[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, NORTHWESTERN UNIVERSITY]

Nature of Amino Acids in Solvents of Low Dielectric

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The infrared absorption spectra of an α-, β- and γ-amino acid in solution in CCl_4, $CHCl_3$ and *n*-butyl alcohol have been obtained. The α-amino acid occurs as a zwitterion dimer in concentrated $CHCl_3$ solutions, and in dilute $CHCl_3$ and CCl_4 as an internally hydrogen bonded monomer. In *n*-butyl alcohol a zwitterion species forms. The β- and γ-amino acids have less tendency to dimerize and show in $CHCl_3$ and *n*-butyl alcohol a chelated monomer which exhibits a tautomeric equilibrium between a hydrogen bonded complex and a zwitterion species.

Amino acids have been shown to exist in a zwitterion form in aqueous solution[1] and in the solid state.[2] In less polar media, however, this ionic form will be less favored and for solvents of sufficiently low dielectric constant or solvating power, or for amino acids with an environment of such properties, the non-ionic form may be predominant. In these low dielectric solvents, furthermore, the amine and acid groups will tend to associate, with or without proton transfer, and the molecular geometry is likely to control the intra- or intermolecular nature of this association. To include some of the different geometric situations an α-, β- and γ-amino acid have been investigated.

Previous work in this Laboratory has shown that the species present in solutions of amines and carboxylic acids can be investigated by infrared spectroscopy.[3] This procedure appears to be applicable to the amino acid problems. For this approach the solvents CCl_4, $CHCl_3$ and *n*-butyl alcohol are convenient and the N,N-diethyl-derivatives of glycine, β-aminopropionic and γ-aminobutyric acid are sufficiently soluble.

Experimental

Materials. N,N-Diethylglycine.—The sodium salt of N,N-diethylglycine was prepared from chloroacetic acid and diethylamine by the method of Michaelis and Schubert.[4] An aqueous solution was brought to *p*H 7 by hydrochloric acid and the neutral solution evaporated to dryness. The product was taken up in $CHCl_3$ and crystallized from a $CHCl_3$–CCl_4 solution.

Anal. Calcd. for $C_6H_{13}O_2N$: C, 54.9; H, 10.0; N, 10.7. Found: C, 54.4; H, 9.3; N, 10.5.

N,N-Diethyl-β-aminopropionic Acid.—Similar procedure with β-chloropropionic acid and diethylamine yielded the desired product.

Anal. Calcd. for $C_7H_{15}O_2N$: C, 58.0; H, 10.4; N, 9.6. Found: C, 57.8; H, 9.8; N, 9.7.

N,N-Diethyl-γ-aminobutyric Acid.—γ-Chlorobutyronitrile was refluxed for 10 hours with a twofold excess of diethylamine in absolute alcohol. After evaporation to near dryness, an excess of concentrated HCl was added and the solution again refluxed. After evaporation to dryness the residue was extracted with a $CHCl_3$–alcohol solution leaving a residue of NH_4Cl. The solvent was removed and the crude hydrochloride was washed with $CHCl_3$. An aqueous solution of the hydrochloride was neutralized with NaOH, evaporated to dryness and extracted with $CHCl_3$. The solvent was removed and the hygroscopic product washed with CCl_4 and ether.

Anal. Calcd. for $C_8H_{17}O_2N$: C, 60.3; H, 10.7; N, 8.8. Found: C, 59.5; H, 10.6; N, 8.7.

Procedure.—All spectra were obtained on a Baird Associates instrument with rock salt optics. Cells of thickness 0.1, 0.7 and 10 mm. were used. Absorption frequencies were obtained from spectra with superimposed polystyrene calibrations and except for some of the broad carboxylate absorptions are accurate to ±5 cm.$^{-1}$.

Results

N,N-Diethylglycine.—In $CHCl_3$ solutions both a monomeric and a dimeric species are observed. At concentrations greater than about 0.01 *M* a strong absorption at 1640 cm.$^{-1}$ occurs and the carbonyl region is transparent. On dilution, however, a new absorption at 1764 cm.$^{-1}$ comes in and at about 2×10^{-4} *M* the two absorptions have approximately the same intensity.

The slight solubility in CCl_4 permits only solutions of less than about 10^{-4} *M* to be investigated. Below this concentration a single absorption band is observed at 1786 cm.$^{-1}$. This absorption can probably be attributed to a monomeric species since at these concentrations some dissociation of any dimer would be expected.[3] Comparison with the monomer frequency in $CHCl_3$ and the interpretation of these frequencies further support this conclusion.

In *n*-butyl alcohol in the workable concentration range of 0.5 to 0.01 *M*, an absorption band occurs at 1640 cm.$^{-1}$. This can again be attributed o at monomer on the basis, for instance, that even at concentrations of 0.2 *M*, a solution of triethylamine and acetic acid shows appreciable unreacted material, in butyl alcohol. Association at two sites in the glycine case could not be expected to prevent some dimer dissociation from appearing at the lowest concentration studied.

The observed frequencies for the glycine derivative are shown along with the results for the β- and γ-amino acids in Table I.

TABLE I

CARBONYL AND CARBOXYLATE ABSORPTION FREQUENCIES (CM.$^{-1}$) FOR SOME AMINO ACIDS

	N,N-Diethylglycine		N,N-Diethyl-β-aminopropionic acid		N,N-Diethyl-γ-aminobutyric acid	
	Monomer	Dimer	Monomer	Dimer	Monomer	Dimer
CCl_4	1786	..	1740	..	1740	..
$CHCl_3$	1764	1640	1718 ~1630	1610	1695 ~1612	1600
Butyl alc.	1630	..	1710 1600	..	1707 1592	..

N,N-Diethyl-β-aminopropionic and -γ-aminobutyric Acids.—As with the glycine compound the longer chain amino acids show, in the 1500 to 1800 cm.$^{-1}$ region, a single absorption in dilute solution, 10^{-3} to 10^{-4} *M*, in CCl_4 which can be attributed to

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[1] E. J. Cohn and J. T. Edsall, "Proteins, Amino Acids and Peptides," Reinhold Publ. Corp., New York, N. Y., 1943; J. T. Edsall and M. H. Blanchard, THIS JOURNAL, **55**, 2337 (1933).

[2] I. M. Klotz and D. M. Gruen, *J. Phys. Chem.*, **52**, 961 (1948).

[3] G. M. Barrow and E. A. Yerger, THIS JOURNAL, **76**, 5211 (1954); **77**, 6206 (1955).

[4] L. Michaelis and M. P. Schubert, *J. Biol. Chem.*, **115**, 221 (1936).

a monomer. The normal carbonyl frequency of 1740 cm.$^{-1}$ is, however, observed. An additional broad weak band centered at about 2700 cm.$^{-1}$ also shows up.

Both amino acids in $CHCl_3$ show some dimer formation which, however, unlike the glycine case is not appreciable below about 0.1 *M*. At higher concentrations a fairly strong, slightly broadened absorption occurs at about 1600 cm.$^{-1}$ along with a considerably weaker band at about 1700 cm.$^{-1}$. On dilution the 1600 cm.$^{-1}$ band quickly decreases relative to that at 1700 cm.$^{-1}$ but does not entirely disappear and below about 0.01 *M* maintains a constant intensity relative to the band at 1700 cm.$^{-1}$. These results indicate monomeric species in $CHCl_3$ with absorptions both in the carbonyl and the carboxylate regions.

In butyl alcohol no evidence for the dimer is found but again two absorptions at approximately the same frequencies (see Table I) as those attributed to the $CHCl_3$ monomer are observed. Now, however, the carbonyl absorption is very weak compared to that of the carboxylate and for the β-amino acid is, at room temperature, just detectable.

The ratio of the intensities of the carbonyl and carboxylate bands for both amino acids is dependent on the solvent and on the temperature. For mixed $CHCl_3$–butyl alcohol solvents this intensity ratio shows a gradual decrease of the carbonyl and increase of the carboxylate, the frequencies being only slightly affected, as the solvent composition is changed from $CHCl_3$ to butyl alcohol. For butyl alcohol solutions, the spectra at a temperature of about 100° show an increase in the carbonyl absorption and a decrease in the carboxylate absorption compared to room temperature which indicates a heat of reaction of several kilocalories.

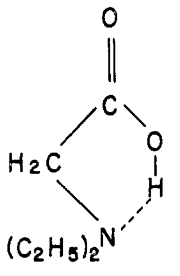
Discussion

The N,N-diethylglycine monomer in both $CHCl_3$ and CCl_4 is characterized by the unusually high frequency carbonyl absorption. These frequencies suggest the strained internally hydrogen bonded structure I analogous to the lactone structures which, as shown in Table II, also show a high frequency carbonyl absorption. The monomer in butyl alcohol can be assigned the similar but proton transferred structure II. Here the increase in the absorption frequency from a normal carboxylate at about 1580 cm.$^{-1}$ may be attributed to some asymmetry in the carboxylate group resulting from the adjacent positive charge or a hydrogen bond.

TABLE II

CARBONYL ABSORPTION FREQUENCIES

	CCl_4 soln.	$CHCl_3$ soln.
N,N-Diethylglycine	1786 cm.$^{-1}$	1764 cm.$^{-1}$
β-Propiolactone	1841	..
γ-Butyrolactone	1780	1760
γ-Valerolactone	1748	..
Esters	1745	1735



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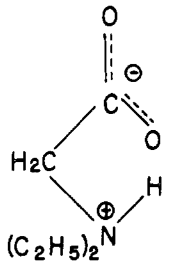
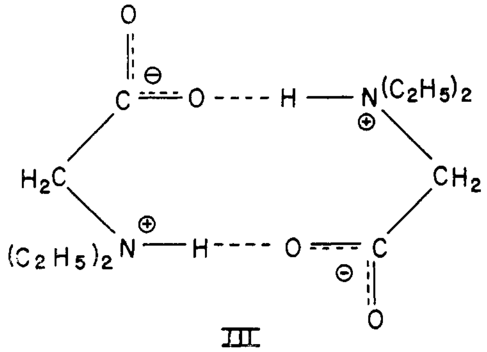


II

The dimer, as occurs only in $CHCl_3$, must result from a "head-to-tail" neutralization to produce the double zwitterion structure III



III

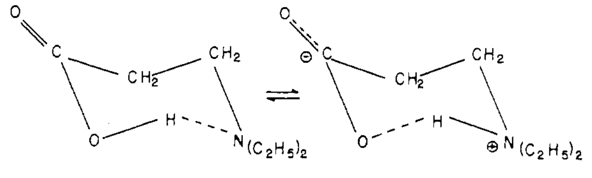
The proton transfer occurring here is expected in view of the similar transfer in the association product of triethylamine and acetic acid in $CHCl_3$.[3]

The dimer of the β- and γ-amino acids can be assigned a structure like that of III to account for the absence of a carbonyl and the presence of the carboxylate.

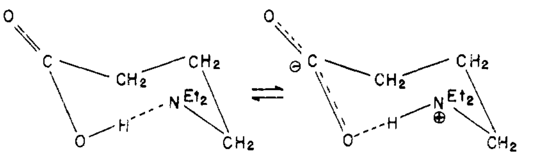
Likewise the monomers in CCl_4 would be expected to have an internal hydrogen bond which, for these larger rings, would be expected to have an almost normal carbonyl frequency.

The monomers in $CHCl_3$ and butyl alcohol, showing both carbonyl and carboxylate absorption, must be assigned the tautomeric structures of IV and V. The geometry of both compounds is capable of accommodating an internal bond of the hydrogen bond or ion-pair type.

The possibility of a symmetrically shared proton between the amine and carboxylate groups is not



IV



V

borne out. This situation follows that previously found for pyridine–carboxylic acid system where, for a proton equally attracted to the two groups, a double minimum potential energy curve and the existence of tautomers resulted.[5]

The experimental difficulties for both dilute $CHCl_3$ and butyl alcohol solutions prevent a quantitative determination of the ratio of the zwitterion to hydrogen bonded complex for the two amino acids. In $CHCl_3$ both amino acids show carbonyl absorptions several times stronger than carboxylate absorptions. In butyl alcohol, however, the carbonyl is only about one tenth as strong as the carboxylate, with the non-zwitterion form favored in the γ-amino acid by about a factor of 2 over the β-amino acid.

The presence of some non-proton transfer species is in contrast to the exclusive formation of an ion-pair in the reaction of triethylamine and acetic acid in chloroform. This difference can be assigned either to the geometric requirements of the chelate products or to the decrease in solvation at the reaction site due to the shielding by the amino acid chain.

EVANSTON, ILL.

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[5] G. M. Barrow, THIS JOURNAL, **78**, 5802 (1956).