endothermic maxima in aqueous *t*-butyl alcohol than they do in aqueous ethanol and show them in more highly aqueous solutions. Very recent measurements by Dr. Donald McKelvy in our laboratory (which will be presented fully elsewhere) completely fulfill this prediction. He has also demonstrated that the same pattern of $\Delta \bar{H}_s$ results described in this paper for ethanolic solutions carries over to aqueous acetone and dioxane as well as *t*-butyl alcohol.

We have said little about the contribution of specific solvation of functional groups up to this point. Several facts show that these less easily generalized influences must play a role which may be important. Although the over-all shapes of our curves in Figures 6, 7, and 8 are similar, there are distinct differences which seem to be related to functional variation (*e.g.*, ethyl acetate and *t*-butyl alcohol in Figure 6). Only further experimentation will delineate the importance of this factor relative to the more general ones given above—in the present series it is not large.

We have also avoided discussion of the solute behavior in solutions on the more alcoholic side of the $\Delta \bar{H}_s$ maximum. Here the present situation is unmanageably complex, and specific interactions may play a greater role because the solvent structure has collapsed.

Finally, we do not feel that these experiments say anything definitive pro or con on the subject of "solvent sorting," in the sense of selective covalent binding of one solvent component to the solute, except that it need not be involved in the thermodynamic or kinetic phenomena discussed here. It does seem reasonable however that the difference between the behavior of cations and anions of the same size is derived from their modes of interaction with the hydroxylic solvent components. The cations would be expected to interact with the negative end of the O–H dipole and so have hydrogens directed out while anions should be acting as hydrogen bond acceptors.[35,41]

(41) A. Allerhand and P. von R. Schleyer, *J. Am. Chem. Soc.*, **85**, 1233 (1963).

Effect of Structural Changes in Reactants on the Position of Hydrogen-Bonding Hydrogens and Solvating Molecules in Transition States. The Mechanism of Tetrahydrofuran Formation from 4-Chlorobutanol[1]

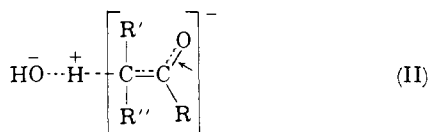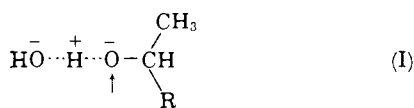C. Gardner Swain, David A. Kuhn, and Richard L. Schowen

*Contribution from the Department of Chemistry and the Laboratory for Nuclear Science, Massachusetts Institute of Technology, Cambridge, Massachusetts.
Received May 25, 1964*

Reasons are advanced for expecting that a proton being transferred in an organic reaction from one oxygen (or nitrogen) to another should lie in an entirely stable potential at the transition state and be closer to the more basic atom, but increasingly remote as substituents are changed to make this atom less basic. This "solvation rule" predicts no ordinary primary isotope effect for such "hydrogen-bonding" hydrogens, and a dependence of position on structure of the reactants which is opposite to that for hydrogens which separate "reacting bonds," e.g., the α-hydrogens of ketones undergoing enolization, which follow the "reacting-bond rule" previously proposed. However, secondary hydronium (DO⁺ + HO → DO + HO⁺) or hydroxide (DO⁻ + HO → DO + HO⁻) isotope effects cannot be ignored. The simplest procedure for calculating them is described. The k_H/k_D isotope effects in the reactions of water or hydroxide ion with 4-chlorobutanol to form tetrahydrofuran are quantitatively interpretable as secondary and solvent isotope effects, with no ordinary primary isotope effect from the alcoholic hydrogen being transferred. The change in structure of the transition state for reaction of hydroxide ion with 2-chloroethanol is in accord with the reacting-bond rule. A fundamental fallacy in anthropomorphic arguments used to choose among reaction mechanisms is illustrated by the hydrolysis of Schiff bases. The decomposition of hyponitrous acid, the Cannizzaro reaction, the benzilic acid rearrangement, and the alkaline cleavage of 2,6-dihalobenzaldehydes illustrate further the method for calculating isotope effects from assumed transition states.

Proton transfers from electronegative atoms such as oxygen are extremely rapid whereas those from carbon are kinetically slow. This is understandable from transition-state models for the reaction of hydroxide ion with an alcohol (I) or ketone (II). The low electronegativity or Coulomb integral of carbon necessitates delocalization of the negative charge on the enolate

$$\overset{-}{HO}\cdots\overset{+}{H}\cdots\overset{-}{O}-\underset{\underset{R}{\diagdown}}{\overset{\diagup CH_3}{CH}} \qquad (I)$$

$$\overset{-}{HO}\cdots\overset{+}{H}\cdots\left[\underset{\underset{R''}{|}\diagdown}{\overset{R'}{\underset{|}{C}}=\overset{\diagup O}{\underset{R}{C}\diagdown}}\right]^{-} \qquad (II)$$

portion of II, putting the center of negative charge (near arrow) farther from the center of position charge than in I. This greater electrostatic charge separation results in a larger activation energy for forming II and makes proton transfer from carbon slow, and rate determining for deuterium exchange in D_2O, for racemization, and for bromination of ketones.[2]

Because proton transfer is rate determining in these reactions, large primary α-hydrogen isotope effects are observed. The decomposition mode of II is approximately

$$H-\overset{\delta-}{O}\cdots H\cdots C = C \overset{\delta-}{O}$$
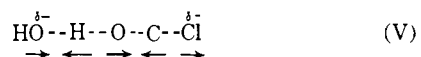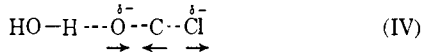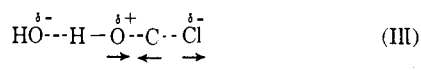$$\rightarrow \quad \leftarrow \quad \rightarrow$$
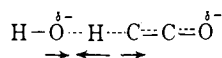
Since this translational mode is roughly the asymmetric stretch of the O–H–C system, the attendant loss of zero-point energy by hydrogen in the transition state is the origin of these large primary isotope effects. They change with structure in a way consistent with the "reacting-bond rule" previously proposed.[3,4]

Alkaline chlorohydrin cyclizations

$$HO^- + HO(CH_2)nCl \longrightarrow H_2O + O\underset{\diagdown(CH_2)_{n-1}}{\overset{\diagup CH_2}{\underset{|}{|}}} + Cl^-$$
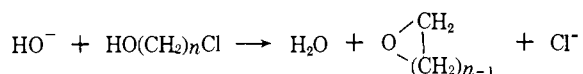
exemplify a third possibility, in which proton transfer may be occurring concertedly with another process, viz., the displacement of chloride by the oxygen function of the chlorohydrin. Since this proton transfer between oxygens is known to be rapid, the chloride displacement must take place in the decomposition mode. Thus the three possible (approximate) forms for the decomposition mode are

$$\overset{\delta-}{HO}\cdots H-\overset{\delta+}{O}\cdots C\cdots \overset{\delta-}{Cl} \qquad (III)$$
$$\rightarrow \leftarrow \quad \rightarrow$$

$$HO-H\cdots \overset{\delta-}{O}\cdots C\cdots \overset{\delta-}{Cl} \qquad (IV)$$
$$\rightarrow \leftarrow \quad \rightarrow$$

$$\overset{\delta-}{HO}\cdots H\cdots O\cdots C\cdots \overset{\delta-}{Cl} \qquad (V)$$
$$\rightarrow \leftarrow \quad \rightarrow \leftarrow \quad \rightarrow$$

III and IV represent decomposition modes involving only the OCCl system but having the proton in different potential minima of the OHO hydrogen bond. In these transition states, the asymmetric stretching motion of the OHO system (vibration of hydrogen along a line between the oxygens) is a genuine vibration with a restoring force and full complement of zero-point energy; consequently primary deuterium isotope effects are not expected. V, on the other hand, represents a fully concerted reaction involving translation of the proton in the decomposition mode and ought to give rise to primary isotope effects.

(2) Cf. the calculation given by R. P. Bell in "The Proton in Chemistry," Cornell University Press, Ithaca, N. Y., 1959, pp. 173, 174.
(3) C. G. Swain and E. R. Thornton, J. Am. Chem. Soc., 84, 817 (1962); C. G. Swain and A. S. Rosenberg, ibid., 83, 2154 (1961).
(4) C. G. Swain and R. L. Schowen, paper in process.

Transition state III or IV, whichever is stabler, must be stabler than V, other things being equal, because the positions of the alcoholic hydrogen in III and IV correspond to the potential energy minima of stable hydrogen bonds; the small but finite extra activation energy to put this hydrogen in an intermediate "in-transit" position as in V must therefore give V more total energy than at least one of the two forms represented by III and IV. Therefore no primary isotope effects should be expected.

Arguments favoring V which involve such statements as "concerted removal of the proton aids expulsion of chloride ion by release of the H–O bonding electrons" are fallacious in attributing motivation to the catalyzing base and are invalid on the basis of transition-state theory unless they can be couched in thermodynamic terms. This point is discussed and illustrated further below.

Thus chlorohydrin cyclizations and other reactions in which a base removes a proton from an electronegative atom should result in kinetic isotope effects interpretable purely as secondary effects, not primary ones arising from participation of hydrogen in the reaction coordinate. We have now determined some relative reactivities of different bases toward 4-chlorobutanol and corresponding isotope effects in light and heavy water which agree with these expectations.

Procedure for Calculating Kinetic Isotope Effects. In calculating secondary isotope effects for O–H–O systems we have employed the simplest possible procedure. Any OH bond in the reactants must be either an H–O⁻, H–O⁺–, or H–O– bond; the same is true of product OH bonds. Transition-state OH bonds may be of intermediate character. Taking n for any OH bond as the fraction in energy representing extent of conversion to products ($n = 0$ for a reactant-like and $n = 1$ for a product-like transition state), we took K^n as the contribution from this OH bond, where K is the limiting isotope effect corresponding to conversion from its form in the reactants to its form in the products. The complete isotope effect is then given by the product of such contributions for all the OH bonds. For estimation of limiting isotope effects K, the ratios K_H/K_D for the conversions HO $\rightarrow$ HO⁺ and HO $\rightarrow$ HO⁻ are 1.5 and 2.0. In other words, we have adopted the values $K_1 = 1.5$ and $K_2 = 2.0$ at 25° for equilibria 1 and 2 in which the symbols represent the indicated

$$DO^+ + HO = DO + HO^+ \qquad (1)$$
$$DO^- + HO = DO + HO^- \qquad (2)$$
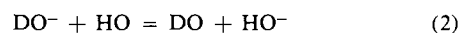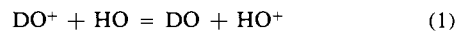
bonds in any environment, their isotopic partition function ratios being assumed independent of environment. These values are derived empirically from recent measurements of deuterium distribution between water and hydronium ion[5,6] and of the autoprotolysis constant for deuterium oxide[5,7] and represent an improvement over other values (1.41 for K_1 and 1.8 for K_2) which we previously derived[8] from spectroscopy and older values for the heavy water autoprotolysis con-

(5) V. Gold and B. M. Lowe, Proc. Chem. Soc., 140 (1963); V. Gold, ibid., 141 (1963).
(6) A. J. Kresge and A. L. Allred, J. Am. Chem. Soc., 85, 1541 (1963).
(7) P. Salomaa, L. L. Schaleger, and F. A. Long, ibid., 86, 1 (1964).
(8) C. G. Swain and E. R. Thornton, ibid., 83, 3884, 3890 (1961); C. G. Swain and R. F. W. Bader, Tetrahedron, 10, 182 (1960).

stant. The empirical values are compatible with the theory because they can be matched by theoretical estimates based on the previously proposed model of the structure differences of light and heavy water[8] if relatively small adjustments are made in the librational frequencies of either hydroxide and hydronium ions themselves or the water molecules solvating these ions. However, in the absence of any experimental justification for these minor frequency adjustments, we have used the theoretical models only to estimate the temperature dependence of K_1 and K_2, the solvent isotope effect for chloride ion, and its temperature dependence.

Assumption of a simple exponential dependence on T^{-1} (with unit temperature-independent factor and corresponding to all frequencies greater than $6kT/h$) predicts a 3% decrease in K_1 and a 5% decrease in K_2 on going from 25 to 50°, while the complete theoretical expressions yield a 2.7-3% decrease in K_1 and a 5-7% decrease in K_2. Therefore we suggest the values $K_1 = 1.45$ and $K_2 = 1.90$ for 50°. The uncertainties in these numbers are smaller than those arising from the unknown solvent isotope effects in mechanism studies.

For chloride ion the solvent isotope effect at 25° was

$$Cl^-(D_2O)_4 + 4H_2O = Cl^-(H_2O)_4 + 4D_2O \qquad (3)$$
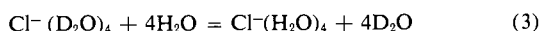
previously calculated to be $K_3 = 1.48$. Recalculation for 50° gives 1.42.

Tetrahydrofuran Formation from 4-Chlorobutanol. The Solvation Rule. 4-Chlorobutanol reacts not only with hydroxide ion but also with weaker bases in aqueous solution to form tetrahydrofuran. On the other

$$B: + HO(CH_2)_4Cl \longrightarrow BH^+ + \underset{O}{\boxed{}} + Cl^-$$
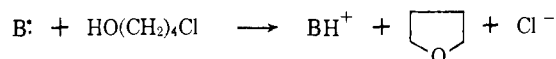
hand, 2-chloroethanol reacts only with hydroxide ion to form ethylene oxide; its reaction with water gives ethylene glycol directly.[9]

Figure 1 is a Brønsted catalysis law plot for the formation of tetrahydrofuran from 4-chlorobutanol and three bases (water, borate ion, and hydroxide ion) in aqueous solution. The K_B values are corrected to be dimensionless (55 M used for H_2O). The constant slope implies a common mechanism[10] and its value, 0.25, implies that the transfer of the alcoholic proton is about 25% complete at the transition state.[11]

To calculate the isotope effect, we assume that the chloride is undissociated at the transition state and therefore solvated by only three water molecules instead of four.[8] It should then contribute a factor of $(1.42)^{0.75} = 1.30$ if completely ionized. If both the proton transfer and the ionization of the C–Cl bond are 25% complete, the calculated factors are

$$\frac{k_{H_2O}}{k_{D_2O}} = [(1.45)^3]^{0.25}(1.30)^{0.25} = 1.41$$

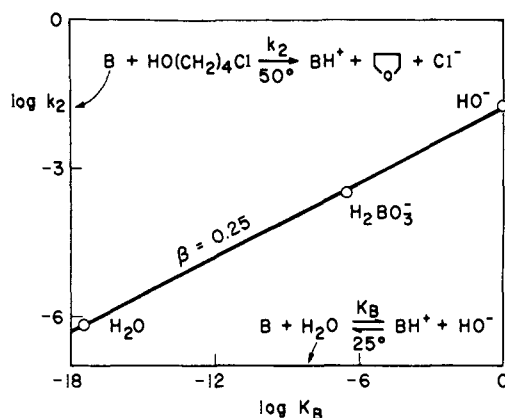$$\frac{k_{DO^-}}{k_{HO^-}} = (1.90)^{0.25}(1.30)^{-0.25} = 1.10$$

Figure 1. Log–log plot of rate of reaction of three bases with 4-chlorobutanol *vs.* their basicities.

The observed isotope effects are so close to these calculated figures as to leave no room for an ordinary primary isotope effect. The reaction of water with 4-chlorobutanol is 1.28 times faster with H_2O than with D_2O; the reaction of hydroxide ion with 4-chlorobutanol is 1.07 times faster with DO^- in D_2O than with HO^- in H_2O; both are within 10% of the calculated figures.

Although this result was predicted above, it is surprising for the following reason. Primary kinetic isotope effects might have been expected to be even larger for proton transfers between oxygens than for proton transfers between carbons or from carbon to oxygen (where k_{CH}/k_{CD} isotope effects of 6–7 are common), because stretching frequencies are higher for OH than for CH, and this larger difference in zero point vibrational energy of the reactant must lead to a larger isotope effect if the transition states are similar.

An apparently untenable explanation is that the transition state in this particular system is so asymmetric that there is enough motion of the alcoholic hydrogen and zero-point vibrational energy in the "symmetrical" vibration (and in the two bends) to nearly offset that in the reactant.[12,13] The calculated isotope effect k_H/k_D for 50% transfer is 8.1 for linear transfer between two oxygen atoms using reasonable force constants,[14] in contrast to a maximum of 6.9 for 40% transfer from carbon to oxygen. For 25% transfer the corresponding isotope effects are 4.0 between oxygens and 4.9 between carbon and oxygen. However, there seems to be no room for a primary isotope effect as large as 4.0, or even as large as 1.5. In OHC systems large isotope effects are observed for all values of β. For different ketone enolizations in which β varies from 0.1 to 0.9, the CH isotope effect (k_H/k_D) ranges from 3.8 to 6.5. For different OHO systems, reported isotope effects have never exceeded 3.8 (have rarely exceeded

(9) A. A. Frost and R. G. Pearson, "Kinetics and Mechanism, John Wiley and Sons, Inc., New York, N. Y., 1953, p. 253; 2nd Ed., 1961, p. 301.
(10) A. J. Kresge and Y. Chiang, *J. Am. Chem. Soc.*, 83, 2883 (1961).
(11) J. E. Leffler, *Science*, 117, 340 (1953).

(12) It was suggested (C. A. Bunton and V. J. Shiner, Jr., *J. Am. Chem. Soc.*, 83, 3214 (1961)) earlier that hydrogen isotope effects may be small if (1) the transition state is very asymmetric, or (2) zero point vibrational energy is high in the transition state because of very strong hydrogen bonding, or (3) the proton transfer occurs in a fast step both preceded and followed by slower steps, because hydrogen bonding so facilitates the transfer from A–H---A* to A---H–A* that formation of the first complex from AH and A* and decomposition of the second to A and HA* are actually slower.
(13) See also the excellent discussion by F. H. Westheimer, *Chem. Rev.*, 61, 265 (1961).
(14) C. G. Swain and R. L. Schowen, paper to be published.

3.0) and in general are interpretable like the cyclization of 4-chlorobutanol in terms of secondary hydronium or hydroxide contributions only. The universal smallness of OH isotope effects in the mutarotation of glucose or other reactions involving proton transfers between oxygens has been noteworthy for a long time.

A more satisfactory way to account for the high zero-point vibrational energy in the transition state is to exclude the alcoholic hydrogen from the reaction coordinate so that the asymmetric stretch of the OHO also is a real vibration at the transition state with zero-point energy, not a translation. The asymmetric stretch of the OCCl system alone then leads to cyclization, as in III.

A rule (the "reacting-bond rule") was proposed and illustrated earlier[3]: electron-supplying substituents lengthen the nearest reacting bond(s), but have an alternating effect on more remote reacting bonds. A reacting bond is a bond being made or broken at the transition state, i.e., one absent in either the reactants or the products of the rate-determining step. A more electron-supplying substituent is one which is more basic toward a proton. However, the facts above suggest that the bonds joining the alcoholic hydrogen to the two oxygens are not reacting bonds. Therefore the following additional generalization ("solvation rule") may prove useful: a proton being transferred from one oxygen to another in an organic reaction (a reaction with bond changes on carbon in the rate-determining step) should lie in an entirely stable potential at the transition state and not form reacting bonds nor give rise to primary hydrogen isotope effects. It should be closer to the more basic oxygen at the transition state, but increasingly remote as substituents are changed to make this oxygen less basic. If another oxygen in the transition state is made most basic as a result of structure changes, nature relocates the proton to be closest to it, again to provide the most stabilization. This rule may also apply when oxygens are replaced by nitrogens, halogens, or other atoms with one or more unshared pairs of electrons in the reactant state, but certainly does not hold when they are replaced by carbons. We call this a "solvation rule" rather than a "hydrogen-bond rule" because the underlying principle of locating a species to provide maximum stabilization is more widely applicable than just to hydrogen bonds; the same considerations determine the best positions for the elements of all solvating solvent molecules and molecular, ion-pair, or ionic solutes which are in the transition state but not involved in the reaction coordinate. Solvation bonds to solvent molecules constitute the largest class of such nonreacting bonds. Unlike the reacting-bond rule, this rule is a restatement of thermodynamic laws governing the structure of all stable aggregates and so should apply to reactants as well as to the stable parts of transition states.

The observed Brønsted slope of 0.25 for 4-chlorobutanol cyclization implies that the alcoholic hydrogen is closer to the alcoholic oxygen than to the oxygen of the basic reagent at the transition state. The rule then requires the alcoholic oxygen to be more basic than even a hydroxide ion oxygen at the transition state. This means that, if one could remove the proton without otherwise altering the reacting system, the transition state minus the proton would have close to a full charge on the alcoholic oxygen.
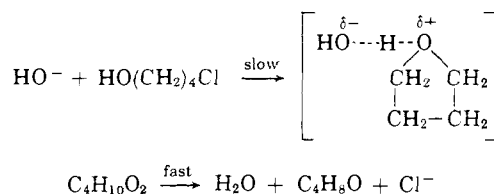
$$\text{HO}^- \qquad \bar{\text{O}} \overset{\delta^+ \ \delta^-}{-\!-\!-\!-} \text{C}\!-\!\text{Cl}$$
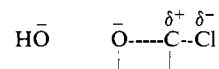
Before removing or after returning the proton (closer to the more basic oxygen), the transition state would be

$$\overset{0.75^-}{\text{HO}}\!-\!-\!-\!\text{H}\!-\!\overset{0.25^-}{\text{O}}\!-\!-\!-\!-\overset{\delta^+ \ \delta^-}{\text{C}\!-\!\text{Cl}}$$
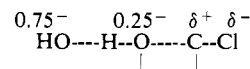
This much negative charge on the alcoholic oxygen requires a particularly long, loose bond between oxygen and carbon at the transition state. However, no conclusion is possible about the exact extent of C–Cl bond breaking (magnitude of δ) without data bearing on that particular bond (e.g., the chlorine isotope effect). It would be useful to determine the chlorine isotope effect for both this reaction and that of hydroxide ion with 2-chloroethanol.
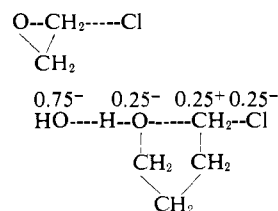
A further consequence of not translating the alcoholic hydrogen in the rate-determining step is the conclusion that this and similar reactions are stepwise, producing a hydrogen-bonded oxonium ion pair intermediate with a partial positive charge on the alcoholic oxygen as the product of the rate-determining step, which then transfers a proton to the base in a subsequent fast step.

$$\text{HO}^- + \text{HO(CH}_2)_4\text{Cl} \xrightarrow{\text{slow}} \begin{bmatrix} \overset{\delta^-}{\text{HO}}\!-\!-\!\text{H}\!-\!-\!\overset{\delta^+}{\text{O}} \\ \diagup \quad \diagdown \\ \text{CH}_2 \quad \text{CH}_2 \\ | \qquad | \\ \text{CH}_2\!-\!\text{CH}_2 \end{bmatrix}$$

$$\text{C}_4\text{H}_{10}\text{O}_2 \xrightarrow{\text{fast}} \text{H}_2\text{O} + \text{C}_4\text{H}_8\text{O} + \text{Cl}^-$$

Quite a different kind of intermediate is involved in the reaction of hydroxide ion with 2-chloroethanol, one with a full negative charge on the organic portion of the transition state as a result of complete transfer of the proton in a prior equilibrium step preceding the rate-determining step. What is the cause of this major change of mechanism between two members of the homologous series $\text{HO(CH}_2)_n\text{Cl}$?

A superficial answer is the higher acidity of the alcoholic hydrogen for $n = 2$ than for $n = 4$ (field effect). This causes the equilibrium concentration of $^-\text{O(CH}_2)_n\text{Cl}$ to be just enough higher that this species now provides a faster route to products; acidity differences in the equilibria outweigh nucleophilic differences in rates of cyclization of the anions, just as the effect of changing structure on a pre-equilibrium is usually found to be greater than on a subsequent slow step.

A more fundamental answer involves comparison of the two transition states

$$\text{O}\!-\!\text{CH}_2\!-\!-\!-\!\text{Cl}$$
$$\diagdown \diagup$$
$$\text{CH}_2$$

$$\overset{0.75^-}{\text{HO}}\!-\!-\!-\!\text{H}\!-\!\overset{0.25^-}{\text{O}}\!-\!-\!-\!-\!-\overset{0.25^+ \ 0.25^-}{\text{CH}_2\!-\!\text{Cl}}$$
$$| \qquad |$$
$$\text{CH}_2 \quad \text{CH}_2$$
$$\diagdown \diagup$$
$$\text{CH}_2$$

The charges in the first one are assigned to account for the observed isotope effect $k_{\text{D}_2\text{O}}/k_{\text{H}_2\text{O}}$ of 1.54 since one

predicts 2.0 for all the charge on oxygen, (2.0)·
$[(1.48)^{-0.75}]^{0.5}$ = 1.72 for half on chloride, and (2.0)·
$(1.48)^{-0.75}$ = 1.50 for all on chloride. This suggests
that carbon–chlorine bond breaking is much more com-
plete in the transition state for formation of ethylene
oxide. This at first appears to violate the reacting-
bond rule: since the alcoholic proton has completely
separated, the alcoholic oxygen should be more nega-
tive and basic in the first case, and its bond to carbon
should be less fully formed (other things being equal).
However, there is an important difference, between the
two reactions, the approximately 15 kcal. of strain
energy in forming a three-membered ring. This com-
parison could be advanced as evidence for a third general
rule, a steric effect on transition state structure: the
more strained, hindered, or crowded the product of a
rate-determining step becomes (basicities and other
electrical factors remaining equal), the more the tran-
sition state should resemble the product. However,
there are many exceptions to rules which ascribe
changes in transition state structure to changes in the
stability of intermediates or products.[3] Therefore it
seems simpler and sounder to note that this can be
accommodated within the framework of the reacting-
bond rule if one uses leaving group reactivity in the
microscopic reverse reaction instead of basicity toward
a proton as a measure of electron-supplying tendency;
a better leaving group in the microscopic reverse
reaction is a weaker base for the forward reaction.
This slight modification was suggested in another
paper,[4] and is one which takes the ring strain into
account so that the oxygen in the reaction forming
ethylene oxide should behave as a weaker base, because
ethylene oxide is more reactive with chloride in neutral
water solution than even the completely protonated
conjugate acid of tetrahydrofuran. This causes the
OC bond to be shorter in the transition state of the
ethylene oxide-forming reaction, with relatively even
less negative charge left on this oxygen than might have
been anticipated from comparison of acidities of the
reactant chloro alcohols. Then it is understandable
why the stablest transition state for ethylene oxide is
one with the alcoholic proton on hydroxide ion (*i.e.*,
in a water molecule) rather than on the organic portion.

A Fallacy in Anthropomorphic Arguments. Chemists
often draw perilous inferences by considering "what
would I do in that particular situation if I were an un-
shared pair of electrons?" For example, from this
standpoint general base catalysis by carboxylate ions
in the hydrolysis of Schiff bases[15] in solutions which
are just acidic enough to protonate the Schiff bases
practically completely (>90%) seems better explained
by mechanism VI than by mechanism VII because in

AcO⁻ + H₂O + C₆H₅CH=NRH⁺ ⟶
AcOH + HO—C₆H₅CH—NRH (VI)

H₂O + C₆H₅CH=NRH⁺ + AcO⁻ ⟶
H₂O⁺—C₆H₅CH—NRH + AcO⁻ (VII)
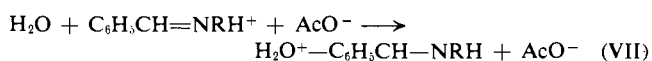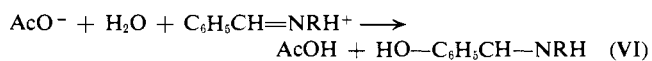
mechanism VI acetate ion functions either as an active
nucleophile (removing a proton from a water molecule
in the rate-determining step) or possibly as a base (re-
moving this proton in a prior equilibrium), and such
roles would clearly *assist* the attack by water. In

(15) E. H. Cordes and W. P. Jencks, *J. Am. Chem. Soc.*, **85**, 2848 (1963).

mechanism VII, it merely solvates the initially more
positive NH⁺ group, a less challenging role, and one
which would seem to *hinder* the attack by water by
reducing the protonic activation of the C=N bond.
Hence this dynamic or anthropomorphic approach
suggests that mechanism VI is correct.

Such inferences are entirely unsound. The rate of a
chemical reaction having a single rate-determining
step depends *only* on the difference in free energy be-
tween reactants and transition state. For a fixed
initial state of the reactants, the lower the energy of the
transition state the faster will be the rate. The most
difficult bond changes in a Schiff base hydrolysis are
the ones involving carbon directly. A part structure
for the transition state about carbon is

$$\underset{H}{\overset{H_5C_6 \quad t\text{-Bu}}{\delta+H_2O\cdots C\!=\!NH^{\delta+}}}$$
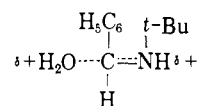
The placement of the remaining acetate ion should be
such as to minimize the energy. This is accomplished
by placing it closest to the most acidic hydrogen.
That will be an oxonium hydrogen (mechanism VI) if
the O–C bond is short and the C–N bond long, *i.e.*,
if the transition state is close to products. However,

$$\underset{H}{\overset{H \quad Ph \quad t\text{-Bu}}{AcO\text{--}H\text{--}O\!—\!C\!—\!NH}}$$
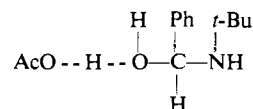
it should be the iminium ion hydrogen (mechanism
VII) if the water–carbon distance is long and the C=N
short, *i.e.*, if the transition state is close to reactants.

$$\underset{H}{\overset{H \quad Ph \quad t\text{-Bu}}{H\!—\!O\text{--}C\!=\!N\text{--}H\text{--}OAc}}$$
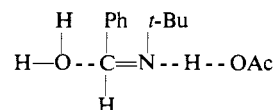
A way to tell whether the transition state can be close
to products or close to reactants is by the magnitude
of the Brønsted catalysis law slope β. If it is close to
products, so that mechanism VI operates, the hydrogen
solvated by acetate will be closer to acetate than to the
alcoholic group to minimize the energy, since acetate
is a stronger base than the alcohol. Therefore the pro-
ton transfer to form acetic acid is more than half com-
plete, and β should be greater than 0.50. On the other
hand, if the transition state is close to reactants, so that
mechanism VII operates, the hydrogen on nitrogen will
be closer to nitrogen than to acetate, since the Schiff
base is a stronger base than acetate. The pK_A of the
Schiff base[15] is 6.7, while that of acetic acid is 4.7.
Therefore a proton transfer to form acetic acid is less
than half complete, and β should be less than 0.50.
The observed β of 0.25 excludes the first extreme (tran-
sition state close to products, mechanism VI) but is
compatible with the second (transition state close to
reactants, mechanism VII). However, to cover all
possibilities, we must also consider transition states
between these two extremes.

For more nearly symmetrical transition states, not
close to either products or reactants, as the transition
state becomes more like reactants, β should *fall* for
mechanism VI (until the mechanism changes to VII),
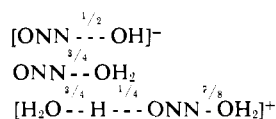but it should *rise* for mechanism VII. For example,

with a more electron-withdrawing substituent in the R group on nitrogen, the transition state must come earlier by the reacting-bond rule, and the hydrogen-bonding basic center beside the acetate ion, discounting the proton which forms the hydrogen bond, should shift from product alcohol toward hydroxide ion (more basic) by mechanism VI, but away from amide anion and toward imine (less basic than amide anion) by mechanism VII. Since this variation of β with structure has not yet been determined, we cannot yet be sure which mechanism is incorrect, but certainly mechanism VII has not been disproved, and the above experiment might disprove mechanism VI instead.

If the proton on nitrogen were replaced by an alkyl group, as in benzaldehyde dimethyliminium ion, acetate ion might still interact preferentially at the iminium end, by solvating the nitrogen of the iminium ion directly.

One may object that transition state bonds to reactant solute bases in most general base catalyzed reactions (including mutarotation of glucose and mechanisms VI or VII) seem too weak to hold the components of the transition states together if they are nonreacting bonds as we have suggested. For solvation catalysis by acetate ion at a center HB of the transition state, the complex will be either AcO---HB (if HB is a weaker acid than acetic acid) or AcOH---B (if B is a weaker base than acetate ion). Yet ordinary, stable acetate ion and acetic acid (when not parts of a transition state) are mostly *not* associated even when both are as concentrated as 0.1 *M* in water at 25°. It then seems unlikely that either AcO---HB or AcOH---B (both less stable than AcO---HOAc) should be in higher concentration than H_2O---HB.

The answer to this paradox, we believe, lies in the polarizability of the electron cloud occupying the reacting orbitals, the same property of activated complexes which accounts for the reacting-bond rule. Although the hydrogen-bonding protons in the 4-chlorobutanol, glucose, and Schiff base transition states are not in the reaction coordinate, they are attached to atoms (oxygen or nitrogen) which are; electrons in the valence shell of such atoms are more polarizable than in any stable molecules, and may be able to rearrange to stabilize a hydrogen-bonded complex with base B over that with base water to a degree that is not possible when the internal electron cloud is less mobile. Every difference in rate behavior as opposed to equilibrium behavior may well arise from this great polarizability of reacting orbital electrons, due to the longer-than-normal bond distances for the reacting bonds.

Calculation of Isotope Effects for Other Reactions. For the nonchain decompositions of hyponitrite ion, hyponitrous acid (HON=NOH), and hyponitrous acidium ions (at H_0 = 8, 2, and -3) to give N_2O, assuming transition states

$$[ONN\overset{1/2}{\text{---}}OH]^-$$
$$ONN\overset{3/4}{\text{--}}OH_2$$
$$[H_2O\overset{3/4}{\text{--}}H\overset{1/4}{\text{---}}ONN\overset{7/8}{\text{-}}OH_2]^+$$

with bond orders equal to the fractions shown above the bonds, one calculates isotope effects (k_{H_2O}/k_{D_2O}) of $(2.0)^{1/2} = 1.41$, $((1.5)^2)^{1/4} = 1.84$ and 1.5 (for the change from $3HO^+$ bonds in H_3O^+ to $3(^3/_4) + 2(^7/_8) =$

4 HO^- bonds in the third transition state). These assignments of bond order are quite reasonable. By the reacting-bond rule the leaving group bond orders must increase (bond lengths decrease) as leaving group basicity decreases or when the O of N_2O is partially protonated (as they do, from $^1/_2$ to $^7/_8$). By the solvation rule the hydrogen-bonding proton must be closer to H_2O (bond order $^3/_4$) than to ON_2OH_2 (bond order $^1/_4$) because water is more basic. These rules impose definite limitations on the range of isotope effects that can be calculated, and these isotope effects would be good *a priori* estimates.

The observed isotope effects are 1.30, 1.95, and 1.45,[16] close enough to the calculated 1.41, 1.84, and 1.5 to be compatible with these assumed transition states. By very small further adjustment of assumed bond orders, exact agreement with experiment is obtainable.

The Cannizzaro reaction of benzaldehyde,[17] the benzilic acid rearrangement,[18] and the alkaline cleavage of 2,6-dihalobenzaldehydes to *m*-dihalobenzenes and formate ion[19] are all twice as fast in D_2O-containing solvents as in those containing H_2O. This has been taken as evidence that no oxygen-to-oxygen proton transfers are occurring in the rate-determining steps of any of these reactions. According to the solvation rule they would have been expected not to be part of slow steps. These isotope effects are consistent with the transition states
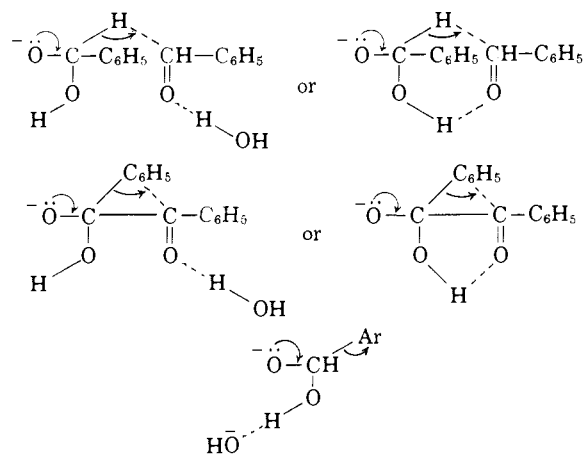
in each of which one HO^- bond of the reactants is now HO (ROH or H_2O).

Experimental[1]

4-Chlorobutanol was prepared from tetrahydrofuran which had been refluxed over calcium hydride for 8 hr. and distilled in apparatus protected from atmospheric moisture by drying towers filled with Drierite.[20] The 4-chlorobutanol was distilled through a column 50 cm. long and 2 cm. in diameter filled with glass helices, b.p. 58–65° (*ca.* 4 mm.), n^{20}D 1.4536; lit.[21] 70–71° (7 mm.), n^{20}D 1.4518. A freshly distilled sample

(16) J. R. Buchholz and R. E. Powell, *J. Am. Chem. Soc.*, **85**, 511(1963).
(17) C. R. Morgan, Ph.D. Thesis in Organic Chemistry, M.I.T., May 1963.
(18) J. Hine and H. W. Haworth, *J. Am. Chem. Soc.*, **80**, 2274 (1958).
(19) J. F. Bunnett, J. H. Miles, and K. V. Nahabedian, *ibid.*, **83**, 2515 (1961).
(20) D. Starr and R. M. Hixon, "Organic Syntheses," Coll. Vol. 11, John Wiley and Sons, Inc., New York, N. Y., 1943, p. 571.
(21) W. R. Kirner and G. H. Richter, *J. Am. Chem. Soc.*, **51**, 2503 (1933).

was diluted with a measured volume of water. After extracting this solution with chloroform, chloride ion equivalent to 1.5% of that in the 4-chlorobutanol was found in the water by Volhard titration. The chloride ion, released by a known weight of 4-chlorobutanol during a kinetic run from initial to final titer, was 98.8% of that calculated.

4-Chlorobutanol-d. Deuterium oxide (50 g., 2.5 moles) in a pressure-equalizing addition funnel was dropped slowly into benzoyl chloride (453 g.) at 100–120° in a 1-l., three-necked flask. The deuterium chloride produced was swept through the system (including water condenser, Dry Ice–acetone trap, and three-necked receiver flask) for 5 min. to remove any remaining moisture or to exchange any exchangeable protons. Deuterium chloride was then bubbled through a sintered tube into refluxing tetrahydrofuran (35 g., 0.5 mole) in the receiver until the temperature of the reaction solution had risen to 105°. The reaction solution was allowed to cool, stoppered, and stored in a desiccator over phosphorus pentoxide. A 25-ml. portion was distilled in a Vigreux column 18 cm. long and 1.3 cm. in diameter with a Claisen head, b.p. 65–70° (1–2 mm.). A redistilled fraction was used for spectral work, b.p. 54–55° (1.8–2 mm.), $n^{25}D$ 1.4462, purity 99.7% by saponification equivalent after 30 half-lives at 50.3°.

4-Chlorobutanol-*d* was prepared also by addition of tri-4-chlorobutyl borate to a portion of deuterium oxide insufficient to react with all the ester in a centrifuge tube. The open end of the tube was drawn to a capillary and sealed and the mixture was shaken. Boric acid-d_3 precipitated immediately but the reactants were allowed to stand for 8 hr. to ensure complete reaction. The tube was centrifuged and the 4-chlorobutanol-*d* was removed, placed in a Claisen flask, and distilled at 0.3 mm., b.p. 30–31°. 4-Chlorobutanol was prepared in the same fashion. Tri-4-chlorobutyl borate was prepared from boron trichloride and 4-chlorobutanol,[22] b.p. 129.5–130.5° (0.06 mm.); lit.[22] 136–140° (0.1 mm.).

Other Materials. Reagent grade chemicals were used unless otherwise specified. Water was redistilled from potassium permanganate, then boiled to remove carbon dioxide, and stored in a flask attached to a drying tower filled with sodium hydroxide. Deuterium oxide (">99.5%") was obtained from the Stuart Oxygen Co. For some of the runs it was degassed by boiling at reduced pressure.

Sodium deuteroxide was prepared from sodium freshly cut under petroleum ether. A solution 50% by weight was made by dropwise addition of deuterium oxide in a prepurified nitrogen atmosphere, centrifuging, and diluting with deuterium oxide. Sodium hydroxide was reagent grade except for runs involving measurement of the isotope effect. Then it was made analogously to sodium deuteroxide. Sodium perchlorate was G. F. Smith anhydrous, dried in an oven at 130° for 24 hr. and stored in a desiccator over Drierite. Hydrogen chloride was Matheson Co. anhydrous.

Products and Kinetic Methods. The reaction of 4-chlorobutanol with water or with hydroxide ion in

(22) J. D. Edwards, W. Gerrard, and M. F. Lappert, *J. Chem. Soc.*, 1470 (1955).

water produced tetrahydrofuran, isolated in 74 and 95% yield, respectively.[23–25] The reactions were conducted in Pyrex vessels in a 50.3° thermostat. Reactions were followed by Volhard titration with or without prior extraction with chloroform or by acid titration.

Reaction of 4-Chlorobutanol with Water. The average first-order rate constant k_1 for five runs was 3.60 × 10⁻⁵ sec.⁻¹ (Table I). The average k_1 for five runs in heavy water is 2.82 × 10⁻⁵ sec.⁻¹. The isotope effect for the neutral cyclization of 4-chlorobutanol is therefore $k_H/k_D = 1.28$.

Table I. Isotope Effect on Cyclization of 4-Chlorobutanol in Water at 50.3°

Run[a] no.	Cl(CH₂)₄OH, M	NaClO₄, M	$k_1 \times 10^5$, sec.⁻¹
2	0.0129	0.00	3.73
3	0.0157	0.00	3.55
28	0.0569	0.00	3.52
30	0.496	0.00	3.40
60	0.0198	0.00	3.75
15	0.0546	0.50	3.61
58	0.0204	0.50	3.50
11	0.0519	1.00	3.61
59	0.0231	1.00	3.60
12	0.0521	1.00[b]	3.85
16	0.0546	0.50[c]	3.58
21	0.0616[d]	0.00	2.82[d]
22	0.0616[d]	0.00	2.82[d]
23	0.0616[d]	0.00	2.82[d]
29	0.0575[d]	0.00	2.80[d]
31	0.0502[d]	0.00	2.83[d]

[a] Chronological run numbers. [b] 0.0389 M HCl also present. [c] 0.0972 M HCl present. [d] Cl(CH₂)₄OD in D₂O.

The reaction was tested for general acid catalysis using acetic acid–acetate ion buffers and a neutral salt, sodium perchlorate (Table II). At constant ionic

Table II. pH Effect on Cyclization of 4-Chlorobutanol in Water at 50.3°

Run no.	pH[a]	NaClO₄, M	μ,[b] M	$k_1 \times 10^5$,[c] sec.⁻¹
9	4.37	0.000	1.00	3.61
10	4.37	0.900	1.00	3.27
13	4.37	0.400	0.500	3.85
14	4.37	0.100	0.500	3.58
77	4.82	0.000	1.038	3.72
78	4.82	0.600	1.015	3.55
79	4.82	0.960	1.052	3.81
17	9.17	0.000	0.0286	5.55
18	9.98	0.000	0.0457	5.92
56	10.1	0.465	0.582	7.37
57	10.1	0.349	0.582	11.8
55	10.1	0.000	0.582	26.0

[a] NaOAc–HOAc buffers for pH 4.37–4.82; NaH₂BO₃–H₃BO₄ for 9.17–10.1. [b] Ionic strength from NaClO₄ plus buffers anion. [c] Cl(CH₂)₄OH initially 0.0132–0.0681 M for these runs.

strength no general acid or specific hydronium ion catalysis was found. When the reaction was run in aqueous hydrochloric acid there was no change in

(23) J. L. Everett and W. C. J. Ross, *ibid.*, 1972 (1949).
(24) H. W. Heine, A. D. Miller, W. H. Barton, and R. W. Greiner, *J. Am. Chem. Soc.*, 75, 4778 (1953).
(25) H. W. Heine and W. Siegfried, *ibid.*, 76, 489 (1954).

rate. The reaction is also little affected by neutral salt. However, borate ion buffers accelerate the rate more than can be accounted for by hydroxide ion.

Reaction of 4-Chlorobutanol with Hydroxide Ion. The isotope effect was measured in four series of runs using different methods of manipulation and measurement (Table III).[1] The average $10^2 k_2$ values in H_2O

Table III. Isotope Effect on Alkaline Cyclization of 4-Chlorobutanol in Water at 50.3°

Run no.	Cl(CH₂)₄OH, M	NaOH, M	Water	$k_2 \times 10^2$, M^{-1}sec.$^{-1}$
19	0.01059	0.01032	H_2O	1.96
20	0.01039	0.01032	H_2O	1.97
24	0.05346	0.05967	D_2O	1.98
25	0.05346	0.05967	D_2O	2.02
26	0.05648	0.02980	D_2O	2.07
27	0.05648	0.02980	D_2O	2.02
39	0.07194	0.05264	H_2O	1.90
40	0.07322	0.05264	H_2O	2.00
41	0.06197	0.05264	H_2O	1.83
42	0.08840	0.03510	D_2O	2.17
43	0.04665	0.04197	D_2O	2.17
44	0.04478	0.03928	D_2O	2.21
45	0.03945	0.05154	H_2O	1.89
46	0.04030	0.05258	H_2O	1.82
47	0.03296	0.05179	H_2O	1.92
48	0.02448	0.05142	H_2O	1.98
49	0.03607	0.04775	D_2O	2.12
50	0.03479	0.04458	D_2O	2.14
95	0.03430	0.04623	D_2O	1.97
96	0.03636	0.04456	H_2O	1.75
97	0.02701	0.04456	H_2O	1.81
98	0.02461	0.04623	D_2O	2.02

are 1.96, 1.91, 1.90, and 1.78; in D_2O 2.02, 2.20, 2.12, and 2.00; the corresponding average isotope effects are 0.97, 0.95, 0.90, and 0.89. Sodium perchlorate decreased the rate (Table IV).

Table IV. Ionic Strength Effect on Alkaline Cyclization of 4-Chlorobutanol in Water at 50.3° with Sodium Perchlorate as Neutral Salt

Run no.	Cl(CH₂)₄OH, M	NaOH, M	μ, M	$k_2 \times 10^2$, M^{-1} sec.$^{-1}$
96	0.03636	0.04456	0.04456	1.81
97	0.02701	0.04456	0.04456	1.75
73	0.02627	0.05660	0.05660	1.66
76	0.04605	0.05660	0.09660	1.56
75	0.03670	0.05660	0.45660	1.40
74	0.03211	0.05660	1.05660	1.34

Spectral Measurements. Infrared spectra of 4-chlorobutanol and 4-chlorobutanol-*d*, synthesized from tetrahydrofuran and hydrogen or deuterium chloride, were measured from 3800 to 640 cm.$^{-1}$ in 10% carbon tetrachloride solution in 0.1-mm. sodium chloride cells with a Perkin-Elmer Model 21 double-beam spectrophotometer equipped with a sodium chloride prism. The spectra were calibrated with the 1601.5-cm.$^{-1}$ line of the polystyrene spectrum. These spectra were identical with the spectra of 4-chlorobutanol and 4-chlorobutanol-*d* synthesized from tri-4-chlorobutyl borate and water or deuterium oxide, demonstrating that the samples contain no impurities dependent on the particular synthesis.[1] Infrared spectra were obtained from

the pure alcohols from 3800 to 640 cm.$^{-1}$ by measurement in 0.01-mm. sodium chloride cells using the Perkin-Elmer spectrophotometer. Both a 0 and a 100% transmission line were recorded and the spectrum of each alcohol, measured with the same instrument setting and the same cell, was recorded on a single chart to compare the spectra quantitatively. Spectra of the pure alcohols, pressed between two 3-mm. thick potassium bromide plates, were measured from 800 to 385 cm.$^{-1}$ in a Baird Model AB-2 double-beam spectrophotometer equipped with a potassium bromide prism. The spectra were calibrated with the spectrum of ammonia. Difference spectra were also obtained using both pure alcohols in the Perkin-Elmer equipment. All of these spectra and the discussion of their interpretation are recorded in a thesis.[1]

Table V lists the frequencies observed to change on deuteration. Assignments may be more secure than the previous ones for 2-chloroethanol[26] because the

Table V. Frequencies Displaced by Isotopic Substitution in 4-Chlorobutanol and 4-Chlorobutanol-*d*

Frequency, cm.$^{-1}$	Assignment	ν_R/ν_D	Frequency, cm.$^{-1}$	Assignment
3325	ν_{HO}	1.35	2460	ν_{DO}
1420[a]	$\delta_{CH} + \delta_{HO}$	1.03	1384[a]	δ_{CH}
1335[a]	$\delta_{CH} + \delta_{HO}$	1.37	975[a]	δ_{DO}
1250[b]	$\delta_{CH} + \delta_{HO}$	1.02	1222[b]	δ_{CH}
1200[b]	$\delta_{CH} + \delta_{HO}$	1.38	868[b]	δ_{DO}
1155[a]	ν_{OC}	1.05	1097[a]	ν_{OC}
931[b]	ν_{OC}	1.02	916[b]	ν_{OC}
675	τ_{HO}	1.41	480	τ_{DO}

[a] High-lying frequencies used in the calculation. *[b]* Low-lying frequencies used in the calculation. The remaining frequencies were common to both conformations.

product of all frequency ratios must not exceed $(m_D/m_H)^{3/2} = 2.83$ for one conformation of a monodeuterated species (as calculated from the Redlich–Teller product rule approximating the molecular weight and moment of inertia ratios as unity). For 4-chlorobutanol the product of the high-lying frequency ratios is 2.82; the product for the other conformation is 2.74. However, the assignments for 2-chloroethanol[26] gave 3.04 for one and 3.05 for the other conformation. There is accordingly some doubt about the assignments with 2-chloroethanol. Possibly the 1420- and 1395-cm.$^{-1}$ absorptions are a doublet formed from the splitting of δ_{HO} by the 1360-^{1}-cm.$^{-1}$ band, which is prominent in the spectrum of 2-chloroethanol, with the true δ_{DO} absorption near 975 cm.$^{-1}$ as in the case of 4-chlorobutanol, but concealed by its characteristic broadness. The 773 peak previously assigned to this was a very weak one in the Raman spectrum, not greater than the noise in other parts of the Raman spectrum.

Isotope effects for 4-chloroethanol at 50° were calculated earlier from these frequencies for various mechanistic extremes, with inclusion of reasonable bending frequencies as well as stretching frequencies for the transition state.[1] For the reaction with water they were 1.37 for an oxonium chloride with an HO⁺ bond like H_3O^+ at the transition state, 7.0 for one with

(26) C. G. Swain, A. D. Ketley, and R. F. W. Bader, *J. Am. Chem. Soc.*, 81, 2358 (1959).

the proton being transferred and symmetrically located at the transition state (chlorine considered to have not changed), and 4.2 for complete proton transfer (chloride not changed). For the reaction with hydroxide ion they were 0.64 for a transition state like 4-chlorobutoxide ion and 2.54 for one with the proton being transferred and symmetrically located (chlorine not changed). Thus the conclusion from these more detailed calculations agrees with the one earlier in this paper that the observed isotope effects (1.28 with water and 0.93 with hydroxide) are inconsistent with proton transfer during the rate-determining step.

Transannular Cyclizations in Medium-Sized Unsaturated Lactams. Apparent Dependence of Transannular Interaction upon Conformational Factors[1,2]

Leo A. Paquette and Lawrence D. Wise[3]

Contribution from the Evans Chemistry Laboratory, The Ohio State University, Columbus, Ohio 43210. Received October 30, 1964

A series of azabicyclic amides of varying ring size (eight to ten members) are shown to be readily transformed to α,β-unsaturated lactams by the Hofmann elimination procedure. These unsaturated secondary lactams of the azacyclooctane and azacyclononane series undergo transannular cyclization when treated with acids. The related N-methylamides, as well as the azacyclodecane example, merely undergo protonation of the dimethylamino group under identical conditions. These results are discussed in terms of conformational factors.

Of the number of features exhibited by medium ring compounds which do not relate to other cyclic and acyclic structures, the phenomenon of transannular reaction is perhaps the most remarkable. Numerous examples of such reaction pathways in carbocyclic rings of eight to ten members can be found, most notably in the work of Cope[4] and Prelog.[5] In medium-sized rings containing nitrogen,[6] sulfur,[7] and phosphorus[8] atoms, the demonstration of transannular interaction of the heteroatom (properly substituted in some cases, e.g., sulfoxide) with the carbon atom of a ketone group placed diametrically across the ring[9] has been thoroughly elucidated by Leonard and his co-workers. We have observed an additional type of transannular reaction in a heterocyclic system and the present paper reports the results of our investigation.

Results

In a previous communication,[10] the Hofmann degradation of 9-methyl-3,9-diazabicyclo[4.2.1]nonan-4-one methiodide (Ia) was shown to give rise exclusively to the α,β-unsaturated amide II. Treatment of an ethereal solution of II with ethanolic perchloric acid has now afforded in quantitative yield a perchlorate

Ia, X = I
b, X = ClO₄
c, X = Cl
d, X = Br

salt. The n.m.r. spectrum of this material was superimposable on that of methiodide Ia and was therefore confirmatory for the bridged perchlorate structure Ib. An authentic sample of Ib prepared directly from Ia showed the two samples to be identical.

Careful re-examination of the perchlorate salt formation revealed that the product of kinetic control was actually the salt III (n.m.r. similar to II),[11,12] which

(1) Unsaturated Heterocyclic Systems. XIII. For paper XII in this series, see L. A. Paquette, J. Org. Chem., 30, 228 (1965).

(2) We gratefully acknowledge the partial support of this research by the National Science Foundation.

(3) Taken in part from the M.S. thesis submitted by L. D. W., 1964.

(4) A. C. Cope and D. M. Gale, J. Am. Chem. Soc., 85, 3747 (1963), and earlier papers in this series.

(5) V. Prelog and V. Boarland, Helv. Chim. Acta, 38, 1776 (1955), and other papers in this series; see also V. Prelog, Record Chem. Progr. (Kresge-Hooker Sci. Lib.), 18, 247 (1957).

(6) N. J. Leonard and M. Oki, J. Am. Chem. Soc., 77, 6245 (1955), and earlier papers in this series; see also N. J. Leonard, Record Chem. Progr. (Kresge-Hooker Sci. Lib.), 17, 243 (1956).
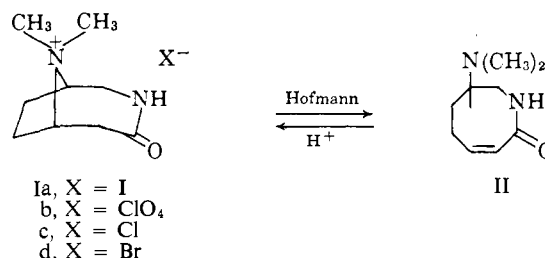
(7) N. J. Leonard and W. L. Rippie, J. Org. Chem., 28, 1957 (1963), and other pertinent references cited therein.

(8) N. J. Leonard, S. E. Cremer, and A. L. Ternay, Jr., Abstracts, 146th National Meeting of the American Chemical Society, Denver, Colo., Jan. 20-22, 1964, p. 21C.

(9) Transannular reactions in heterocyclic systems were first recognized more than 50 years ago; for example, F. L. Pyman [J. Chem.

Soc., 817 (1913)] observed and studied the conversion of the des-base of l-canadine (i) to the quaternary of dl-canadine (ii).

i   ii
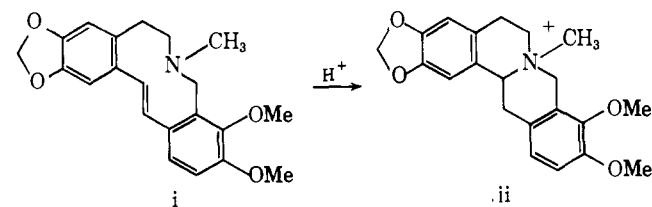
(10) L. A. Paquette and L. D. Wise, J. Org. Chem., 30, 228 (1965).

(11) This material melted at ca. 140° when rapidly heated. With slow heating, the solid softened at 140-150°, resolidified, and melted with decomposition at 327° (pure Ib melts at 334° dec.). The bridging reaction therefore can proceed under purely thermal conditions.

(12) Although III was the major component, the various samples prepared in this manner were always contaminated with varying minor quantities of the bridged salt Ib.