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THE INTERACTION BETWEEN SOME ETHYL ESTERS OF AMINOACIDS AND ACETIC ACID IN CARBON TETRACHLORIDE

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Abstract—The dimerization constant, K_1, of acetic acid in CCl_4 is determined by an IR spectrometric method and is found to have a value of 2252M^{-1} at 20°. The association constants, K_2, for the interaction between the acetic acid monomer and some aminoacid ethyl esters are determined by the same method and found to have the values given (in M^{-1} at 20°) for the esters of the following aminoacids: glycine (282 ± 24), DL-alanine (236 ± 33), DL-α-aminobutyric acid (139 ± 11), α-aminoisobutyric acid (172 ± 18), DL-norvaline (104 ± 13), DL-valine (150 ± 8), DL-leucine (108 ± 18) and 3-phenyl-DL-alanine (140 ± 21). A correlation of these experimental values with some structural parameters related to the steric effect of the substituents on the esters is proposed.

THE ring-opening reactions of oxazolinones by ethyl esters of aminoacids that are being studies in this laboratory[1] require a quantitative understanding of the interactions between acetic acid and the aminoacid esters in CCl_4. It has been known for some time that acetic acid dimerizes in aprotic solvents with low dielectric constants, and that in dilute solutions only the monomer and the dimer exist.[2] The dimerization constant of acetic acid in CCl_4 has been determined by several authors.

Harris and Hobbs,[3] measuring the IR absorption of the OH stretching vibration of the acid monomer at 25°, found values for the dimerization constant of 3200 and 5550M^{-1}, respectively, for two concentration ranges between $2{\cdot}5 \times 10^{-4}$ and 25×10^{-4}M, and 3×10^{-3} and 70×10^{-3}M.

Barrow and Yerger[4] reported the determination of the same constant without giving the temperature at which it was made; they measured the IR absorptions of the C=O stretching vibrations of both the monomer and the dimer, finding values that varied between 1000 and 2650M^{-1} for a range of concentrations between 5×10^{-2} and $1{\cdot}12 \times 10^{-4}$M.

Wenograd and Spurr,[5] using a modification of Harris and Hobbs' method, measured the integrated intensities of the OH stretching absorption bands of the monomer at 24°, finding a value of 2375M^{-1} for a range of concentrations between 4×10^{-4} and 3×10^{-2}M.

No detailed work appears to have been done on the interaction between acetic acid and aminoacid esters, but there are some reports on the interactions of amines and acetic acid.

Bruckenstein *et al.*,[6,7] using a combination of IR spectroscopy and differential vapour pressure determination, have shown that, at concentrations lower than 0·01M in benzene or CCl_4, primary, secondary and tertiary amines form 1:1 adducts or ion pairs with different acids, but at higher concentrations other species can exist.

Barrow and Yerger[8] found that, at acetic acid concentrations higher than 0·02M in CCl_4, triethylamine interacts with the acetic acid dimer to form a species $Et_3N \cdot (AcOH)_2$ that is converted into $Et_3N \cdot AcOH$ at higher amine concentrations; however, when the acetic acid concentration is of the order of 10^{-3} M, only the 1:1 ion pair is formed, with no participation of the acetic acid dimer.

Yerger and Barrow[9] studied the diethylamine-acetic acid system in CCl_4 and showed that the only 1:1 species present in the solution at acetic acid concentrations of about 8×10^{-4}M is $Et_2NH \cdot AcOH$, the main pieces of evidence for this claim being the fact that a satisfactory equilibrium constant could be calculated, and the appearance of two IR bands at 2496 and 1629 cm^{-1} due, respectively, to the NH stretching and bending modes of NH_2^+, and one at 1739 cm^{-1}, midway between the positions of the C=O stretching bands of the monomer (1770 cm^{-1}) and the dimer (1712 cm^{-1}). The number of different species increases at acetic acid concentrations between 0·1 and 0·3M.

In this paper the interaction constants of acetic acid and the ethyl esters of glycine (**1**), DL-alanine (**2**), DL-α-aminobutyric acid (**3**), α-aminoisobutyric acid **4**), DL-norvaline (**5**), DL-valine (**6**), DL-leucine (**7**) and 3-phenyl-DL-alanine (**8**) in CCl_4 at 20° are described.

RESULTS AND DISCUSSION

In a dilute solution of an aminoacid ester and acetic acid in CCl_4 it can be assumed that, within a certain range of concentrations, the following are the most important equilibria:

$$2\,\underset{\substack{\text{monomer}\\(\mathbf{9})}}{CH_3\text{—}CO_2H} \xrightleftharpoons{K_1} \underset{\substack{\text{dimer}\\(\mathbf{10})}}{(CH_3\text{—}CO_2H)_2} \tag{1}$$

$$\underset{(\mathbf{9})}{CH_3\text{—}CO_2H} + \underset{\text{ester}}{NH_2\text{—}R} \xrightleftharpoons{K_2} \underset{\text{ion pair}}{CH_3\text{—}CO_2H\cdots NH_2\text{—}R} \tag{2}$$

This is based on the observation of Allen and Caldin[2] who, in a review of the literature, had found that, in aprotic solvents, only **9** and **10** can be accounted for by several different methods; only one exception is cited of the existence of higher aggregates of acetic acid in benzene and nitrobenzene, but this observation has not been confirmed in dilute solutions.

The assumption that the aminoacid ester interacts mainly with **9** is borne out by Bruckenstein's observation[6,7] that, at concentrations smaller than 0·01M in CCl_4, the amines studies by him only form 1:1 adducts with the acids, but do not associate with themselves.

Dimerization constant K_1. In view of the discrepancy in the values of the dimerization constant of acetic acid determined by Harris and Hobbs,[3] Barrow and Yerger,[4] and Wenograd and Spurr,[5] K_1 of Eq. (1) was determined at 20°, using a modification of the method described by Harris and Hobbs.[3] The results obtained for an acetic acid concentration range between 2·97 × 10^{-4} and 13·37 × 10^{-4} M are shown in Table 1.*

TABLE 1. EXPERIMENTAL RESULTS USED FOR THE DETERMINATION OF K_1^a

A	[AcOH] M × 10^4	$\frac{[\text{AcOH}]}{A}$ M × 10^4
0·193	2·97	15·389
0·279	4·46	15·992
0·337	5·94	17·636
0·377	7·43	19·705
0·437	8·91	20·364
0·467	10·40	22·245
0·506	11·88	23·487
0·537	13·37	24·889

[a] The value of the dimerization constant K_1 was obtained by combining the Lambert–Beer Law ($A = abc$, where A is the absorbance, a the absorptivity, b the sample path length and c the concentration of the substance; Eq. (3)) with the equilibrium expression derived from Eq. (4).

$$[\text{monomer}] = \frac{A}{ab} \tag{3}$$

$$K_1 = \frac{[\text{dimer}]}{[\text{monomer}]^2} \tag{4}$$

and since

$$[\text{dimer}] = \frac{[\text{AcOH}] - [\text{monomer}]}{2} \tag{5}$$

then

$$K_1 = \frac{[\text{AcOH}]a^2b^2 - Aab}{2A^2} \tag{6}$$

and

$$A = \frac{[\text{AcOH}]a^2b^2}{2K_1A} - \frac{ab}{2K_1} \tag{7}$$

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* The following abbreviated expressions shall be used subsequently to denote, respectively, the concentrations of total acetic acid, **9**, **10**, total ester, ester at equilibrium and the ion pair: [AcOH], [monomer], [dimer], [ester], [ester_{eq}] and [IP].

Now, if we take $a^2b^2/2K_1 = m$, and $-ab/2K_1 = n$, by the least squares method we find that $m = 332{\cdot}23$ and $n = -0{\cdot}2716$, with a correlation $r = 0{\cdot}977$. Since a 2 cm cell was used, $m = 2a^2/K_1$ and $n = -a/K_1$, and the solution for this system of two simultaneous equations is $a = -m/2n$. Therefore, $a = 611{\cdot}62\text{M}^{-1}\ \text{cm}^{-1}$, and since $K_1 = -a/n$, a value of 2252M^{-1} is obtained for K_1, in close agreement with that of Wenograd and Spurr[5] and with that of Barrow and Yerger[4] for the more dilute solutions.

Association constant K_2. It is assumed that, as shown in Eq. (2), only **9** interacts with the aminoacid ester to form an ion pair. The concentration of **9** was determined by IR spectroscopy, and the association constants K_2 were obtained by combining the Lambert–Beer Law with the equilibrium expressions derived from Eqs. (1) and (2):

$$[\text{IP}] = [\text{AcOH}] - \{[\text{monomer}] + 2[\text{dimer}]\} \tag{8}$$

$$[\text{ester}_{\text{eq}}] = [\text{ester}] - [\text{IP}] \tag{9}$$

$$K_2 = \frac{[\text{IP}]}{[\text{ester}_{\text{eq}}]\,[\text{monomer}]} \tag{10}$$

A fixed acetic acid concentration of $17{\cdot}04 \times 10^{-4}$M, and ester concentrations that varied between 25×10^{-4} and 150×10^{-4}M were used. Higher concentrations of ester can not be used because there is interference with the IR bands of **9** and **10**, and other equilibria become important. Table 2 shows the experimental data used for calculating the value of K_2 for **6**, and Table 3 the values of K_2 obtained for all the aminoacid ethyl esters studied, each of which was determined from a minimum of seven readings.

TABLE 2. EXPERIMENTAL DATA FOR **6**

[Ester] M × 10^3	*A*	K_2 M^{-1}
0	0·629	—
6·01	0·542	151·4
7·51	0·518	159·8
9·00	0·505	150·6
12·01	0·485	133·0
13·52	0·453	151·2
15·02	0·444	144·6
16·52	0·417	157·6

TABLE 3. VALUES OF K_2 FOR THE ETHYL ESTERS OF AMINOACIDS

Ester	K_2 M^{-1}
1	282 ± 24
2	236 ± 33
3	139 ± 11
4	172 ± 18
5	104 ± 13
6	150 ± 8
7	108 ± 18
8	140 ± 21

Although some assumptions have been made, the fact that a constant is obtained would mean that these assumptions are well founded; moreover, the constant that shows the highest dispersion, that of **2**, has been used to describe the system of the acid-catalysed reaction between **2** and 2-phenyl-4,4-dimethyl-2-oxazolin-5-one in CCl_4, accounting satisfactorily for the kinetic behaviour of the system.[1] The same kind of supporting evidence has also been found for other aminoacid esters,[10] thus confirming the values obtained for K_2.

Further confirmation of the values of the constants is provided by the fact that, when the concentration of **9** at equilibrium is plotted against the initial concentration of aminoacid ester, straight lines are obtained which, when extrapolated to zero ester concentration, should give the initial concentration of **9**.* In Table 4 the values obtained by extrapolation are compared with those calculated from the expression

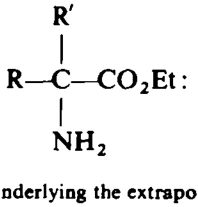
$$[\text{monomer}]^2 + \frac{[\text{monomer}]}{2K_1} - \frac{[\text{AcOH}]}{2K_1} = 0$$

obtained by combining Eqs. (4) and (5), and from the Lambert–Beer Law, showing that there is very good agreement between the three sets of values.

Table 4. Comparison of the values of [monomer] obtained by different methods (all values in M × 10^4)

Ester	[AcOH]	Extrapolated	Eqs (4) and (5)	Lambert–Beer
1	15·64	4·231	4·886	4·888
2	11·40	3·919	4·040	3·302
3	15·52	4·833	4·864	4·864
4	15·04	4·613	4·774	4·774
5	16·10	5·039	4·971	4·975
6	17·04	4·961	5·140	5·142
7	15·64	5·154	4·886	4·888
8	14·70	4·886	4·710	4·708

Correlation of K_2 *with Taft's polar and steric parameters.* No correlation is observed between K_2 and Taft's substituent constant, σ^*, showing that polar factors are not the most important ones controlling the equilibria. But if $\log K_2$ is correlated with Taft's steric parameter E_s, the points approach a straight line, even though with a rather wide dispersion, showing that the interaction is influenced mainly, but not exclusively, by steric factors. This is reasonable because it is the acetic acid molecule that interacts, and it does have considerable steric requirements. Further support for this assumption is provided by the fact that a correlation can be established between the values of K_2 and the number and arrangement of the carbon atoms in the substituents R and R′ of the aminoacid esters,



$$\mathrm{R{-}C(R')(NH_2){-}CO_2Et}: \qquad \log K_2 = \log K_{2_0} - (p + q)C \qquad (11)$$

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* The equation underlying the extrapolation is, according to Eqs (8) and (9), $[\text{monomer}] = [\text{AcOH}] - 2[\text{dimer}] + [\text{ester}_{eq}] - [\text{ester}]$ and when $[\text{ester}] = 0$, $[\text{monomer}] = [\text{AcOH}] - 2[\text{dimer}]$. The variation of [dimer] with that of [ester] is small, so that the term $[\text{AcOH}] - 2[\text{dimer}]$ is approximately constant. The equation shows that the slope is −1, which is in agreement with the experimental values, all of which had correlations of at least 0·99.

where K_{2_0} is the equilibrium constant for the interaction between acetic acid and **1** (R = R′ = H); p is the number of unfulfilled branching possibilities of R′; q is the number of carbon atoms in (R + R′); and C is an empirical constant whose value is 0·1. Table 5 shows the results of these correlations which, if dependent to an important extent on the influence of the arrangement of the substituents, would be governed by entropic phenomena, and therefore the main factors involved in the value of K_2 should be steric.

TABLE 5. CORRELATION BETWEEN K_2 AND THE SUBSTITUENTS ON THE AMINOACID ESTERS

Ester	R	R′	$K_{2_{exp}}$ M^{-1}	$K_{2_{calc}}$ M^{-1}	p	q
1	H	H	282 ± 24	282	0	0
2	H	Me	236 ± 33	224	0	1
3	H	Et	139 ± 11	141	0	2
4	Me	Me	172 ± 18	178	0	2
5	H	Pr	104 ± 13	112	1	3
6	H	i-Pr	150 ± 8	141	0	3
7	H	i-Bu	108 ± 18	90	1	4

Structure of the ion pair. Since no bands attributable to the ammonium or the carboxylate ions appear in the IR, this species is probably an undissociated ion pair.

EXPERIMENTAL

IR spectra and absorbance readings were obtained on a Leitz model IIIG spectrophotometer.

Materials. AcOH and CCl_4 (E. Merck, Darmstadt, reagent grade) were dried as follows: AcOH was treated with silica gel until no OH stretching band could be detected in the IR at 3680 cm^{-1} in a 1 mm cell; CCl_4 was kept over molecular sieves (E. Merck, Darmstadt, type 4A) so that no OH band could be detected in the IR at 3680 cm^{-1} in a 2 cm cell.

Aminoacid esters. The pure aminoacids were converted into their ethyl ester hydrochlorides, from which the free esters were obtained by the method described.[11]

TABLE 6. PHYSICAL PROPERTIES OF THE AMINOACID ETHYL ESTERS

Ester	b.p. found °C/torr	b.p. literature °C/torr	n_D^{20} found	n_D/°C literature	Ref.
1	40/5	65/40	1·4236	1·42417/20	12a, 1
2	32–34/4	48/11	1·4186		12b
3	44/2	61·5/11	1·4235		12c
4	36/6	39–41/11	1·4151	1·4169/17	12d
5	61/3	68·5/8	1·4264		12e
6	59/6	82·5/23	1·4265		12f
7	70/5	84·5/16	1·4280		12g
8	113/2	148/15	1·5108		12h

Determination of K_1 *and* K_2. The solvent and all the solutions were kept at 20 ± 0·02°, and all readings were taken on matched 2 cm NaCl cells. To determine K_1 a stock solution of acetic acid was prepared by weighing the acid directly, and all the required dilutions were obtained from it. The calculations were performed as described,[3] measuring, however, the absorbance of the C═O stretching band of **9** at 1770 cm^{-1} instead of that of the OH. When the method of Barrow and Yerger[4] was applied, the results were not satisfactory because the sum of the concentrations of **9** and **10** differed by about 20% from the total amount of acetic acid, probably because at the higher acid concentrations there was still some monomer present that could actually be detected, but whose concentration could not be determined. The base line method[13,14] was used for all the measurements.

To determine K_2, stock solutions were prepared by weighing each aminoacid ester directly. Aliquots of the ester and acid solutions, measured from a 10 ml buret graduated in 0·02 ml, were mixed together in a volumetric flask already containing some solvent, a precaution that is necessary to avoid the formation of a ppt that does not dissolve on further dilution; after making up the volume to the mark, the concentration of **9** was determined as above. However, since the C═O stretching band of the esters appears between 1740 and 1724 cm^{-1}, it overlaps partially those of **9** and **10** at the higher ester concentrations; a 3:1 abcissa expansion was therefore used, and an equimolar solution of pure ester was placed in the reference beam of the instrument. In this way overlap was minimized and the base line method[13,14] could be applied by considering the C═O bands of **9** and **10** as symmetrical, and extending their overlapping sides until they intersected.

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