[Contribution from the Cobb Chemical Laboratory of the University of Virginia]

Acid-Base Effects in the Ring-Chain Tautomerism of α-[(β-Hydroxyethyl)-amino]desoxybenzoins[1]

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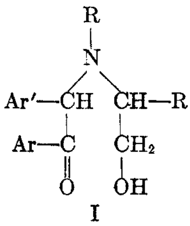
In three α-(hydroxyethyl) secondary amino ketones it has been shown by ultraviolet absorption studies that the ring chain equilibria in $5 \times 10^{-5}M$ 95%-ethanol solution are shifted by acid consistently in the direction of the cyclic hemiketal forms, and it has been shown by infrared absorptivities that in the solid state the hydrochlorides of these three compounds are entirely cyclic. The promotion of cyclization by protonation is explained in terms of the steric effect of the second hydrogen and the positive charge on the nitrogen.

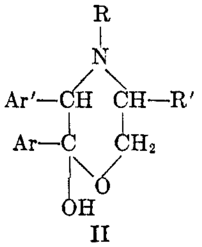
Acidities of the hemiketal hydroxyls of the cyclic compounds in 95% ethanol were demonstrated by conductimetric titrations which gave relative pK'_a values of 9.5–10.4 for this group.

Sodium isopropoxide reduced six cyclic hydroxyethylamino ketones which had resisted reduction by aluminum isopropoxide.

Previous studies on the effect of structure on ring-chain tautomerism in the α-[(β-hydroxyethyl)-amino]desoxybenzoins (I–II)[3] have demonstrated that in certain arrangements a mobile equilibrium exists which depends upon and is affected by sterically active substituents (R and R′) and by *para* substituents in the aroyl group (Ar).[4] This investigation was undertaken to determine acid and base effects on the equilibrium position.



I
(chain form)



II
(ring form)

	R	R′	Ar[a]	Ar′[a]
a.	H	C_2H_5	C_6H_5	C_6H_5
b.	H	C_2H_5	ClC_6H_4	ClC_6H_4
c.	H	C_2H_5	$CH_3OC_6H_4$	$CH_3OC_6H_4$
d.	C_2H_5	H	C_6H_5	C_6H_5
e.	C_2H_5	H	$CH_3OC_6H_4$	C_6H_5
f.	H	H	C_6H_5	C_6H_5
g.	$CH_2C_6H_5$	H	C_6H_5	C_6H_5
h.	C_2H_5	H	C_6H_5	H
i.	C_2H_5	H	ClC_6H_4	ClC_6H_4
j.	H	$CH_2C_6H_5$	C_6H_5	C_6H_5

[a] Indicated substituents are *para*.

α-[2-(1-Hydroxybutyl)amino]desoxybenzoin (Ia–IIa) was chosen for study because the ring-chain equilibrium of its hydrochloride in $5 \times 10^{-5}M$ 95% ethanol solution where extensive hydrolysis or alcoholysis must occur has been shown by the significant aroyl-type ultraviolet absorptivity of ε 3980 at 246 mμ to be evenly balanced.[5] A $5 \times 10^{-5}M$ solution of the base Ia–IIa (which has not been isolated in crystalline form), prepared by adding the calculated amount of standardized sodium hydroxide to a 95% ethanol solution of the hydrochloride and adjusting the volume, showed an aroyl-type absorptivity of ε 6920 at 248 mμ which corresponds to an equilibrium ratio of approximately 40:60 of ring *vs.* chain tautomer, a significantly higher ratio of chain tautomer than is present in a solution of the pure hydrochloride under these conditions. Neutralization of the base with exactly one equivalent of alcoholic hydrogen chloride restored the characteristic absorptivity of the solution of the hydrochloride and showed the change to be reversible. Acidification of the initial solution of the hydrochloride by adding one equivalent quantity of alcoholic hydrogen chloride lowered ε to 1940 at 249 mμ, a result which indicated a marked shift in the equilibrium position in the opposite direction to a point of predominance of the cyclic form. In these experiments there were no significant changes either in the shape of the curve or in the wave length of the absorption maximum which would indicate involvement in solution of any molecular species other than I and II and their hydrochlorides.

The generality of the effect of acid on the equilibrium position was tested by a similar study of solutions of the hydrochlorides of the di-*p*-chloro

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(1) This work was initiated under a research grant from the Eli Lilly Co.

(2) Holder of E. I. du Pont de Nemours Company Postgraduate Fellowship 1954–55. Present location: Department of Chemistry, University of Pittsburgh.

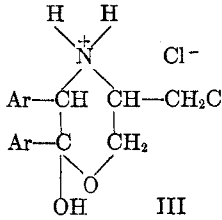
(3) (a) R. E. Lutz, J. A. Freek, and R. S. Murphy, *J. Am. Chem. Soc.*, **70**, 2015 (1948); (b) R. E. Lutz and R. S. Murphy, *J. Am. Chem. Soc.*, **71**, 996 (1949); (c) R. E. Lutz and R. H. Jordan, *J. Am. Chem. Soc.*, **71**, 478 (1949); (d) W. L. Truett, Dissertation, University of Virginia (1950); (e) C. D. Lunsford, R. E. Lutz, and E. E. Bowden, *J. Org. Chem.*, **20**, 1513 (1955); (f) R. E. Lutz and J. W. Baker, *J. Org. Chem.*, **21**, 49 (1956).

(4) C. E. Griffin and R. E. Lutz, *J. Org. Chem.*, **21**, 1131 (1956).

(5) The method of determination of equilibrium mixture composition from the absorption spectral curves has been described previously.[4] The calculation is a rough approximation and is based on the assumption that the aroyl group molar ultraviolet absorptivity of both the ring and the chain tautomers approximate those of reference compounds existing exclusively in ring or chain forms.

and di-*p*-methoxy analogs, Ib and Ic. In the case of the di-*p*-chloro compound where the activating effect of the *p*-chlorine of the aroyl group causes predominance of the cyclic form in $5 \times 10^{-5}M$ solution, acidification shifted the equilibrium position still further in that direction as shown by the depression of ϵ at 261 mμ from 1700 to 1580. In the case of the di-*p*-methoxy compound which is largely acyclic due to the deactivating influence of the *p*-methoxyl on the carbonyl group activity, the effect of one equivalent of excess acid was sufficient to counteract almost completely the marked electronic effect and to shift the equilibrium dramatically toward the cyclic form, as shown by the depression of ϵ at 285 mμ from 17,300 to 1900.

Since excess acid would suppress hydrolysis of the hydrochlorides to bases, maintaining a relatively high degree of protonation of the nitrogen, it seemed probable that the hydrochlorides in the solid state would be completely in the cyclic form, III, because in the crystal lattice the proton would be held at the nitrogen. The absence of benzoyl type bands in the 6 μ region of the infrared absorption spectra[6] of the three crystalline hydrochlorides of Ia, Ib, and Ic, in potassium chloride pellets, proves this to be so. Incidentally, only the di-*p*-chloro compound (IIIb) showed the characteristically strong and sharp bands in the 2.85 μ region which is normal for a free or single-bridge bonded hydroxyl group. In the cases of the other two (IIIa and IIIc) the hydroxyl bands were drastically shifted bathochromically to 3.12 and 3.16 μ respectively, and they were relatively broad and suggestive of polymeric association.



III

a. Ar = C_6H_5
b. Ar = $ClC_6H_4(p)$
c. Ar = $CH_3OC_6H_4(p)$

From the above studies it is clear that the ring-chain equilibrium positions in solutions of the base Ia–IIa and others of this type are shifted in very significant degree in the direction of the cyclic forms by protonation and development of a positive charge on the nitrogen atom. However, similar protonation of the parent hydroxyethyl-secondary-amino ketone If which is without a substituent on the hydroxyethyl chain, although presumably (also) inducing increased activity of the carbonyl group of the acyclic form, does not overcome the factors favoring that form. The effect of protonation therefore appears to be important only when the molecule is so substituted as already to be predisposed or able to cyclize and where a moderately balanced ring-chain equilibrium exists in solutions of the base. The phenomenon may be explained in part in terms of the appreciable added steric restrictions of freedoms of motion in the molecules by the second *N*-hydrogen which completes the tetrahedral onium-ion structure, an effect which would presumably be relatively more important in the chain than in the cyclic tautomer; and it may be explained in part in terms of the inductive effect of the positive charge on nitrogen which should increase the activity at the carbonyl carbon more effectively than it would diminish the donor activity of the alcoholic oxygen. There is an analogy to the significant electronic effect of *para* substitution in the aroyl group which likewise becomes evident and significant *only* when the ring-chain equilibrium is a moderately balanced one.[4,7] The steric effect of the onium-*N*-hydrogen, if it is important, would be analogous to the dramatic steric effect of substitution of an *N*-alkyl group for *N*-hydrogen by which cyclization is promoted in the predominantly acyclic hydroxyethyl secondary amino ketones such as If.

Attempts to study spectrophotometrically the effect of excess of strong base, sodium hydroxide, on compounds of the type I–II at 5×10^{-5} M dilution in 95% ethanol, have not been explored fully because of the sensitivity of alkaline solutions of these compounds. It may reasonably be postulated that the cyclic or hemiketal forms of the bases would have appreciable though weak acidity like that of fructose,[10,11] whereas the acyclic forms like ordinary alcohols would not be acidic in this sense. Concomitantly it may be postulated that the alkoxide ions of the acyclic forms would cyclize to hemiketal anions if maintained in sufficient concentration and if favorable steric elements existed, as in Ia–IIa.

To demonstrate experimentally the expected hemiketal acidities of the predominantly cyclic compounds of type II, acid-base titrations were made[12,13] of a number of examples of ethanolamino ketones representing different ring-chain equilibrium positions (I–II, a–d) and also of the compound If which is important for reference because

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(6) The infrared determinations were made by Dr. Bernard J. Haske.

(7) It should be pointed out that complete separation of electronic and steric factors cannot be made because one necessarily affects the other. Furthermore there may be a difference in effectiveness of intramolecular hydrogen bondings in the two forms and in the cation *vs.* the bases, where nitrogen may donate to the hydroxylic hydrogen and the oxygen may donate to an *N*-hydrogen.[8,9]

(8) E. D. Bergmann, E. Gil-Av, and S. Pinchas, *J. Am. Chem. Soc.*, **75**, 68 (1953).

(9) A. Gero, *J. Org. Chem.*, **16**, 1222 (1951).

(10) T. Madsen, *Zeit. Phys. Chem.*, **36**, 290 (1901).

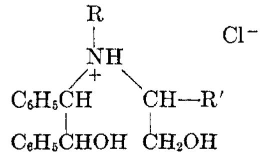
(11) H. Lunden, *Zeit. Phys. Chem.*, **54**, 532 (1906).

(12) Potentiometric titration of the compound was attempted initially but it was found that at the neutralization point of the hemiketal hydroxyl the *p*H of the solution was too high to be measured accurately because of the sensitivity of the glass electrode in strongly alkaline solutions.

(13) The procedure used was that of E. B. Leffler, H. M. Spencer, and A. Burger, *J. Am. Chem. Soc.*, **73**, 2611 (1951).

the evidence indicates that it is entirely acyclic and does not exist in the cyclic form under any of the conditions involved here. It is necessary to use non-aqueous media for titrations because of the water insolubility of the organic bases involved. The most satisfactory solvent was 95% ethanol, and the courses of titrations were followed conductimetrically. The acidities thus measured are not true pK_a values, and therefore are only qualitatively comparable with the true pK_a 12.1 of fructose determined in water;[10,11] but they may be expressed as relative pK_a' values which are significant in the comparison limited to the series I–II.

Under such conductimetric titrations the hydrochlorides of the three compounds IIa, IIb, and IId which had absorption characteristics indicating considerable or high degrees of cyclization, were shown each to possess two acidic groups by their relative pK_a' values in the two ranges, 6.2–6.7 for the amine-onium ion group, and 9.5–10.4 for the hemiketal hydroxyl group of the cyclic forms. Benzyl alcohol itself showed no detectable acidity under these conditions, and the aminodialcohol hydrochlorides IV and V each showed only one inflection point and that for the more strongly acidic amine-onium group, and no inflection in the weakly acid range. Two α-ethanolaminodesoxybenzoin hydrochlorides, Ic–IIc, and the α-(β-hydroxyethylamino) compound If, which had previously been shown to exist, the former predominantly and the latter exclusively in the acyclic form I, showed only one relatively strongly acidic group of the amine-onium type and showed no weakly acidic hemiketal group of sufficient acid strength or availability to detect by titration. Thus these studies demonstrate that the hemiketals of type II have definite though weak acidities which are of a distinctly higher order than those of compounds carrying ordinary benzyl alcohol groups such as are present in the more stable acyclic or chain types (I) and in the carbonyl-reduced types IV and V; and that acidity with ready anion formation is a property peculiar to the cyclic tautomer of the ring-chain tautomeric pair I–II and may be some measure of occurrence and/or stability of the cyclic form.



IV. $R = C_2H_5$; $R' = H$

V. $R = H$; $R' = C_2H_5$

Sodium isopropoxide reductions. Incidental to the study of the effect of base on the ring-chain equilibria in α-[(β-hydroxyethyl)amino]desoxybenzoins, six ethanolamino desoxybenzoins and acetophenones (Ib, d, g, h, i, j) which had been shown to exist chiefly in the cyclic forms II and to be resistant to reduction by aluminum isopropoxide,[3,4] were successfully reduced by means of sodium isopropoxide[14] to dialcohols corresponding to IV–V. Although these results might be accounted for in terms of the greater reducing power or speed of action of sodium isopropoxide as compared with aluminum isopropoxide,[14] it would be of importance in any attempt at explanation to know the effect of aluminum isopropoxide as a Lewis acid and of sodium isopropoxide as a strong base on the ring-chain equilibrium position[cf. 15] and on cyclic (hemiketal) anion formation, and to know to what extent if any the more powerful reagent sodium isopropoxide may directly reduce the cyclic form or its anion.

EXPERIMENTAL

The preparations of the compounds employed in these studies have been previously described.[3,4]

The *ultraviolet absorptivities* were determined using a Beckmann Model DU quartz spectrophotometer. For the spectra of compounds in the presence of acid or base, solutions were prepared by dissolving weighed amounts in 95% ethanol, adding the calculated amount of standardized acid or base from a micro buret, and making up the volume by addition of more ethanol.

Infrared absorption spectra of the hydrochlorides of the three compounds IIa, IIb, and IIc in potassium chloride pellets were determined using a Perkin-Elmer Model 21 spectrophotometer.[6]

Conductimetric titrations at 23.5° were followed by means of an Industrial Instruments Conductivity Bridge Model RC 16 using unplatinized electrodes and a frequency of 1000 cycles per second. The samples were weighed directly on an analytical balance, dissolved in 95% ethanol and titrated with $0.0213N$ sodium hydroxide in 95% ethanol. Equivalence points were obtained from a plot of corrected conductance *vs.* equivalents of base added. Apparent *dissociation constants* of the conjugate acids of the amines were determined[13] by measuring the apparent pH of a solution at 23.5° containing equivalent concentrations of amine and salt. Solutions were prepared by the addition of an amount of 95% ethanolic sodium hydroxide calculated for half neutralization, to a solution of known amount of the salt in 95% ethanol. For the determination of the second acidic group, a total of 1.5 equivalents of base was added. Solutions were made up to a constant volume of 200 ml. by the addition of 95% ethanol. Concentrations of salt and free base at the half neutralization point were in the range $5–10 \times 10^{-5}M$. The pH values were determined by means of a Leeds and Northrup pH Meter employing calomel and glass electrodes.

Relative pK_a' values for the amine-onium ion group thus determined at 23.5° were: Ia,[4] 6.63; Ib,[4] 6.30; Ic,[4] 6.72; Id,[3a] 6.22; If,[3a] 6.22; and for 2,3-diphenylmorpholine hydrochloride,[3f] 6.18. Corresponding relative pK_a' values for the more weakly acidic hemiketal hydroxyls were: Ia, 9.50; Ib, 10.00; Ic, none; Id, 10.23; If, none; the others of the above series showed no second inflection for a weakly acidic group.

Sodium isopropoxide reductions. A mixture of 0.1 mole of freshly prepared sodium isopropoxide, 0.03 mole of the amino ketone and 100 ml. of dry toluene, was refluxed for 10 hr. in an atmosphere of nitrogen, allowed to cool to room temperature, hydrolyzed with ice-cold 5% hydrochloric acid, neutralized with 10% aqueous sodium carbonate, and extracted with ether. The ethereal extracts were washed with

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(14) R. B. Woodward, N. L. Wendler, and F. J. Brutschy, *J. Am. Chem. Soc.*, **67**, 1425 (1945).

(15) R. H. Jordan, Dissertation, University of Virginia (1948).

water, dried over sodium sulfate, decanted, and acidified with ethereal hydrogen chloride. The solid products were recrystallized until constant melting points were obtained and they were identified by mixture melting points with authentic samples of the hydrochlorides of the known dialcohols.

The following amino ketones were successfully reduced, and the yields of identified products (corresponding to IV–V) were: α-[*N*-ethyl-*N*-(β-hydroxyethyl)amino]desoxybenzoin[3a] (IId) (51%); α-[*N*-benzyl-*N*-(β-hydroxyethyl)amino]-desoxybenzoin[3d] (IIg) (43%); α-[*N*-ethyl-*N*-(β-hydroxyethyl)amino]acetophenone[3c] (IIh), product isolated as the picrate (61%); α-[*N*-ethyl-*N*-(β-hydroxyethyl)amino]-*p*,*p*′-dichlorodesoxybenzoin[3b] (IIi) (58%); α-[*N*-(1-hydroxy-2-butyl)amino]-*p*,*p*′-dichlorodesoxybenzoin[4] (IIb) (64%); α-[*N*-2(3-phenyl-1-hydroxypropyl)amino]desoxybenzoin[4] (IIj) (49%); the recrystallization solvents and physical characteristics of the dialcohols prepared, are those given in the references.

Acknowledgment. We wish to thank Dr. Thomas I. Crowell for helpful discussions and criticism during the course of this investigation and Dr. C-K. Dien for checking some of the experiments.

CHARLOTTESVILLE, VA.

[CONTRIBUTION FROM THE BIOCHEMICAL RESEARCH LABORATORY, THE DOW CHEMICAL COMPANY]

Adducts of *tert*-Alcohols Containing an Ethynyl Group with Dihydropyran. Potentially Useful Intermediates

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Acetylenic alcohols of the type $RR'C(OH)C\equiv CH$ have been found to add smoothly and in high yield to dihydropyran to form tetrahydropyranyl compounds of the general structure $RR'C(C\equiv CH)O$—(C_5H_9O). The tetrahydropyranyl grouping is stable to alkali but easily removed by aqueous acid or exchangeable with lower alcohols by acid catalysis. Organometallic intermediates are easily formed by reaction at the acetylenic hydrogen and compounds such as the γ-hydroxy-α,β-acetylenic acids, esters, and ketones thus are readily available.

Woods and Kramer[1] introduced dihydropyran for the protection of hydroxyl groups. Alcohols and phenols were added to dihydropyran by acid catalysis and the resulting adducts were found to be stable to alkali.

Later (1948), Parham and Anderson[2] extended this work to include adducts of other monohydric phenols and some dihydric phenols. The adducts were found to be stable to lithium alkyls. For example, the *p*-bromophenol–dihydropyran adduct was treated with butyllithium and carbonated. Removal of the tetrahydropyranyl group was then accomplished with aqueous acid.

In 1950, Henbest, Jones, and Walls[3] prepared an adduct with propargyl alcohol and in 1953, Jones and Mann[4] used the same adduct in the preparation of 4,4-diethoxy-2-butyn-1-ol.

On hydrolysis, the tetrahydropyranyl group is converted to γ-hydroxyvaleraldehyde.[2] Alcoholysis gives 2-alkoxytetrahydropyrans.[1] Both are easily separated from the desired products.

A British patent (698,736) claims the addition of primary and secondary alcohols to selected dihydropyrans but gives no examples with secondary alcohols. Crombie and Jocklin[5] have reported the addition of a secondary alcohol to dihydropyran.

In each of the above cases, either concentrated hydrochloric acid or phosphorus oxychloride was employed as catalyst and the products worked up with ether. We have extended this work to include a number of tertiary ethynyl alcohols of the general formula $RR'C(OH)C\equiv CH$, where R is alkyl or phenyl and R′ is methyl and where R and R′ make up a cycloalkyl ring. Although tertiary alcohols are known to present steric problems in some reactions, we have found that each of the alcohols employed here gave pure products in good yield (see Table I).

In order to avoid volatile catalysts and to simplify work-up of the reaction mixture, *p*-toluenesulfonic acid was used as catalyst. Anhydrous potassium carbonate was added to the cooled reaction mixture to neutralize the acid and the product could then be distilled after a simple filtration.

If ether or other solvents are used in the work-up it should be noted that a basic or neutral drying agent *must* be employed. *Magnesium sulfate* is sufficiently *acid* to reverse the addition in only a few hours.

The tetrahydropyranyl compound thus formed provides protection for the hydroxyl group and, even where the hydroxyl group may not need protection, provides a degree of solubility which can be useful. For example, in the carbonation

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[1] G. F. Woods and D. N. Kramer, *J. Am. Chem. Soc.* **69**, 2246 (1947).

[2] W. E. Parham and E. L. Anderson, *J. Am. Chem. Soc.* **70**, 4187 (1948).

[3] H. B. Henbest, E. R. H. Jones, and I. M. S. Walls, *J. Chem. Soc.*, 3646 (1950).

[4] R. G. Jones and M. J. Mann, *J. Am. Chem. Soc.* **75**, 4048 (1953).

[5] L. Crombie and A. G. Jocklin, *Chem. & Ind. (London)*, **1954**, 1197.