JOURNAL OF PHYSICAL ORGANIC CHEMISTRY, VOL. 7, 171–177 (1994)

STUDY OF THE ASSOCIATION OF 2-OXOINDOLINES IN CARBON TETRACHLORIDE SOLUTIONS BY IR SPECTRA, DIPOLE MOMENTS AND AVERAGE MOLECULAR WEIGHT MEASUREMENTS

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Dipole moments, average molecular weights and IR spectra of 2-oxoindoline (I), 2-oxo-3-methylindoline (II) and 2-oxo-3,3-dimenthylindoline (III) and their *N*-methyl-substituted analogues were studied in CCl_4 solutions at various concentrations. It was shown that the molecules with an N—H bond associate exclusively to cyclic dimers. The values of the association constants (*K*) were determined by IR spectrometry. Other methods gave too broad intervals of possible *K* values. The spectroscopic association constants of compounds I–III are very similar, 380, 350 and 370 $dm^3 mol^{-1}$, respectively. The ν_s(NH) band shift on association is 275 cm^{-1}.

INTRODUCTION

The hydrogen bonding between C=O and H—N bonds of amide groups is responsible for the structure and activity of many biologically important compounds such as peptides and nucleic acids.[1,2] The interactions in solutions between small amides and related compounds have been studied as model systems of these compounds of biological interest.[3] When C=O and N—H bonds are in a *cis* configuration, the cyclic forms of associates predominate. For molecules with a *trans* arrangement of these bonds the chain associates prevail.[4] The steric effects and concentration may however, influence the form of aggregates in individual cases.[5–8] The structure of aggregates, including cyclic ones, is a controversial problem.[5,6]

Previously we have reported ^{13}C and ^{15}N NMR spectra in solution for a series of 2-oxoindolines[9,10] and solid-state ^{13}C and ^{15}N CP MAS NMR data for these compounds.[11] Recently, we have determined the crystal structures of 2-oxoindoline (I), 2-oxo-3-methylindoline (II) and 2-oxo-3,3-dimethylindoline (III).[12] The results show that two different types of associates are present in the crystal state of the compounds studied, depending on the steric hindrance. The 2-oxoindoline molecules form cyclic dimers, whereas those with one or two methyl groups form hydrogen-bonded chains.

The aim of this study was to trace the association of 2-oxoindolines in non-polar solution and compare the structures of aggregates in solution with the solid-state structures. The dipole moments, IR spectra and average molecular weights of six derivatives of 2-oxoindoline (see Scheme 1) were studied at various concentrations in CCl_4 solutions.

Our systems resemble 2-pyrrolidinone, the self-association of which was studied in cyclohexane and CCl_4 by Walmsley *et al.*[8] It was also of interest to establish the role in association of the phenyl ring condensed with 2-pyrrolidinone.

The concentration dependence of dipole moments, IR spectra and average molecular weight of compounds I–III should allow the construction of an association model. The molecular characteristics of monomers

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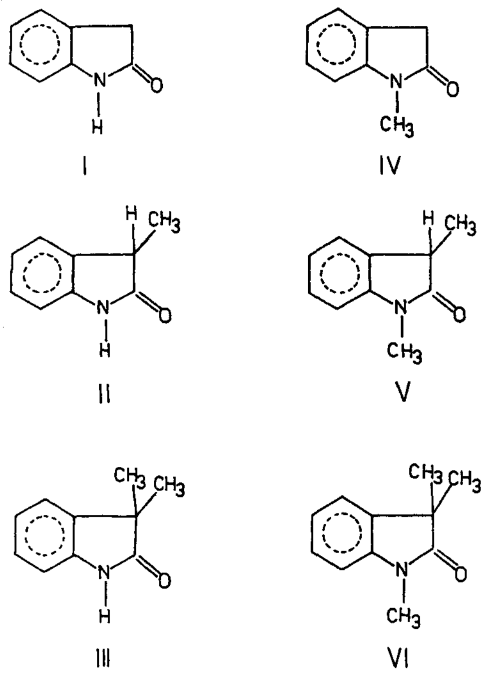
CCC 0894–3230/94/040171–07

Received 1 June 1993
Revised 22 November 1993



Scheme 1

derived from this model by extrapolation to very low concentration should coincide with the respective characteristics of analogous *N*-methyl-substituted compounds **IV–VI**. The characteristics studied in this work belong to two different groups: average molecular weight and effective dipole moment describe some collective properties of associating systems, while IR spectra in the ν_s(NH) region allow the amount of non-associated forms to be determined. Such a combination of methods can give a reliable model of association.[13] Dipole moments additionally allow discussion of the structure of aggregates.

EXPERIMENTAL

The 2-oxo-indolines were prepared using published procedures.[9,10]

Dipole moments were determined in CCl_4 solutions at concentrations 1×10^{-3}–50×10^{-3} mol dm^{-3}. Electric permittivity was measured using the heterodyne beat method at 2 MHz on a DM01 (WTW) dipolmeter. Measurements were performed at 25 and 50 °C. Density was determined by the pycnometric method with a precision of $\pm 2 \times 10^{-4}$ g cm^{-3}. Calculations were performed by the Hedestrand method.[14] Refractive indices were determined using an Abbé refractometer with a precision of ±0·00005. R_D was assumed to be the sum of electron and atom polarizations. It was calculated either as a sum of standard atom polarizations or from measured refractive indices. Differences in calculated values of dipole moments obtained using both procedures were lower than the experimental uncertainty.

The average molecular weights were determined using a Perkin-Elmer VPO apparatus in the concentration range 1×10^{-3}–70×10^{-3} mol dm^{-3} at 40 °C.

The IR spectra in the ν_s(NH) region were measured at 25 ± 1 °C on a Nicolet Model 205 Fourier transform IR spectrophotometer at 2 cm^{-1} resolution in quartz cells, with typical Specord UV–visible cell holders thermostated by a water-bath. Other details concerning the IR spectra are given later.

RESULTS AND DISCUSSION

Dipole moments

A dependence of the measured dipole moments of compounds **I–III** on concentration is observed at both temperatures (Figure 1). The values at 50 °C are higher than those determined at 25 °C for corresponding concentrations. No influence of concentration on dipole moments was observed for the *N*-methylated derivatives **IV–VI**.

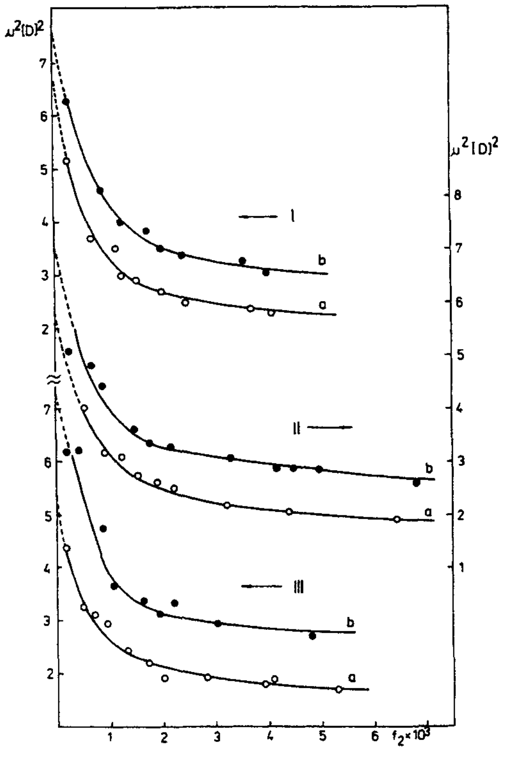


Figure 1. Dependence of the square of the apparent dipole moment on the total concentration at (a) 25 °C and (b) 50 °C for the compounds **I**, **II** and **III**

Table 1. Comparison of estimated values of monomer dipole moments for compounds **I–III** and experimentally determined values for compounds **IV–VI**

Substituent in position 3	Compounds with *N*-H group (compound number)		Compounds with *N*—CH_3 group (compound number):
	μ (D), 25 °C	μ (D), 50 °C	μ (D), 25 °C
H	2·64 ± 0·18 (**I**)	2·71 ± 0·16 (**I**)	2·79 ± 0·01 (**IV**)
CH_3	2·45 ± 0·21 (**II**)	2·65 ± 0·18 (**II**)	2·75 ± 0·01 (**V**)
$(CH_3)_2$	2·41 ± 0·20 (**III**)	2·65 ± 0·15 (**III**)	2·69 ± 0·01 (**VI**)

On the basis of the results obtained, one can conclude that for compounds **I–III** the association leads mainly to cyclic forms. Higher values of μ at 50 °C are caused by a stronger dissociation of aggregates to more polar monomers. In order to obtain dipole moments of monomers (μ_M), an extrapolation of apparent μ^2 values to infinite dilution was performed. The dipole moments of monomers for compounds **I–III** (cf. Figure 1) are compared with experimentally determined average dipole moments of compounds **IV–VI** in Table 1.

Average molecular weight

In order to verify the assumption of association, we measured the average molecular weights ($\bar{M}$) of compounds **I–III** in CCl_4 in the same concentration range as in dipole moments measurements. The results obtained are given in Figure 2.

A distinct increase in molecular weight with increasing concentration was found for all these compounds. However, in the range of concentrations applied the apparent molecular weights did not exceed twice the molecular wight of the monomer. This may indicate that in the concentration range studied aggregates higher than dimers are not formed in significant amounts.

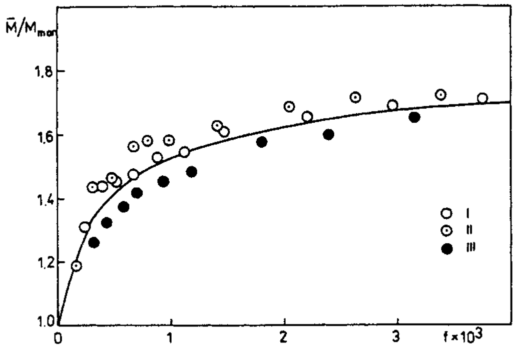


Figure 2. Dependence of $\bar{M}/M_m$ on molar fraction of solute for compounds **I**, **II** and **III**. Symbols, experimental data; solid line, results of calculations based on spectroscopic association constant $K = 370\ dm^3\ mol^{-1}$

IR spectra

The IR spectra in the region of $\nu_s(NH)$ vibrations were measured in the same solvent and concentration range. The spectra were recorded at a constant product of cell thickness (l) and total concentration (c) and spectra for **III** at different concentrations are shown in Figure 3.

The absorption band at 3450 cm^{-1} may be assigned to the free $\nu_s(NH)$ vibrations. The relative intensity of this band (at constant cl) increases on dilution whereas the intensity of the group of bands within the frequency range 2800–3100 cm^{-1} decreases. The spectrum of the *N*-methylated derivative **VI** is shown for comparison. It is seen that the 3100–3400 cm^{-1} spectral range is not overlapped by the CH absorption. The absorption in this region and changes with concentration in the region of $\nu_s(CH)$ bands (2800–3100 cm^{-1}) is attributed to bonded NH groups, with the maximum absorption located at 3175 cm^{-1}. The relatively large $\nu_s(NH)$ shift on dimerization, 275 cm^{-1} (compare, e.g., Ref. 3), suggests a strong interaction between molecules in the dimer. The band ascribed to the associated NH group is broad and affected by the Fermi resonance. The $\nu(CH)$ band at 2960 cm^{-1} belongs to the ring-substituted CH_3 groups. The evolution of the IR spectrum shown in Figure 3 for **III** is typical of all compounds **I–III**.

The spectra in Figure 3 show that the bonded and free $\nu_s(NH)$ bands are well separated and there is no overlapping of bands at 3450 and 3175 cm^{-1}. The absorptivity at 3450 cm^{-1}, $E(3450)$, was applied to determine the amount of free species. The molar absorption coefficient, $\varepsilon(3450)$, determined at very low concentrations are 237 ± 15, 186 ± 8 and 184 ± 10 $dm^3\ mol^{-1}\ cm^{-1}$ for **I**, **II** and **III** respectively. Owing to the complete separation of bonded and 'free' $\nu_s(NH)$ bands, one can verify these values when assuming that the aggregation leads only to dimers. Then,

$$c_0 = [E(3450)/\varepsilon(3450) + 2E(3175)/\varepsilon(3175)]/l \quad (1)$$

where c_0 is the formal concentration of the solute.

Simultaneous solution of a set of such equations for different c_0 gave $\varepsilon(3450)$ values which agreed with

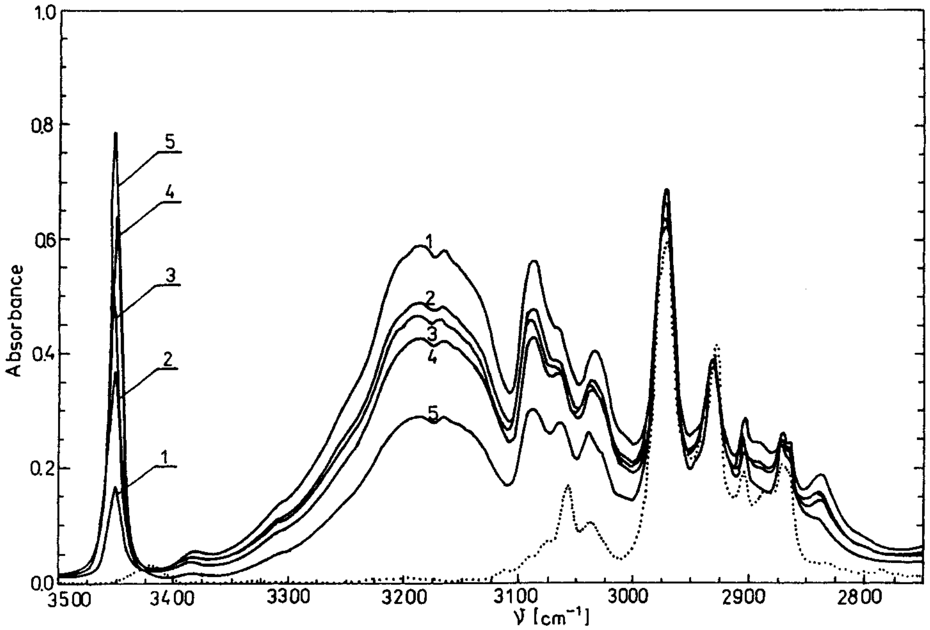


Figure 3. IR spectra of 2-oxo-3,3-dimethylindoline (**III**) as function of concentration: (1) 0·05, (2) 0·01, (3) 0·005, (4) 0·0025 and (5) 0·001 mol dm^{-3}. Dotted line: IR spectrum of *N*-methyl-2-oxo-3,3-dimethylindoline (**VI**)

directly determined values, within the limits of experimental reproducibility of $\varepsilon(3450)$.

Association model

On the basis of dipole moment measurements, the cyclic forms of aggregates can be predicted. The values of the average molecular weights indicate that in the concentration range studied the amount of aggregates larger than dimers is negligibly small. For these reasons the proposed model of association takes into account the cyclic dimers only.

$$A + A \rightarrow A_2$$

$$K = [A_2]/[A]^2 \qquad (2)$$

The association constants can be evaluated from the total concentration of solute and from the IR spectra. Experimental results and the results of calculations are given in Table 2.

The amount of monomers was determined from the intensity of the free ν_s(NH) band. The average calculated K values are 380 ± 16, 350 ± 19 and 370 ± 24 dm^{3}mol^{-1} for **I**, **II** and **III**, respectively.

Association constants can be determined independently from the dipole moment values measured as a function of concentration. Generally, the simultaneous determination of the dipole moments of monomer (μ_M) and dimer (μ_D) and the K value is possible. However, it was demonstrated by Exner[15,16] that such a procedure gives a high uncertainty of K determination and often unrealistic values of μ_D. Following Exner's reasoning,[15,16] we tried to reproduce the function $\mu^2_{app} = f(c_0, K, \mu_M, \mu_D)$. Our apparent values of dipole moments were determined by the Hedestrand method so we optimized equation (3), which is a rearranged version of equation (17) from Ref. 16:

$$\mu_{app}{}^2(x_M + 2x_D)/(x_M + x_D) = \mu_D{}^2 + x_M(\mu_M{}^2 - \mu_D{}^2) \qquad (3)$$

where $x_M = c_M/(c_M + c_D)$ and $x_D = 1 - x_M$.

The results of calculations of association constant on the basis of dipole moment measurements are given in Table 3. We give a detailed discussion of the results only for the case of compound **I** measured at 25 °C.

Assuming the association constant, one can calculate x_M and fit a linear dependence of $\mu_{app}{}^2$ $(x_M + 2x_D)$ on x_M [equation (3)]. The slope gives $\mu_M{}^2 - \mu_D{}^2$ and the intercept gives $\mu_D{}^2$. From the best fitting $\{s^2 = \Sigma_i\ [(\mu_i^2 - f(c_{0i}, K, \mu_M, u_D))]^2$ is a minimum$\}$, one can select the optimum K value. For **I** at 25 °C the best fitting gives $K = 311$ dm^{3}mol^{-1}, $\mu_D = 1{\cdot}31$ D and $\mu_M = 2{\cdot}95$ D. The values obtained seem to be reasonable in comparison with $K = 370$ dm^{3}mol^{-1} (from IR spectra) and $\mu_M = 2{\cdot}64$ D from $\mu_{app}{}^2$ extrapolation to $c_0 = 0$ and 2·79 D found for **IV**. According to Exner,[15] the estimation of the confidence interval of K and μ_M and μ_D determination can be found from the points where s^2 is equal to double its minimum value (Figure 4).

Table 2. Association constants (K) of the compounds I–III from IR spectrometric measurements in CCl_4 at 25 °C (cell thickness = 0·5 cm)

Compound	$c_0 \times 10^3$ (mol dm^{-3})	E(3450)	$c_M \times 10^3$ (mol dm^{-3})	K(dm^3 mol^{-1})
I	37·12	0·738	6·228	398
	25·80	0·624	5·266	370
	16·08	0·466	3·933	393
	7·26	0·304	2·565	357
	7·11	0·288	2·430	396
	3·73	0·198	1·671	368
II	36·04	0·615	6·613	336
	15·63	0·387	4·161	331
	10·72	0·295	3·172	375
	6·13	0·222	2·387	328
	5·02	0·187	2·011	372
	3·78	0·158	1·699	360
III	50·15	0·675	7·337	398
	17·82	0·405	4·402	346
	9·70	0·285	3·098	344
	7·64	0·233	2·533	398
	5·16	0·192	2·087	352
	4·88	0·164	1·783	387

Table 3. Association constant (K) from dipole moment measurements

Results with μ_D fitting	I		II		III	
	25 °C	50 °C	25 °C	50 °C	25 °C	50 °C
K(dm^3/mol)	311	103	665	67	198	40
μ_D^2(D^2)	1·72 ± 0·22	2·29 ± 0·45	1·52 ± 0·42	1·86 ± 0·53	0·98 ± 0·31	−3·46 ± 0·72
μ_M^2(D^2)	8·69 ± 0·62	7·53 ± 1·23	11·30 ± 2·71	6·64 ± 0·85	6·30 ± 1·22	11·08 ± 2·53
K limits (dm^3 mol^{-1})	37; >1000	3; >1000	21; >1000	11; 544	27; >1000	3; 675
μ_M limits (D)	2·56; 3·54	5·10; 3·66	2·51; 3·63	2·77; 3·30	2·41; 3·18	7·10; 3·79
Results with assumed $\mu_D = 0$						
K(dm^3 mol^{-1})	71	35	60	25	78	104
μ_M^2(D^2)	6·34 ± 0·13	6·50 ± 0·20	5·64 ± 0·08	5·81 ± 0·10	5·24 ± 0·11	8·69 ± 0·28
K limits (dm^3 mol^{-1})	31; 158	11; 106	27; 155	13; 48	33; 187	31; 375
μ_M^2 limits (D^2)	5·38; 8·22	5·72; 9·52	4·48; 7·83	5·01; 6·93	4·12; 6·99	6·26; 13·61

Such an estimation gives for the lower limit of K a value of 37 dm^3 mol^{-1} with $\mu_M = 2{\cdot}56$ D, but μ_D^2 appears to be unreasonable (−0·964 D^2). The higher limit of K exceeds 5000. One can perform a fitting with the assumption that $\mu_D = 0$.[16] This gives $K = 71$ dm^3 mol^{-1} within limits of 158 and 31 dm^3 mol^{-1}. Dipole moments of the monomer are 2·52, 2·87 and 2·32 D for these K values, respectively. K values obtained for the same set of experimental results are different for different assumptions. The interval of possible values is very broad. In a search for the reasons for such wide limits of K determinations we fitted the experimental dependence of $\mu_{app}{}^2$ on concentration by a polynomial and generated from this polynomial three times more 'idealized' points within the same concentration limits. However, such a smoothing procedure and an increase in the number of points within the same concentration limits did not give any improvement in K estimation limits. It appears that a necessary condition for this is an extension of the concentration limits, particularly in the direction of low concentrations where dimerization is the determining step in aggregation. For these reasons, the determination of the association constants from IR spectra is much more precise. These conclusions are valid for other results in Table 3.

Association constants determined from the values of

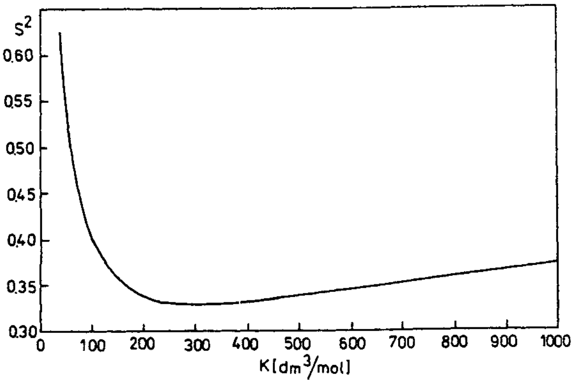
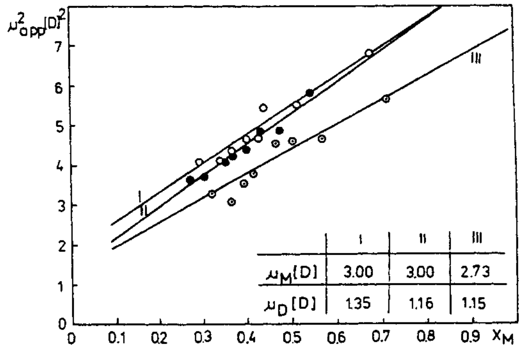


Figure 4. Dependence of the square of the standard deviation, s^2, on K for compound **I** at 25 °C



	I	II	III
μ_M[D]	3.00	3.00	2.73
μ_D[D]	1.35	1.16	1.15

Figure 5. Dependence of the square of the apparent dipole moment on the molar fraction of monomer for 2-oxoindolines **I**, **II** and **III** [equation (3)]

the average molecular weight:

$$K = \{c_0 - [c_0(M_D - \bar{M})/M]\}/2[c_0(M_D - \bar{M})/M]^2 \quad (4)$$

are 393 ± 37, 520 ± 68 and 237 ± 20 dm^3 mol^{-1} for **I**, **II** and **III**, respectively. As can be seen, the reproducibility of K determination for a given compound is much better than that from dipole moments. Nevertheless, the precision is much worse than for K calculated from IR measurements. The estimated average K value is 374 ± 110 dm^3 mol^{-1} and is of the same order as the spectroscopic values, but the differences between particular compounds are much larger and they change irregularly with the number of CH_3 groups.

Comparing all three methods, one can state that the best K values are obtained from the spectroscopic measurements. For spectroscopic K values the differences between compounds **I**, **II** and **III** are not significant in comparison with the uncertainty of determination. The best average association constant for **I**–**III** is 370 ± 20 dm^3 mol^{-1}. It is possible to show that this value satisfactorily describes the results of dipole moment and average molecular weight measurements. From the dependence of the square of the apparent dipole moment [equation (3)] on the molar fraction of monomer, x_M, the dipole moments of the monomer and dimer can be determined. The values of μ_M and μ_D found in this way are shown in Figure 5.

As can be seen, the dipole moments of monomers are close to those obtained earlier (Table 1) from the extrapolation of μ^2 to zero concentration at 50 °C and the values for **IV**–**VI**. Some increase in the dipole moments of dimers from the expected value $\mu_D = 0$ could result from the deformation of dimers, enhanced atomic polarizability or the presence of some amount of noncyclic forms.[4,5]

The best spectroscopic K value can be also used for reproduction of the concentrational dependence of average molecular weight. The results of such calculations are shown on the plot and compared with experimental data (Figure 2). The qualitative agreement is fairly good. The character of the dependence is the same for the results obtained from calculations based on spectroscopic values of K and experimental values.

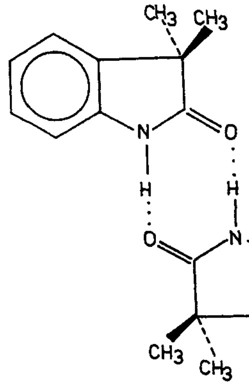
CONCLUSIONS

The dipole moments, IR spectra in the region of ν_s(NH) vibrations and average molecular weights of three 2-oxoindolines in CCl_4 solutions show strong dependences on concentration. On the basis of the strong decrease in apparent dipole moments with increase in concentration and the fact that the average molecular weight approaches the mass of dimers, we conclude that the observed dependences result from the association proceeding mainly to cyclic dimers. The equilibrium constants of this process appear to be independent of the number of methyl groups attached at position 3 in the five-membered ring. It is clear from the most probable structure of a dimer shown in Scheme 2 that no steric influence of methyl groups or phenyl rings on association can be expected from such a model structure.

An increasing number of methyl groups could strengthen the basicity of the C=O group but simultaneously decrease the acidic properties of NH groups. The mutual compensation of these effects explains why also electronic interaction of methyl groups does not influence the association constant.

Drastic differences found in the solid-state structure[12] of **I**–**III** are probably due to the steric influence of the methyl groups on the crystal packing forces.

In comparison with 2-pyrrolidinone,[8] 2-oxoindolines show stronger intermolecular hydrogen bonding; the $\Delta\nu_s$(NH) value is 20 cm^{-1} higher in the latter case and the dimerization constant is three times higher. The



Scheme 2

difference results from the strengthening of the acidic properties of the NH group when the phenyl ring is condensed to the 2-pyrrolidinone ring. This fact and the lower concentration limits explain why we did not detect any trimers as observed for 2-pyrrolidinone by Walmsely *et al.*[8] The IR spectra show a strong interaction between two molecules; the ν_s(NH) band shift on association is about 275 cm^{-1}. The bonded band is broad, amplifying the intensity of ν_s(CH) bands in the region of 3100–2800 cm^{-1}. The properties of 2-oxoindolines studied by three independent methods at various concentrations are internally consistent. The results for the *N*-methylated derivatives **IV**–**VI** correlate with those for the monomers of **I**, **II** and **III**.

The dimerization constants reported[8,15–18] for secondary amides with a *cis* configuration are generally much smaller. Using ^{1}H NMR spectrometry, Purcell *et al.*[19] calculated the association constant of δ-valerolactam in CCl_4 and $CDCl_3$ solutions. They reproduced the concentration dependence of the NH proton chemical shifts by fitting the association constant and chemical shifts for the monomer and dimer. Variation of the chemical shift of the monomer within the range of possible values led to a tenfold change in the *K* values obtained. Wagner *et al.*[20] applied three different methods (IR spectrometry, dielectric measurements and average molecular weight determination by ebulliometry) to determine the association constants of γ-butyrolactam, δ-valerolactam and ε-caprolactam in CCl_4, benzene and cyclohexane solutions. The average values differed between the methods much more than the precision stated for each particular method. Literature data and our results show that among the different techniques used, only IR spectrometry is sufficiently precise for the determination of association constants. This allows for the direct determination of the concentration of one of the species being in equilibrium. Other methods for measuring the collective properties of the system are not sensitive enough to changes in concentration of particular species, especially in the low concentration range. Our results demonstrate that the IR association constant properly describes these collective properties of the system.

Direct results of dipole moment measurements (dependence of dipole moments of **I**–**VI** on concentration at 25 and 50 °C; three tables) and the dependence of the average molecular weight of **I**–**III** on concentration (one table) are available from the authors on request.

ACKNOWLEDGEMENT

The authors are very grateful to Professor L. Sobczyk for help and extensive discussions.

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