carbon is lower in neat 2-pyrrolidinone than in neat 1-methyl-2-pyrrolidinone and 1-ethyl-2-pyrrolidinone. Proton-donating solvents further decrease the electron density of the carbonyl carbon in 2-pyrrolidinone, as in 1-methyl-2-pyrrolidinone and 1-ethyl-2-pyrrolidinone.

The direct participation of the oxygen atom of 2-pyrrolidinone in the intermolecular hydrogen bonding suggests that ^{17}O NMR spectroscopy would be a useful tool in studying the molecular interaction properties of 2-pyrrolidinone in mixtures. The shielding order of the ^{17}O nucleus of the carbonyl group is opposite to the shielding order of the carbon atom in the three lactams being compared. The most highly shielded oxygen atom is in 2-pyrrolidinone (282 ppm) and the shielding decreases from 294 ppm in 1-methyl-2-pyrrolidinone to 300 ppm in 1-ethyl-2-pyrrolidinone.[1]

In general, the solvent effect on the NMR chemical shift of the ^{17}O nucleus is notable (Table 1), being 14 ppm towards lower frequencies for the 2-pyrrolidinone–2,2,2-trifluoroethanol mixture compared with neat 2-pyrrolidinone. As already noted, hydrogen bond formation occurs through the oxygen atom of 2-pyrrolidinone, so that the shielding of the carbonyl oxygen atom increases in a proton-donating solvent and the amide resonance shifts more to the right:



(a) (b)

On the other hand, the ^{15}N nucleus is more shielded in the neat amide ($-262{\cdot}2$ ppm) than in 2-pyrrolidinone–2,2,2-trifluoroethanol ($-260{\cdot}9$ ppm) mixture, in agreement with the resonance form (b). A basic solvent, such as acetone, dimethyl sulphoxide or 1,4-dioxane, can interact with the NH proton of 2-pyrrolidinone, as is reflected in the greater shielding of the ^{15}N nucleus in 2-pyrrolidinone–basic solvent mixtures than in the neat amide.

From the above, the NH proton appears to be a sensitive probe for the study of specific molecular interactions, e.g. hydrogen bonding, in 2-pyrrolidinone mixtures. The nitrogen proton signal is normally fairly broad, however, because of a $^{1}H-^{14}N$ scalar interaction, which is time modulated by the rapid relaxation of the quadrupolar ^{14}N nucleus. A hydrogen bonding interaction at the amide proton would induce a shift of this proton signal towards lower or higher frequencies, depending on whether the interaction is weaker or stronger than the hydrogen bond interaction between self-associated 2-pyrrolidinone molecules. The $^{1}H(NH)$ NMR chemical shifts of 2-pyrrolidinone neat and in various solvents (Table 1) clearly show that both the proton-accepting and the proton-donating solvents have a structure-breaking effect on 2-pyrrolidinone association; the signal of the NH proton is shifted towards lower frequencies in both the basic and acidic solvents (Table 1). Table 3 shows that the NMR chemical shifts of the other protons of the 2-pyrrolidinone ring are nearly independent of the solvent, within experimental error. The only exception is proton 3 adjacent to the carbonyl group, the NMR chemical shift of which parallels the ^{15}N NMR chemical shift in moving slightly towards higher frequencies in proton-donating solvents and towards lower frequencies in electron-donating solvents, compared with the neat amide.

The effects of solvents on NMR coupling constants are usually small. The values of $^{1}J_{^{1}H-^{13}C}$ of $CHCl_3$ increase markedly, however, on formation of a hydrogen bond.[18] Significant changes in the J_{NH} values of aniline and related compounds with the solvent are also described in the literature.[19] It was of interest in this work, therefore, to look for changes in the J_{NH} value with

change of the solvent in 2-pyrrolidinone–solvent mixtures. In the case of trigonal bonding to nitrogen, as in amides, the J_{NH} value usually lies at about 90 Hz and varies with the solvent over a range comparable to that of the substituent effects.[20] As shown for acetamides, through enhanced delocalization, the protonation of amides increases the $^1J_{NH}$ values.[21,22] Table 1 shows a clear increase in the $^1J_{NH}$ values of 2-pyrrolidinone in various solvents in proton-donating solvents whose proton donor ability exceeds that of the NH group of 2-pyrrolidinone. The values are about the same in some of the solvents as in the neat amide, but they increase again in the proton-accepting solvents, reflecting changes in the self-associated species of 2-pyrrolidinone in mixtures.[10,11]

In all the experiments on mixtures discribed above we used a 1 : 1 molar ratio of amide to solvent. In an inert solvent such as carbon tetrachloride, however, the amount of self-associated species of 2-pyrrolidinone varies with the concentration of the amide. There is therefore both a concentration and a solvent dependence of the ^{15}N nuclear screening of 2-pyrrolidinone (Table 4). This is seen in the movement of the ^{15}N NMR chemical shift from $-265{\cdot}1$ to $-262{\cdot}7$ ppm for the $X_{amide} = 0{\cdot}3072$ mixture in acetone compared with the neat amide. The difference is smaller in dimethyl sulphoxide ($-1{\cdot}1$ ppm), which is a more basic solvent. However, both of these aprotic solvents increase the shielding of the ^{15}N nucleus relative to the neat amide (Fig. 1). In general, the results show that the addition of a basic (or electron-donor) solvent, e.g. acetone or dimethyl sulphoxide, to 2-pyrrolidinone disturbs the self-association of 2-pyrrolidinone more in a dilute amide solution (the molar fraction of the solvent is then the greatest) than in a more concentrated solution.

Whereas ^{15}N nuclei give sharp resonance lines, allowing accurate frequency measurements, ^{14}N NMR studies suffer from quadrupolar line broadening. The line widths of ^{14}N resonance signals increase markedly and systematically with increased concentration of 2-pyrrolidinone in carbon tetrachloride, however (Fig. 2a), perhaps owing to the increasing amount of self-associated species of 2-pyrrolidinone.[10,11] They also increase with increasing amounts of proton-donating solvent–amide (2,2,2-trifluorethanol : amide = 1 : 1) or proton-accepting solvent–amide mixture (dimethyl sulphoxide : amide = 1 : 1) in carbon tetrachloride (Fig. 2b) and c), but less so than for corresponding increases in the amounts of the pure amide in carbon tetrachloride. The amount of self-associated species and the presence of other hydrogen-bonding partners therefore affect both the line widths and the chemical shifts of various nuclei of 2-pyrrolidinone.

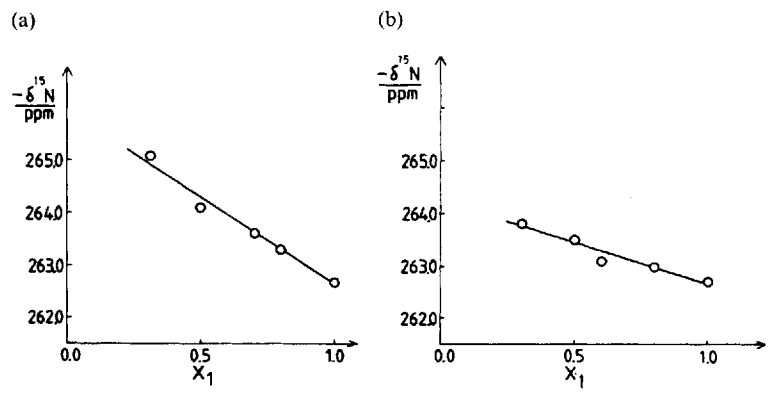


Figure 1. ^{15}N NMR chemical shifts for (a) 2-pyrrolidinone–acetone mixture and (b) 2-pyrrolidinone–dimethyl sulphoxide mixture as a function of the molar fraction of the amide

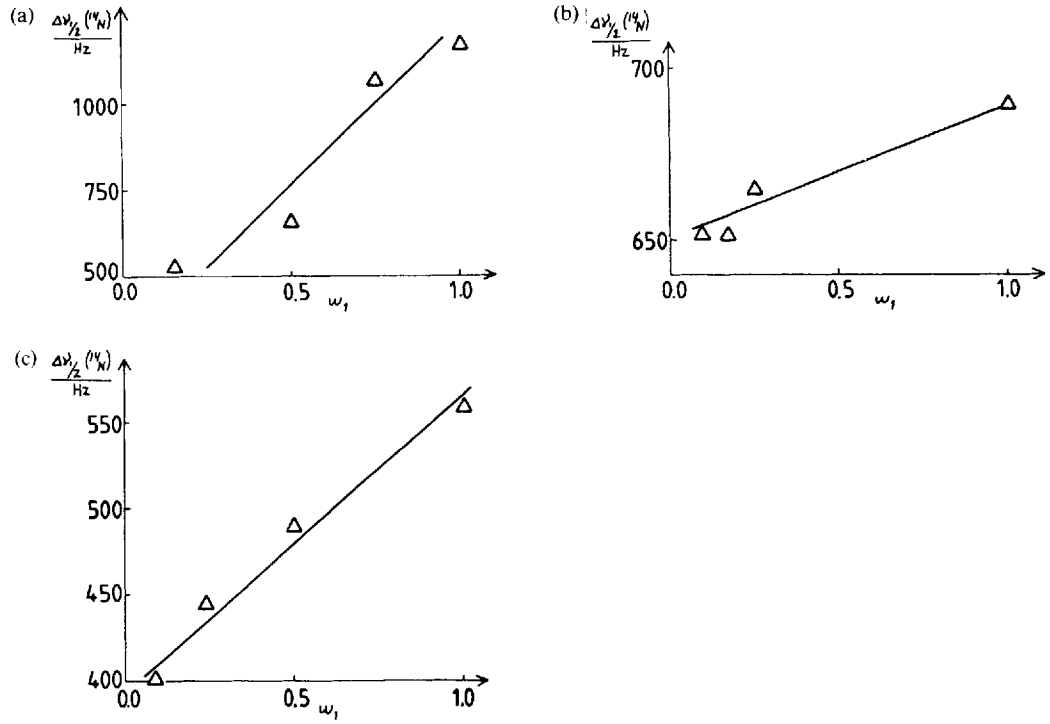


Figure 2. ^{14}N line widths for (a) 2-pyrrolidinone in carbon tetrachloride vs volume fraction of the amide, (b) 2-pyrrolidinone–2,2,2-trifluorethanol mixture (molar ratio = 1 : 1) in carbon tetrachloride vs volume fraction of the mixture and (c) 2-pyrrolidinone–dimethyl sulphoxide mixture (molar ratio = 1 : 1) in carbon tetrachloride vs volume fraction of the mixture

Taken together, the NMR spectroscopic results in Tables 1–4 clearly demonstrate the nature of molecular interactions between the solute–solute and the solute–solvent molecules in 2-pyrrolidinone–solvent systems. The situation is complex, however, because proton-donating and proton-accepting solvents disturb the self-association of 2-pyrrolidinone in different ways. The forces of interaction may also be dielectric in nature. In view of this, Kamlet *et al.*[23] used a polarity–polarizability (π^*) parameter in addition to the hydrogen-bond donor (α) and hydrogen-bond acceptor (β) parameters. Thus,

$$\delta = \delta_0 + s\pi^* + a\alpha + b\beta \tag{1}$$

where δ = NMR chemical shift of the nuclei and s, a and b are constants obtained by fitting Eqn (1) to the experimental results and applying multiple linear regression analysis.

For the ^{15}N NMR chemical shifts of 2-pyrrolidinone, Eqn (1) takes the form

$$\delta = -264{\cdot}07 + 1{\cdot}06\pi^* + 2{\cdot}07\alpha - 0{\cdot}57\beta \tag{2}$$

and for the ^{17}O NMR chemical shifts of 2-pyrrolidinone the form

$$\delta = 280{\cdot}3 + 8{\cdot}1\pi^* - 14{\cdot}3\alpha + 3{\cdot}5\beta \tag{3}$$

Equations (2) and (3) show that both the dielectric and hydrogen-bonding interactions occur in the mixtures used in this study, the most dominant solvent effect being the hydrogen-bond donor property of the solvent on the carbonyl oxygen atom of 2-pyrrolidinone.

In addition to the changes in the ^{17}O and ^{15}N NMR chemical shifts of 2-pyrrolidinone with the solvent, there are smaller differences in the other NMR parameters: the $^{1}J_{NH}$ values tend to increase with the proton-donating ability of the solvent, and the NH proton and C-2 and C-3 chemical shifts change in response to the different electronic densities on the atoms of 2-pyrrolidinone induced by the solvents. Most sensitive to the solvent, however, are the line widths of the ^{17}O and ^{14}N resonance lines, the former ranging from 138 to 487 Hz and the latter from very broad (1174 Hz for neat pyrrolidinone) to 396 Hz in our experiments.

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