amine. In sodium chloride–trichloroacetate buffer, the isoelectric point of their preparation was at *p*H 1.8.

The mucoprotein described by Weimer, Mehl and Winzler[64] had properties very similar to those of the acid glycoprotein. The concentration in plasma of both was 0.7% of the total proteins. The content of nitrogen, hexose and hexosamine was essentially the same. The sedimentation constant of the mucoprotein was reported to be 3.1 *S* (Spinco ultracentrifuge) at zero concentration as compared with the value of 3.5 *S* (Pickel's ultracentrifuge) for the acid glycoprotein. The difference in the reported sedimentation constants was resolved by a study by Dr. J. L. Oncley of a preparation of mucoprotein.[65] The sedimentation constants of the mucoprotein were estimated to be 3.80 and 3.55 *S*, respectively, in 0.15 *M* NaCl solution at a concentration of 0.28 and 0.45%, respectively. In the electrophoretic studies, the use of different buffers accounts for the different isoelectric points. Indeed, the acid glycoprotein tested in a sodium chloride–trichloroacetate buffer[64] was isoelectric at *p*H 1.8. Moreover, the mucoprotein[64] on electrophoretic analysis had the same mobilities as the acid glycoprotein. In phosphate buffer, ionic strength 0.1 and *p*H 2.4, it was negatively charged and showed a mobility of $+0.72 \times 10^{-5}$ cm.^{2}/volt sec. In acetate buffer *p*H 4.4, ionic strength 0.1, the mobility was -3.10×10^{-5} cm.^{2}/volt sec., and in phosphate buffer *p*H 7.6, ionic strength 0.1, the mobility was -6.67×10^{-5} cm.^{2}/volt sec. These three values for the mucoprotein were, within the error of the method, identical with those obtained for the acid glycoprotein under the same conditions. The solubilities of both protein preparations, as far as investigated, were also the same.

Other investigators have studied protein mixtures, derived from plasma, with properties similar to those of the acid α_1-glycoprotein. Such preparations were obtained either from sulfosalicylic acid filtrates of plasma,[45,47] from filtrates of plasma after deproteinization by boiling[45] or by fractional precipitation with ammonium sulfate or sodium sulfate.[45,66,67] These mixtures were designated as seromucoids, serum polysaccharides or blood proteoses.

Because the proteins of Fraction I to V of Method 10, representing slightly over 98% of the plasma proteins, would be denatured and rendered insoluble by boiling[68] and since Fraction VII and its supernatant solution were free of protein, the protein mixture previously called "seromucoids, etc. . .," was concentrated in Fraction VI. The acid glycoprotein represents the major component of these very soluble glycoproteins.

Acknowledgment.—The author wishes to express his appreciation of the encouragement and advice of Drs. Edwin J. Cohn, John T. Edsall and John L. Oncley.

(65) These preparations were obtained through the courtesy of Dr. R. J. Winzler, Department of Biological Chemistry, University of Illinois, Chicago 12.

(66) A. B. Gutman, *Advances in Protein Chem.*, **4**, 161 (1948).

(67) M. L. Petermann, N. F. Young and K. R. Hogness, *J. Biol Chem.*, **169**, 379 (1947).

(68) Except the α_2-mucoprotein of Fraction IV which was insoluble, in the absence of salt. Its sedimentation constant of 11 *S* at zero concentration (*cf.* (20)) was different from that of the acid glycoprotein.

BOSTON 15, MASS.

[CONTRIBUTION FROM THE WEIZMANN INSTITUTE OF SCIENCE AND THE SCIENTIFIC DEPARTMENT, ISRAELI MINISTRY OF DEFENCE]

Intramolecular Hydrogen Bonds in 2-Aminoalkanols and N-Alkylidene-2-aminoalkanols

BY ERNST D. BERGMANN, E. GIL-AV[1] AND S. PINCHAS

RECEIVED NOVEMBER 23, 1951

Intramolecular hydrogen bonds of the type OH...N involving five-membered rings, have been studied with the help of infrared absorption measurements. 2-Aminoalkanols in carbon tetrachloride solution form such intramolecular hydrogen bonds; in ethanolamine and its N-methyl derivative only intermolecular association has been observed. From the shifts of the hydroxyl absorption, the strength of the intramolecular hydrogen bonds is estimated at about 6 kcal./mole. No analogous effect was observed with certainty in N-alkylidene-2-aminoalkanols, possibly because of the lower basicity of their nitrogen atom.

The strength of internal hydrogen bonding, which depends—among other factors—on the nature of the bonded atoms, the size of the resulting "ring" and possible resonance effects,[2] expresses itself in a shift of the infrared absorption band of the "free" hydroxyl group from about 3600 cm.$^{-1}$ toward longer wave lengths. According to Badger and Bauer,[3] an energy difference of 1 kcal./mole between the two forms causes a shift of 35 cm.$^{-1}$ in the fundamental, of 70 cm.$^{-1}$ in the second, and of 60 cm.$^{-1}$ (estimated) in the first overtone. Six-membered hydrogen bond rings are more favored than five-membered ones.[2-6]

The present paper deals with hydrogen bonds of the type OH···N in amino alcohols and related compounds.

In Table I, the infrared absorption data and (some) molecular weight determinations are listed for a number of 2-aminoalkanols, mostly containing secondary and tertiary nitrogen atoms. Out of 13 substances investigated, all of fairly

(1) Part of a Thesis presented by E. Gil-Av to the Hebrew University, Jerusalem, in partial fulfillment of the requirements for the degree of Ph.D.

(2) L. Pauling, "Nature of the Chemical Bond," 2nd Ed., Cornell University Press, Ithaca, N. Y., 1942, p. 284.

(3) R. M. Badger and S. H. Bauer, *J. Chem. Phys.*, **5**, 839 (1937).

(4) (a) S. B. Hendricks, *et al.*, THIS JOURNAL, **58**, 1991 (1936); (b) O. R. Wulf, *et al.*, *ibid.*, **58**, 2287 (1936).

(5) F. T. Wall and W. F. Claussen, *ibid.*, **61**, 2679 (1939).

(6) L. R. Zumwalt and R. M. Badger, *ibid.*, **62**, 305 (1940).

TABLE I

INFRARED ABSORPTION AND MOLECULAR WEIGHT OF 2-AMINOALKANOLS

Solvent, carbon tetrachloride, unless otherwise stated

(a) HO—CH_2—CH_2—NRR′

No.	R	R′	Subst. (mole per liter)	Cell thickness (mm.)	Absorption bands wave number (cm.$^{-1}$)	Optical density[d]	Mol. wt., calcd.	Mol. wt., found	Concentration mole/liter
I	H	H	0.13	2.0	3210[a]	0.11			
					3300	shoulder			
					3600	.05			
II	H	C_6H_5	.06	2.0	3360	.47	137	148	0.07
					3590	.25			
III	H	CH_3	.09	2.0	3100	.42	75	185	.23
					3280	.41			
					3610	.15			
			.03	2.0	3290	.26[b]			
					3600	weak shoulder			
IV	H	CH_2(o-C_6H_4·OH)	.37[c]	0.1	3300	.38	167	183	.04
					3410	shoulder .35			
			.05	2.0	3300	.29		245	.14
					3420	.26			
					3610	.21			
V	CH_3	n-C_4H_9	.65	0.1	3450	.27	131	137	.21
								175	.58
VI	CH_3	CH_2(p-C_6H_4·OCH_3)	.42	0.1	3450	.21	195	200	.05
			.03	2.0	3450	.18		255	.15
VII	n-C_3H_7	C_6H_5	.57	0.1	3380	Not measured	179	196	.17
					3600	Not measured			
			.17	2.0	3400	.42		226	.34
					3580	.38			

(b) $(CH_3)_2C(OH)\cdot CH\cdot(CH_3)\cdot NRR'$

VIII	H	H	0.06	2.0	3390	0.45	103	117	0.12
					3580	weak shoulder			
IX	H	CH_3	.16	0.1	3380	.07	117	125	.07
								151	.13
X	H	$CH(CH_3)\cdot CH_2$ $CH(CH_3)_2$	.39	.1	3450	.13	...		
XI	H	p-C_6H_{10}·CH_3	.37	.1	3430	.12	...		
			.05	2.0	3410	.24			
XII	n-C_4H_9	$CH(CH_3)\cdot CH_2$	.32	0.1	3320	Not measured	243	240	.21
		$CH(CH_3)_2$	.02	2.0	3320	.13			
			.30	0.1	3430	.09[b]	...		
XIII	H	$(n$-$C_3H_7)_2CH$	.02	2.0	3410	.09			

[a] Broad band. [b] Calculated from the base line of the spectrum. [c] Chloroform as solvent. [d] Unless otherwise stated, difference between the optical density of the solution and that of the solvent.

divergent structure, nine show a shift of the hydroxyl absorption to the region of 3380–3450 cm.$^{-1}$.[7] An examination of the exceptions shows the following: The low frequency band (3300 cm.$^{-1}$) in N-(*o*-hydroxybenzyl)-aminoethanol (IV) is very probably due to chelation, but involving the phenolic and not the alcoholic hydroxyl group. The bands of low frequency observed for ethanolamine (I) and N-methylethanolamine (III) must be ascribed to intermolecular hydrogen bonds persisting in dilute solution. The molecular weight of (III) (found: 185, calcd: 75; in 1% benzene solution) bears out this explanation (I is insoluble in non-polar solvents).

The molecular weights were determined for a number of other aminoalkanols (see Table I). Although their limited solubility in benzene precludes measurements in high concentrations, it can be seen that a certain amount of association may take place in benzene solution (depending both on concentration and structure of the aminoalkanol), but it is far less pronounced than in simple hydroxylic compounds.[8] At about 0.1 mole/liter[9] (in certain cases even at 0.2 mole/liter), the aminoalkanols are practically all non-associated.[10]

(7) The estimated experimental error in the wave number in this region is 10–20 cm.$^{-1}$.

(8) N. D. Coggeshall and E. L. Saier, THIS JOURNAL, 73, 5414 (1951).

(9) W. C. Sears and L. J. Kitchen, *ibid.*, 71, 4110 (1949), have found that even phenols which are much more strongly associated, are monomeric at a concentration of 0.07 mole/liter. The situation is different in the case of the acids; see A. E. Martin, *Nature*, 166, 474 (1950).

(10) The different behavior of compound (IV) is very likely due to the presence of the phenolic hydroxyl group.

As the infrared measurements were mostly carried out in concentrations in which the aminoalkanols show the molecular weight of the monomeric forms, it is very probable that the hydroxyl bands observed in the 3380–3450 cm.$^{-1}$ region are due to intramolecular hydrogen bonding. Only for compounds (II), (VII) and (VIII), the spectrum reveals the presence of free hydroxyl groups—and only weakly at that; it can, therefore, also be concluded that this hydrogen bonding is practically complete.

A relatively small deviation from the above defined region is observed for the bulky 2-(N-butyl - N - [α,γ - dimethylbutyl] - amino) - 3 - methyl-3-butanol (XII), the hydroxyl absorption of which is shifted to 3320 cm.$^{-1}$. The molecular weight determination indicates, however, an intramolecular bond also for this substance.

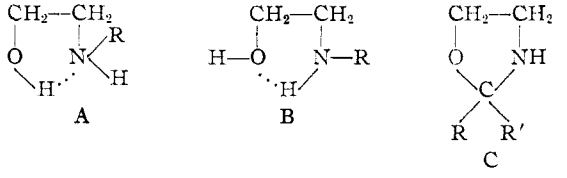
In a number of instances, the relation between the shift of the hydroxyl absorption and the concentration has been investigated. No significant difference could be detected in agreement with the trend observed in the molecular weight determinations.[11]

A priori, chelation in primary and secondary 2-aminoalkanols can occur in two ways indicated by (A) and (B).

It is to be expected that the intensity of the shifted band corresponding to (B) would be weak,[12] and that the peak indicating free hydroxyl groups would appear in the spectrum.[13]

As already pointed out, however, bands due to free hydroxyl are either absent or appear with very low intensity. One must, therefore, conclude that (A) represents the predominant form of chelation.

In connection with these experiments, the products have been studied which arise from the condensation between 2-aminoalkanols and carbonyl compounds.[14] For these products, the structures of either oxazolidines (C) or Schiff bases (D) are



A B C

possible; in the latter, intramolecular hydrogen bonding can be expected to occur (E). Substances known to possess structure (D) were selected for the investigation.

The experimental data summarized in Table II show a shift of the hydroxyl absorption into the 3380–3450 cm.$^{-1}$ region, persisting in dilute solution, only in the cases of N-(*o*-hydroxybenzylidene)-aminoethanol (XVII), and of N-(α-naphthylmethylene)-aminoethanol (XV). For (XVII), there exist two possibilities of chelation of the OH···N type, *viz.*, (F) and (G). The six-membered ring (F) which involves the phenolic hydroxyl has probably greater stability and is, therefore, assumed to be responsible for the observed hydroxyl absorption at 3420 cm.$^{-1}$. That the 3400 cm.$^{-1}$ band of the α-naphthyl derivative (XV) is due to chelation, is confirmed by molecular weight determination (in 1% benzene solution: found, 220; calcd., 199) and by the magnitude of the shift which is appreciably smaller than that expected from an intermolecular hydrogen bond in alcohols.[15] Compound (XV) is thus the only substance among the N-alkylidene-2-aminoalkanols examined, in which the alcoholic hydroxyl group causes chelation.[16]

TABLE II

INFRARED ABSORPTION OF SCHIFF BASES, OH—CH_2—CH_2—N=CRR′

Solvent, carbon tetrachloride, unless otherwise stated

No.	R	R′	Subst., mole/liter	Cell thickness, mm.	Absorption bands cm.$^{-1}$	Optical density
XIV	C_6H_5	C_6H_5	0.35	0.1	3250	0.07
					3460	.09
					3610	.06
XV	H	α-Naphthyl	.07	2.0	3620	.31
			.37[a]	0.1	3400	.15
			.06	2.0	3400	.11
					3600	.17
XVI	H	β-Naphthyl	.33	0.1	3400	.17
			.05	2.0	3210	.11
					3610	.12
XVII	H	2-C_6H_4·OH	.56[b]	0.1	3270	..
			.03	2.0	3420	0.34
					3610	.29
XVIII	H	3-C_6H_4Br	.02	2.0	3570	.06[c]

[a] Chloroform as solvent. [b] Mull in carbon tetrachloride. [c] Calculated from the base line of the spectrum.

In view of the lower basicity of the nitrogen in Schiff bases,[17] it was, indeed, to be expected that they would exhibit a lower tendency to hydrogen bond formation than the corresponding aminoalcohols, which are much stronger bases. In this connection, it is recalled that also in 8-hydroxyquinoline only a slight shift of the hydroxyl frequency has been observed.[18]

The infrared spectra of several compounds formed upon condensation of aromatic aldehydes and ethanolamine have been studied by Daasch and Hanninen[19]; amongst their substances, was also the salicylaldehyde derivative (XVII). In the *homogeneous* state, the condensation products showed a hydroxyl absorption at 3280 cm.$^{-1}$, ascribed to hydrogen bonding; this effect diminished upon dilution with carbon tetrachloride,

(11) These comparisons were made with cells of very different thickness and, therefore, usually with different slit width. The difference between two such compared frequencies would thus be expected to be somewhat greater than with constant cell thickness (see ref. (7)).

(12) A. M. Buswell, J. R. Downing and W. H. Rodebush, THIS JOURNAL, **61**, 3252 (1939).

(13) *Cf.* the case of catechol.[4]

(14) E. D. Bergmann and co-workers, *Rec. trav. chim.*, **71**, 161 ff. (1952).

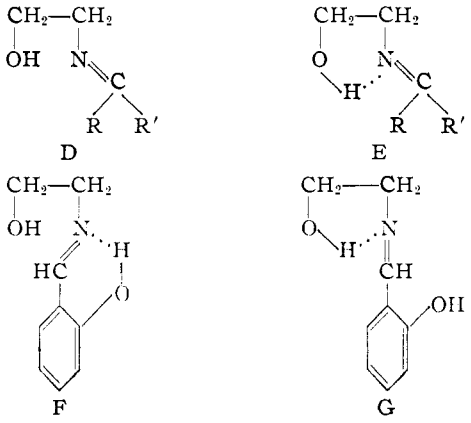
(15) N-Benzylideneaminoethanol absorbs in concentrated solution at 3280 cm.$^{-1}$: L. W. Daasch and U. E. Hanninen, THIS JOURNAL, **72**, 3673 (1950).

(16) For the band at 3210 cm.$^{-1}$ of the β-naphthyl derivative (XVI), no explanation can be offered.

(17) The well-known method for the determination of secondary and tertiary amines in presence of primary amines (C. D. Wagner, *et al.*, THIS JOURNAL, **69**, 2611 (1947); S. Siggia, *et al.*, *Anal. Chem.*, **22**, 1295 (1950)) is founded on this lowered basicity of the azomethine nitrogen atom.

(18) L. Pauling, THIS JOURNAL, **58**, 94 (1936).

(19) L. W. Daasch and U. E. Hanninen, ref. 15.



and the sharp peak (at 3625 cm.$^{-1}$) of the free hydroxyl group appeared. No study of the 3400 cm.$^{-1}$ region is reported; the work of Daasch and Hanninen and the present study appear to be complementary to each other, as far as (XVII) is concerned.[20]

Experimental

The absorption measurements were carried out with a Perkin–Elmer model 12C infrared spectrometer, using a sodium chloride prism. The experimental conditions are summarized in the Tables. Molecular weight determinations were carried out in benzene (about 1% solution) by the cryoscopic method.

Preparations and properties of compounds (XIV)–(XVIII) have been described previously.[14] (I), (II) and (VIII) were commercial products, which were purified by careful fractionation (column of approximately 15 plates). Compound (III) was prepared from ethylene oxide and methylamine according to Knorr and Matthes.[21]

2-Methylamino-3-methyl-3-butanol (IX).—A solution of 15 g. of 4,4,5-trimethyloxazolidine[14] in 60 cc. of methylcyclohexane was hydrogenated in presence of 3 g. of Raney nickel, at 100° and 1300–1500 p.s.i. After removal of the solvent, the product was fractionated in a Todd column; b.p. 155° (760 mm.), yield 10.5 g. (70%), n^{25}D 1.436 (literature[22] b.p. 152–155° (750 mm.), n^{20}D 1.4394).

Compounds (IV), (V) and (VI) were prepared by catalytic hydrogenation of the corresponding Schiff bases or oxazolidines at atmospheric pressure in the presence of palladium–charcoal (10%)[23] and compounds (VII), (X), (XI), (XII) and (XIII) by reduction of the corresponding oxazolidines with lithium aluminum hydride.[24]

(20) A more quantitative discussion of the applicability of structures (C) and (D) is given by E. Bergmann and co-workers, ref. (14).

(21) L. Knorr and H. Matthes, *Ber.*, **31**, 1069 (1898).

(22) C. M. Suter and A. W. Ruddy, THIS JOURNAL, **65**, 762 (1943).

(23) E. Gil-Av, *ibid.*, **74**, 1346 (1952).

(24) E. D. Bergmann, D. Lavie and S. Pinchas, *ibid.*, **73**, 5662 (1951). In this paper, the substances listed as No. 1 in Table I and II are the 4-methylpentamethyleno compound and 2-(*p*-methylcyclohexylamino)-3-methyl-3-butanol, respectively.

REHOVOTH AND TEL-AVIV, ISRAEL

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, NORTHWESTERN UNIVERSITY, AND UNIVERSITY OF ILLINOIS]

Hydrogen-bonding of Esters and Lactones. Site of Bonding and Effect of Ring Size

BY SCOTT SEARLES,[1a] MILTON TAMRES AND GORDON M. BARROW

RECEIVED JULY 10, 1952

The effect of ring size on the electron donor ability of lactones is such that δ-valerolactone is a better donor than γ-butyrolactone, which in turn is more effective than β-propiolactone. This order is the reverse, with respect to ring size, of that found with cyclic ethers. The difference appears to be due to the fact that the carbonyl oxygen is the principal site of hydrogen bonding rather than the alkoxyl oxygen and that the resonance in the carbalkoxyl group is dampened in the smaller ring structures. Evidence is presented which indicates this effect of ring size on the resonance in lactones and shows that the carbonyl oxygen is the primary site of hydrogen bonding with esters and lactones.

Introduction

It was reported recently that the ring size has a marked effect on the donor ability of cyclic ethers in hydrogen-bonding.[1b] When account is taken of the electronic effects of substituents, it is found that the best donor ability is associated with the 4-membered ring, followed by the 5-, 6- and 3-membered rings in that order, the last being markedly poorer. Because of the structural similarity between lactones and cyclic ethers and because of the marked effect of ring size on other chemical properties of lactones, it seemed of interest to extend the hydrogen bonding studies to the 4-, 5- and 6-membered saturated lactones. In addition, the hydrogen-bonding of several esters and ketones was investigated for comparison with the lactones.

As in previous work in this series on hydrogen bonding, both a calorimetric method and a spectroscopic method were used to determine the relative donor abilities. The former involved the determination of the heat of mixing with chloroform, and the latter that of the shift of the OD band in methanol-*d* solutions. The correlation of the two methods has been established, and so their use serves as independent checks.

Experimental

Apparatus and Methods.—Infrared spectra were determined with a Beckman model IR-2T spectrometer. The spectroscopic method of measuring hydrogen bonding by means of comparing the position of the monomeric OD band in 0.1 molar solution of methanol-*d* in carbon tetrachloride with the position of the OD band in 1.0 molar solutions of methanol-*d* in various donor compounds has been described previously.[1,2] A lithium fluoride monochromator with fixed slits was used for scanning the region from about 2000 to 2500 cm.$^{-1}$, and the position of the bonded OD band was determined by subtracting the absorption of the pure compound from the absorption of the 0.1 molar methanol-*d* solution in that compound. Since the bands were quite symmetrical, the position of maximum absorption was taken as the band center.

For the investigation of the shifts of the relatively intense carbonyl and alkoxyl bands, the compounds studied were dissolved in 10 parts by volume of carbon tetrachloride and the methanol or chloroform was present in approximately equimolar amounts with the donor compounds. A rock salt monochromator was used here. The band centers were

(1a) Department of Chemistry, Kansas State College, Manhattan, Kansas.

(1b) S. Searles and M. Tamres, THIS JOURNAL, **73**, 3704 (1951).

(2) W. Gordy, *J. Chem. Phys.*, **7**, 93 (1939).