# Conformational Analysis. IX. Conformational and Substituent Dependence of the Hydroxyl Proton Magnetic Resonance of Arylcarbinols[1,2]

**Robert J. Ouellette, Douglas L. Marks, and Daniel Miller[3]**

*Contribution from the Department of Chemistry, The Ohio State University, Columbus, Ohio 43210.* *Received May 28, 1966*

**Abstract:** Proton magnetic resonance studies of arylcarbinols in dimethyl sulfoxide have revealed that the chemical shift of the hydroxyl proton is sensitive to ring substituents. Correlations with $\sigma$ of the ring substituent are found within each of several series of structurally related arylcarbinols. The sensitivity of the chemical shift to ring substituents is conformationally dependent on the steric bulk of groups attached at the carbinol carbon and at the *ortho* position of the aromatic ring. It is suggested that transmission of substituent effects occurs most efficiently in that conformation in which the hydroxyl proton is directed toward the aromatic ring. At least one molecule of dimethyl sulfoxide may be involved in maintaining the hydroxyl group in the orientation necessary for transmission of substituent effects.

Spin–spin coupling between hydroxyl and carbinol protons generally is not observed in the proton magnetic resonance of alcohols since it is difficult to remove trace quantities of acids or bases which catalyze hydroxyl proton exchange. The chemical shift of the hydroxyl proton is dependent on concentration in solvents which do not hydrogen bond to the alcohol.[4] Hydrogen bond formation in an acceptor solvent may increase the hydroxyl proton lifetime of a given alcohol molecule and allow observation of the splitting of its hydroxyl resonance signal.[5] In addition such a solvent should stabilize the chemical shift position by eliminating the various alcohol aggregates, if the equilibrium constant for solute–solvent hydrogen bonding is high and the concentration of solute is low. Chapman and King[6] have shown that dimethyl sulfoxide is useful for classification purposes in a variety of alcohols. The multiplicity of the hydroxyl resonance serves to identify primary, secondary, and tertiary alcohols. The resonance position is conveniently located in the $\tau$ 5.5–6.3 region and is independent of concentration at low mole fractions of alcohol.

In an earlier paper in this series, the chemical shifts and coupling constants for the hydroxyl proton of *cis*- and *trans*-4-*t*-butylcyclohexanol in dimethyl sulfoxide were reported.[7] That the axial hydroxyl proton appears at higher field than the equatorial hydroxyl proton is not unreasonable and might have been anticipated from the anisotropic nature of the cyclohexane ring.[8] The coupling constant between the carbinol and hydroxyl protons is larger for the equatorial hydroxyl group, which suggests that the hydroxyl group exists in a conformation in which there is a transoid relationship between the two protons. In the axial hydroxyl case, the hydroxyl proton would be expected to be directed away from the plane of the 3,5-*syn*-axial cyclohexane protons. The resultant cisoid arrangement between carbinol and hydroxyl protons results in a lower coupling constant. Thus a parallel is observed between H–O–C–H and the well-established H–C–C–H dihedral angle effects on coupling constants.[9] These observations have recently been confirmed by Rader[10] for several alkyl-substituted cyclohexanols.

In studies of steroid and flexible cyclohexane systems it became evident that the chemical shift of the hydroxyl proton is conformationally dependent when anisotropic groups are present.[11] Since the rate of formation of hydrogen bonds between solute and acceptor solvents is large and the rate of rotation about the C–O bond is several orders of magnitude greater than the differences in the $\tau$ values for various alcohols, it was thought that the relative contribution of rotamers in structures containing a hydroxyl group might serve to define effective steric sizes of substituents attached to the carbinol carbon. The observed chemical shift should reflect only the change in the weighted chemical shift of all possible rotamers, but this time-average resonance should indicate trends in rotamer population as substituents are introduced in the vicinity of the carbinol carbon.

In connection with other work in this laboratory, a number of aryl carbinols were available which would allow a systematic study of chemical shifts of the hydroxyl group as a function of its conformation with respect to the strongly anisotropic aromatic ring. It was noted in preliminary experiments that the chemical shift of the hydroxyl proton also was sensitive to substituents attached to the aromatic ring. In order to determine the mode by which the hydroxyl proton is informed about the attached ring substituents, we have examined a variety of structurally related arylcarbinols.

## Results and Discussion

In order to obtain reproducible chemical shift values for the hydroxyl protons of arylcarbinols in dimethyl

(1) Paper VIII: R. J. Ouellette and G. E. Booth, *J. Org. Chem.*, **31**, 3065 (1966).

(2) The authors acknowledge Grant No. 2410-A4 from the Petroleum Research Fund of the American Chemical Society in support of this research.

(3) National Science Foundation Undergraduate Research Participant.

(4) E. D. Becker, V. Liddel, and J. N. Shoolery, *J. Mol. Spectry.*, **2**, 1 (1958).

(5) P. L. Corio, R. L. Rutledge, and J. R. Zimmerman, *J. Am. Chem. Soc.*, **80**, 3163 (1958).

(6) O. L. Chapman and R. W. King, *ibid.*, **86**, 1256 (1964).

(7) R. J. Ouellette, *ibid.*, **86**, 4378 (1964).

(8) L. M. Jackman, "Nuclear Magnetic Resonance Spectroscopy," Pergamon Press, New York, N. Y., 1959, p 115.

(9) M. Karplus, *J. Am. Chem. Soc.*, **85**, 2870 (1963).

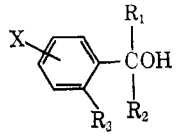
(10) C. P. Rader, *ibid.*, **88**, 1713 (1966).

(11) R. J. Ouellette, unpublished observations.

sulfoxide, concentrations below 0.1 mole fraction were employed, and the temperature of the probe was maintained at approximately 40°. Under these conditions it is possible to examine the effect of structure on the chemical shift. All $\tau$ values are calculated utilizing the 221-cps, low-field, $C_{13}$ satellite of dimethyl sulfoxide as the internal reference.

Compounds 1 through 7 listed in Table I with their respective hydroxyl resonances are monosubstituted benzyl alcohols. The position of the resonance is

Table I. Chemical Shift of Hydroxyl Protons

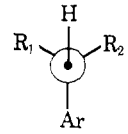


| No. | X | $R_1$ | $R_2$ | $R_3$ | $\tau$ |
|---|---|---|---|---|---|
| 1 | *p*-$CH_3O$ | H | H | H | 4.97 |
| 2 | *p*-$CH_3$ | H | H | H | 4.92 |
| 3 | *m*-$CH_3$ | H | H | H | 4.88 |
| 4 | H | H | H | H | 4.85 |
| 5 | *m*-$CH_3O$ | H | H | H | 4.83 |
| 6 | *p*-Cl | H | H | H | 4.77 |
| 7 | *m*-Cl | H | H | H | 4.70 |
| 8 | *p*-$CH_3$ | $CH_3$ | $CH_3$ | H | 5.15 |
| 9 | H | $CH_3$ | $CH_3$ | H | 5.05 |
| 10 | *p*-Cl | $CH_3$ | $CH_3$ | H | 4.95 |
| 11 | *p*-$CF_3$ | $CH_3$ | $CH_3$ | H | 4.78 |
| 12 | *p*-$CH_3$ | $CH_3$ | $(CH_3)_2CH$ | H | 5.48 |
| 13 | H | $CH_3$ | $(CH_3)_2CH$ | H | 5.38 |
| 14 | *p*-Br | $CH_3$ | $(CH_3)_2CH$ | H | 5.23 |
| 15 | *p*-$CH_3$ | $CH_3$ | $C_6H_5$ | H | 4.53 |
| 16 | *m*-$CH_3$ | $CH_3$ | $C_6H_5$ | H | 4.42 |
| 17 | H | $CH_3$ | $C_6H_5$ | H | 4.38 |
| 18 | *p*-Cl | $CH_3$ | $C_6H_5$ | H | 4.22 |
| 19 | *p*-Br | $CH_3$ | $C_6H_5$ | H | 4.22 |
| 20 | *m*-Cl | $CH_3$ | $C_6H_5$ | H | 4.17 |
| 21 | *p*-$CH_3O$ | $CH_3$ | $CH_3$ | $CH_3$ | 5.33 |
| 22 | *p*-$CH_3$ | $CH_3$ | $CH_3$ | $CH_3$ | 5.27 |
| 23 | H | $CH_2$ | $CH_3$ | $CH_3$ | 5.15 |
| 24 | *p*-Cl | $CH_3$ | $CH_3$ | $CH_3$ | 4.99 |
| 25 | *p*-$CH_3O$ | H | $CH_3$ | H | 5.03 |
| 26 | *p*-$CH_3$ | H | $CH_3$ | H | 4.98 |
| 27 | H | H | $CH_3$ | H | 4.88 |
| 28 | *p*-Cl | H | $CH_3$ | H | 4.81 |
| 29 | *m*-Cl | H | $CH_3$ | H | 4.74 |

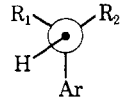
shifted to higher field with increasing electron-donating ability of the substituent. A correlation with $\sigma$ is observed with $\rho = -0.41$. The $\rho = -1.29$ for substituted phenols[12] is larger, as would be expected for molecules in which resonance effects are operative. The sensitivity of the hydroxyl resonance in benzyl alcohols is intriguing, and consideration might be given to transmission of substituent effects through the $sp^3$-hybridized carbon–carbon and carbon–oxygen bonds. If an inductive mechanism through these bonds were operative then modification of the structure by placing alkyl groups on the benzyl carbon or at the *ortho* position of the aromatic ring should change the average field position of the hydroxy resonance but would not be expected to alter the magnitude of $\rho$.

Compounds 8 through 11 are monosubstituted 2-aryl-2-propanols and are listed in Table I with their respective hydroxyl proton chemical shifts. The average chemical-shift difference between benzyl alcohols and 2-aryl-2-propanols containing the same ring substituent is 0.20 ppm with the propanols appearing at higher field. A shift of 0.17 ppm has been found for the difference between the hydroxyl chemical shift of ethanol and *t*-butyl alcohol.[6] Therefore, the observed change in the arylcarbinols is entirely reasonable. However, $\rho = -0.51$ in the 2-aryl-2-propanols, and this suggests that a through-bond transmission mechanism of the substituent effect is not the only mode operative.

Consideration of steric effects on rotamer populations suggests a reason for the change in the magnitude of $\rho$ as a function of the group attached to the carbinol carbon. Two rotamers presented as Newman projections along the carbinol carbon–oxygen bond must be considered.



I



II

With increasing steric size of the R groups the population of rotamer II relative to rotamer I should increase. In the case of monosubstituted benzyl alcohols rotamer I, where $R_1$ and $R_2$ are both hydrogens, should predominate as the aryl group is sterically larger than hydrogen. However, the observed response of chemical shift to substituent may not result from this rotamer. Rotamer II should also be populated, and the substituent effects could be transmitted in some manner in this rotamer. The introduction of two methyl groups on the carbinol carbon should alter the rotamer populations and lead to an increased fraction of rotamer II. Thus, on the average the hydroxyl proton will be oriented more toward the plane of the aromatic ring and an increased response to ring substituent should result.

In rotamers I and II the hydroxyl function is not pictured with the complexed dimethyl sulfoxide. However, the conformational preference of the free hydroxyl and complexed hydroxyl group in cyclohexanol are essentially identical,[7] and this fact suggests that the rotamer population assignments are valid. In addition the question of effective steric size of the complexed hydroxyl group is not a serious one as we are comparing only the size of the group to a series of substituents on the carbinol carbon whose effective sizes are known. The order of increasing size of alkyl groups is all that is necessary in discussing the changes in rotamer populations in compounds which contain a single group of unknown steric size.

The change in $\rho$ as the result of increasing the steric size of alkyl groups attached to the carbinol carbon is in agreement with the results of the infrared studies of Oki and Iwamura.[13] They assigned the two bands in the oxygen–hydrogen stretching region to the rotamers I and II. The ratio of the absorptivities ($A$) of I relative to II decreases from 0.59 to 0.47 in going from benzyl alcohol to 2-phenyl-2-propanol. Thus the change in rotamer populations of the alcohols in dilute carbon tetrachloride solutions parallels that observed from the change in response to ring substituents in dimethyl sulfoxide solutions. In fact the change in the ratios of

(12) R. J. Ouellette, *Can. J. Chem.*, 43, 707 (1965).

(13) M. Oki and H. Iwamura, *Bull. Chem. Soc. Japan*, 35, 1552 (1962).

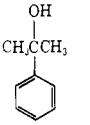
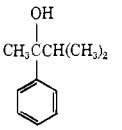
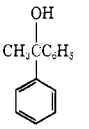
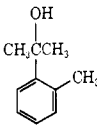
the absorptivities quantitatively parallels the change in $\rho$. The products $\rho(A(\mathrm{I})/A(\mathrm{II}))$ are $-0.242$ and $-0.240$ for benzyl alcohols and 2-aryl-2-propanols, respectively. Unfortunately this striking agreement could well be fortuitous. The ratio of the absorptivities is not necessarily the ratio of the populations of I and II. The respective extinction coefficients of I and II may not be identical for a given alcohol and certainly would be expected to vary with alterations in the structure of the alcohols.

It might be argued that the observed variation of $\rho$ with structure is a reflection of increased hydrogen bonding to the $\pi$ system. Thus an equilibrium between dimethyl sulfoxide hydrogen-bonded alcohol and intramolecular $\pi$ hydrogen-bonded alcohol could be shifted to yield the observed change in $\rho$. Benzyl alcohols were thought to be partially $\pi$ hydrogen bonded in dilute solution.[14] However, the use of infrared in the detection of weak $\pi$ hydrogen bonds has been reexamined by Winstein.[15] The doublet oxygen–hydrogen stretching absorption is merely the result of rotamer populations about the carbon–oxygen bond. We have examined benzyl alcohol (0.01 *M*) in carbon tetrachloride and observed 3632 and 3622 $cm^{-1}$ bands. These are most certainly due to rotamers I and II, respectively, as the separation is not substantially larger than that observed for alkylcarbinols[16] in which $\pi$ hydrogen bonding cannot be invoked. More importantly the introduction of dimethyl sulfoxide into the carbon tetrachloride in quantity sufficient to produce a 0.2 *M* solution is sufficient to eliminate the two bands. Only a broad dimethyl sulfoxide, hydrogen-bonded band centered at 3440 $cm^{-1}$ is observed. Therefore, an alcohol in pure dimethyl sulfoxide is completely complexed by solvent at the concentrations employed in this study.

In summary, it is extremely likely that the observed difference between the values of $\rho$ for benzyl alcohols and 2-aryl-2-propanols is a reflection of changes in rotamer populations. As the steric size of the groups $R_1$ and $R_2$ increases, the population of rotamer II is expected to increase relative to rotamer I. The increased response due to ring substituents in the 2-aryl-2-propanols indicates that transmission of magnetic information is more effective in rotamer II.

Three 2-aryl-3-methyl-2-butanols are listed in Table II with their respective chemical shifts. A correlation with $\sigma$ is observed with $\rho = -0.63$. The average chemical shift difference between 2-aryl-2-propanols and 2-aryl-3-methyl-2-butanols is 0.30 ppm with the latter class of compounds located at higher field. The difference in chemical shift between *t*-butyl alcohol[5] and 2,3-dimethyl-2-butanol ($\tau$ 6.10) is 0.28 ppm, and, therefore, the average chemical-shift difference observed for the two classes of arylcarbinols is in good agreement with the model aliphatic alcohols. The increased response to ring substituents in the 2-aryl-3-methyl-2-butanols again suggests a conformational dependence. The replacement of a methyl group by an isopropyl group on the carbinol carbon leads to a change in rotamer population favoring the location of the hydroxyl group near the plane of the benzene ring.

**Table II.** Response of Chemical Shift to Substituent

| Compound | $\rho$ |
|---|---|
|  | −0.41 |
|  | −0.45 |
|  | −0.51 |
|  | −0.63 |
|  | −0.68 |
|  | −0.67 |

The chemical shifts of compounds 15 through 20, which are 1-phenyl-1-arylethanols, are listed in Table I. The $\rho = -0.68$ again illustrates that the steric bulk of groups attached to the carbinol carbon leads to an increase in the sensitivity of the hydroxyl resonance signal to the ring substituents. Placement of a methyl group in the *ortho* position of the 2-aryl-2-propanols in compounds 21 through 24 produces an increase in the response to ring substitution over that of the 2-aryl-2-propanols without *ortho* substituents. $\rho = -0.67$ for the compounds containing an *o*-methyl group.

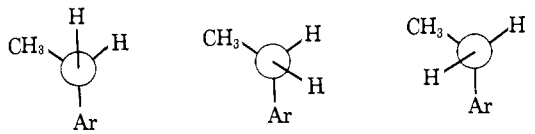
The various series of arylcarbinols exhibit changes in response to the effect of ring substituents in a direction which is coincident with the expected increase in the population of conformers in which the hydroxyl oxygen is directed toward the aromatic ring. Consideration of the coupling constant between the hydroxyl and carbinol carbon protons also supports the conformational arguments. In the benzyl alcohols the coupling constants are uniformly 5.5 cps. In 1-arylethanols (compounds 25–29) the coupling constants are uniformly 4.0 cps. The response to ring substituents, $\rho = -0.45$, for the 1-arylethanols is intermediate between the benzyl alcohols and the 2-aryl-2-propanols. The dihedral angles between the hydroxyl and carbinol protons of benzyl alcohol in I are both 60°, whereas in II they are 60 and 180°. The observed coupling constant will be a time-averaged one which represents both the dihedral angles and the rotamer populations of I and II. The 1-arylethanols are represented in Newman projections as the three rotamers III, IV, and V. From steric considerations, ignoring any attractive interaction between the hydroxyl proton and the aromatic ring, the

(14) (a) P. Schleyer, D. S. Trifan, and R. Bacskai, *J. Am. Chem. Soc.*, 80, 6691 (1958); (b) D. S. Trifan, R. Bacskai, P. von R. Schleyer, and C. Wintner, Abstracts, 135th National Meeting of American Chemical Society, Boston, Mass., 1959, p 98-O.

(15) R. Piccolini and S. Winstein, *Tetrahedron Letters*, 4 (1959).

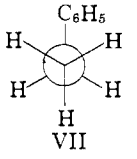
(16) M. Oki and H. Iwamura, *Bull. Chem. Soc. Japan*, 32, 950 (1959).

relative populations should be III > IV > V. In rotamers III and IV only dihedral angles of 60° are present. In the least favorable conformer there is a dihedral angle of 180°. Therefore, the time-averaged coupling constant of the 1-arylethanols should be smaller than that of the benzyl alcohols, owing to the decreased contribution of the rotamer with a transoid arrangement. It is assumed that the dihedral angle dependence of the coupling constants in H–C–O–H systems parallels those of H–C–C–H systems.[9] The coupling constant arguments are weakened somewhat by the fact that substitution of a methyl group on $CH_3CH_2X$ compounds to yield $CH_3CHXCH_3$ leads to a decrease of 0.5 to 1.0 cps in the coupling constant.[17] In this case no conformational effects are possible. Lending support to our use of $J$ in determining conformation is the observation that the coupling constants between hydroxyl and carbinol protons are 5.1 and 4.3 cps for ethyl and isopropyl alcohols, respectively. The decrease in $J$ is greater in the case of the arylcarbinols, as would be expected from conformational changes. Additional studies on the coupling constants of H–C–O–H systems are needed before they may be used unambiguously in conformational problems.

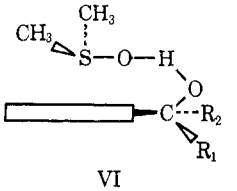



The role of dimethyl sulfoxide in the transmission of substituent effects to the hydroxyl proton is ill defined, as it is difficult to define experimentally how the dimethyl sulfoxide is complexed to the hydroxyl group. Oki and Iwamura[18] did not observe any substituent dependence of the hydroxyl proton resonance of benzyl alcohols in carbon tetrachloride at infinite dilution. The total variance in chemical shift at infinite dilution is 0.13 ppm. However, only random scatter was observed. Extrapolation of chemical shifts has experimental uncertainties which could lead to the observed scatter. Experimentally, the use of dimethyl sulfoxide allows the accurate determination of the hydroxyl proton resonance. While it appears that there is a larger response to substituents in dimethyl sulfoxide as solvent, the agreement of our data with the infrared results of Oki and Iwamura suggests that the nmr dilution results should be rechecked.

It is tempting to speculate about the structural relationship between dimethyl sulfoxide and arylcarbinols. The oxygen atom of dimethyl sulfoxide undoubtedly is bonded to the hydroxy proton. Placement of the sulfur atom above the plane of the aromatic ring is geometrically feasible, resulting in a $\pi$ complex. The $\pi$ complex is largely speculative but serves as a reasonable rational in explaining the extent of substituent dependence on chemical shift. Model compounds should contain the same number of bonds separating the aromatic ring and the probe proton. In addition the steric environment at the junction of the chain of atoms to the ring should be identical with that of the arylcarbinols. The methoxyl protons of anisoles are substituent dependent with $\rho = 0.27$, although the correlation coefficient is not high.[19] The oxygen atom attached to the ring eliminates these compounds as models owing to electronic interactions with the aromatic ring. The contribution to the chemical shift of a probe proton as the result of an oxygen attached to the ring is significant, as indicated by comparing toluenes with phenols: $\rho = 0.21$ for toluenes[20] and $\rho = -1.29$ for phenols.[12] In addition the oxygen atom is not sterically equivalent to the methylene group of arylcarbinols, which also suggests that a comparison with anisoles should not be made. Ethylbenzenes ($\rho = -0.11$) are the best models for arylcarbinols as the steric environments at the junction to the aromatic ring are identical. In addition the methylene group effectively eliminates any resonance contributions between the aromatic and the probe proton. In conformer VII representing ethylbenzene, two of the three protons are always cisoid to the aromatic ring. These two protons correspond in geometric position to the hydroxyl proton in conformer II of benzyl alcohol. The transoid proton in ethylbenzene corresponds to the hydroxyl proton in conformer I of benzyl alcohol. Assuming that steric factors are unimportant in benzyl alcohol and that conformers I and II are statistically populated (*i.e.*, $N_{II}/N_I = 2$), the time-averaged $\rho$ for benzyl alcohols should be equal to the $\rho$ for ethylbenzenes. Clearly this is not the case. The observed variance in $\rho$ for arylcarbinols also indicates that the conformers are not statistically populated. If only conformer II were populated, then $\rho$ should be approximately three-halves that of ethylbenzene or $-0.15$.




The substantial difference between the observed $\rho$ for benzyl alcohols and any approximated $\rho$ for ethylbenzene suggests that a different mechanism of transmitting substituent information is operative. It is possible that dimethyl sulfoxide plays a key role in increasing the transmission of substituent information. In the above discussion an implied equivalence of the ability of oxygen and carbon to transmit substituent information through $\sigma$ bonds has been assumed. The variance in $\rho$ with structure of the benzyl alcohols indicates that a through-space mechanism accounts for the observed trends. However, it is not possible to rule out some




VI

(17) J. W. Emsley, J. Feeney, and L. H. Sutcliffe, "High Resolution Nuclear Magnetic Resonance Spectroscopy," Vol. 2, Pergamon Press, New York, N. Y., 1966, p 680.
(18) M. Oki and H. Iwamura, *Bull. Chem. Soc. Japan*, **36**, 1 (1963).
(19) C. Heathcock, *Can. J. Chem.* 40, 1865 (1962).
(20) S. H. Marcus, W. F. Reynolds, and S. I. Miller, *J. Org. Chem.*, **31**, 1872 (1966).

through-bond contribution. Therefore, some of the difference in the benzyl alcohols and ethylbenzene could be due to a more effective transmittive ability of oxygen compared to carbon. In order to account for the differences between benzyl alcohols and ethylbenzenes by using only an enhanced $\sigma$-bond contribution through oxygen, it would be necessary for oxygen to be at least three times more effective than carbon in transmitting substituent information. There is no unambiguous data available to distinguish between the alternative explanations of transmission of substituent effects *via* dimethyl sulfoxide complexation or through $\sigma$-bond oxygen contributions. Both mechanisms could be operative.

# Hydroxyl Group Participation in Amide Hydrolysis. The Influence of Catalysts on the Partitioning of a Tetrahedral Intermediate

**Bruce A. Cunningham and Gaston L. Schmir**

*Contribution from the Department of Biochemistry, Yale University, New Haven, Connecticut 06510.* *Received October 14, 1966*

**Abstract:** The hydrolysis of 4-hydroxybutyranilide in weakly alkaline solution is catalyzed by phosphate and bicarbonate buffers, while imidazole buffers have little effect. The rate of hydrolysis varies linearly with catalyst at low buffer concentration but reaches a limiting value at high buffer concentration. These findings have been interpreted in terms of a change from rate-limiting breakdown to rate-limiting formation of an addition intermediate as catalyst concentration increases. It is suggested that intramolecular nucleophilic attack by the neighboring hydroxyl group is followed by bifunctional catalysis of the conversion of intermediate to products. This interpretation is supported by a quantitative comparison of buffer effects in 4-hydroxybutyranilide hydrolysis and in the hydrolysis of 2-phenyliminotetrahydrofuran, both reactions proceeding *via* identical intermediates.

The rapid hydrolysis of 4-hydroxybutyramide (relative to that of butyramide) in acidic, neutral, and basic solution has been explained on the basis of a pathway involving intramolecular nucleophilic displacement by the hydroxyl group on the amide function.[1,2] No direct evidence was obtained for the formation of intermediates in this process, although, in a number of recent investigations, it has been shown that nucleophilic attack at the carbonyl, acyl, or imino group affords tetrahedral addition intermediates.[3]

The present report describes our studies of the hydrolysis of 4-hydroxybutyranilide. Our findings provide kinetic evidence for the existence of an addition intermediate derived from intramolecular nucleophilic attack by the neighboring hydroxyl group. Furthermore, we demonstrate the susceptibility of this intermediate to bifunctional acid–base catalysis of its transformation to hydrolysis products, a process leading to major rate increases, in addition to those resulting from the initial intramolecular reaction.

## Results and Discussion

The rate of hydrolysis of 4-hydroxybutyranilide in acid or alkaline solution (10% ethanol–water, 30°) depends linearly upon the concentration of hydronium or hydroxide ion (Table I). The value of the rate constant for the acid-catalyzed reaction is very similar to those reported for the hydrolysis of 4-hydroxybutyramide under comparable conditions.[1a,c]

Table I. Rates of Hydrolysis of 4-Hydroxybutyranilide[a]

| pH | HCl, *M* | NaOH, *M* | $k_0 \times 10^3$,[b] $hr^{-1}$ | $k_2 \times 10^2$,[c] $M^{-1}$ $hr^{-1}$ | |
|---|---|---|---|---|---|
| 1.06 | 0.098 | | 20.9 | 21.3 | |
| 1.36 | 0.049 | | 10.8 | 22.0 | |
| 2.07 | 0.0098 | | 2.08 | 21.2 | |
| | | | | | $21.5 \pm 0.3$ |
| 12.65 | | 0.047 | 4.5 | 9.6 | |
| 13.03 | | 0.119 | 11.6 | 9.7 | |
| 13.27 | | 0.237 | 22.8 | 9.6 | |
| | | 0.474 | 44.0 | 9.3 | |
| | | | | | $9.55 \pm 0.1$ |

[a] At 30° in 10% ethanol–water, $\mu = 0.5$. [b] Observed first-order rate constants for anilide disappearance. [c] Second-order rate constants for acid- and base-catalyzed reactions.

For reasons which will become apparent in the sequel, rates of hydrolysis in weakly alkaline media (buffered solution, pH 9–10) were also determined at 30°, although reaction rates were very slow under these conditions. Nevertheless, acceptable first-order kinetics were followed during periods of measurement as long as 80 days (*e.g.*, Figure 1). The results of initial experiments possessed two features of interest: (a) hydrolysis at pH 9 was accelerated about 25-fold by 0.1 *M* phosphate or carbonate buffers, although an equal

(1) (a) L. Zürn, *Ann. Chem.*, **631**, 56 (1960); (b) T. C. Bruice and F. H. Marquardt, *J. Am. Chem. Soc.*, **84**, 365 (1962); (c) R. B. Martin, R. Hedrick, and A. Parcell, *J. Org. Chem.*, **29**, 158 (1964).

(2) For a review of the mechanisms of neighboring hydroxyl group participation in ester and amide hydrolysis, see T. C. Bruice and S. J. Benkovic, "Bioorganic Mechanism," Vol. 1, W. A. Benjamin, Inc., New York, N. Y., 1966, p 146.

(3) (a) W. P. Jencks, *Progr. Phys. Org. Chem.*, **2**, 63 (1964). (b) For a compilation of references to recent work in this area, see A. J. Kirby and W. P. Jencks, *J. Am. Chem. Soc.*, **87**, 3217 (1965), footnote 3; (c) G. L. Schmir, *ibid.*, **87**, 2743 (1965); (d) G. E. Lienhard and W. P. Jencks, *ibid.*, **87**, 3855 (1965); (e) J. E. Reimann and W. P. Jencks, *ibid.*, **88**, 3973 (1966).