

formed by the plant from atmospheric carbon dioxide. This carbohydrate has now been identified as D-glucose. The monosaccharide is then cyclized to shikimic acid. This cyclohexene derivative is then aromatized, probably *via* the prephenic acid pathway, to *p*-hydroxyphenylpyruvic acid. This phenylpropane derivative then serves as a common precursor for the primary lignin building stones (III, IV, V) by a series of successive oxidation and methylation reactions.²⁸ For

example, in softwoods, two building stones (III and IV) may form lignin by repeated condensations. However, for the formation of hardwood lignins, a syringyl-type building stone (V) is also required before the final polymerization into the higher methoxyl-containing lignins characteristic of hardwood species.

(28) F. F. Nord and G. De Stevens, in "Handbuch d. Pflanzenphysiol.," Vol. X, J. Springer, Heidelberg, 1958, p. 389.

NEW YORK 58, N. Y.

[CONTRIBUTION FROM THE SCHOOL OF CHEMISTRY OF THE UNIVERSITY OF MINNESOTA]

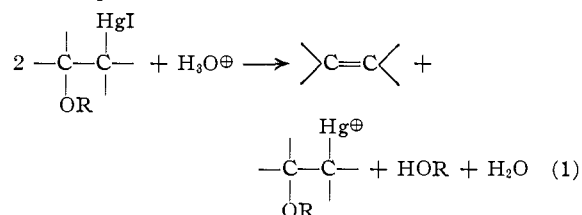
The Nature of the Rate-determining Step in Deoxymercuration¹

BY MAURICE M. KREEVOY AND FRANCES R. KOWITT

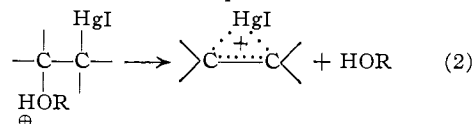
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For deoxymercuration of α -2-methoxycyclohexylmercuric iodide by non-halogen acid ΔH^\ddagger is 17.75 ± 0.19 kcal. mole⁻¹ and ΔS^\ddagger is 4.6 ± 0.6 cal. mole⁻¹ deg.⁻¹. For the same reaction of the β -isomer ΔH^\ddagger is 26.2 ± 0.7 kcal. mole⁻¹ and ΔS^\ddagger is 4.5 ± 2.0 cal. mole⁻¹ deg.⁻¹. In both cases, strong evidence is presented that a fast, prototropic equilibrium precedes the rate-determining step. From this it is concluded that the rate-determining step in deoxymercuration is the conversion of the protonated substrate to the mercuric olefin complex, and that the α -isomer has the *trans* configuration. Other pertinent findings are discussed in terms of this mechanism.

In previous work² it has been shown that the first step in reaction 1 is



the reversible protonation of the substrate oxygen, and that the rate-determining step is some sort of reaction of the protonated substrate not involving the formation of covalent bonds to the solvent. The present paper confirms these conclusions and reports that the enthalpy of activation for reaction 1 with α -2-methoxycyclohexylmercuric iodide (I) is 8.4 kcal. mole⁻¹ lower than that for the β -isomer (II). Since the entropies of activation are essentially the same, the reaction of I is 10^6 – 10^7 times faster than that of II, depending on the temperature of comparison. From these facts it is concluded that the rate-determining step in reaction 1 is the formation of the olefin-mercuric iodide complex, as shown in equation 2, and that compound I must be the *trans* isomer. Other facts about oxymercuration and deoxymercuration^{3,4} are shown to be consistent with this interpretation.



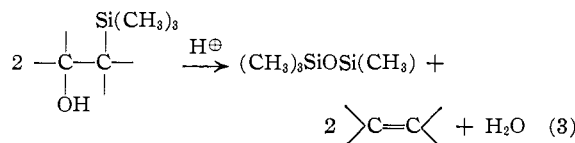
It is suggested that reaction 3, and perhaps other reactions of organometallic compounds, utilize the same sort of rate-determining step.

(1) Presented, in part, before the division of Organic Chemistry, 135th Meeting of the American Chemical Society, Boston, Mass., April, 1959.

(2) M. M. Kreevoy, *THIS JOURNAL*, **81**, 1099 (1959).

(3) G. F. Wright, *Ann. N. Y. Acad. Sci.*, **65**, 436 (1957).

(4) J. Chatt, *Chem. Revs.*, **48**, 7 (1951).



The nature of the transition state for reaction 2 and of the olefin-mercuric iodide complex are discussed.

Results

Products.—In both cases the ultraviolet spectrum of the product was essentially identical with that expected if each mole of substrate produced half a mole of HgI₂. When 0.5 g. of II was treated with excess 12 *M* HClO₄ and the solution then neutralized, methanol was obtained, identified by its infrared spectrum. Exactly the same result was obtained with I. Since I exhibits a reaction rate not too different from that of 2-methoxy-1-iodomercuripropane (III), it presumably produces analogous products. On the basis of these facts, the stoichiometry shown in equation 2 was assumed for both I and II.

The Rate Law.—Good first-order kinetics were observed in all reactions. No catalysis by products (reported for III²) could be observed with I and II. As before,² rates were measured spectrophotometrically at substrate concentrations around 10^{-4} *M*. Pseudo first-order rate constants, k_1 , were evaluated as previously described.²

Dependence of Rate on Acidity, I.—At 25° and 3.64×10^{-4} *M* aqueous perchloric acid, k_1 had a value of $2.11 \pm 0.10 \times 10^{-3}$ sec.⁻¹ for I.⁵ This gives k_2 ($k_2 = k_1/\text{H}^\oplus$) a value of 5.8 ± 0.3 l. mole⁻¹ sec.⁻¹. The rates were too fast to permit the constancy of k_2 to be verified by measurements at higher perchloric acid concentrations.

(5) (a) In this paper, whenever a value is reported with a measure of its uncertainty in this fashion, the value is the mean of two or more determinations and the uncertainty is the average deviation from the mean. (b) The aqueous solutions referred to in this paper contained up to 2% of methanol.

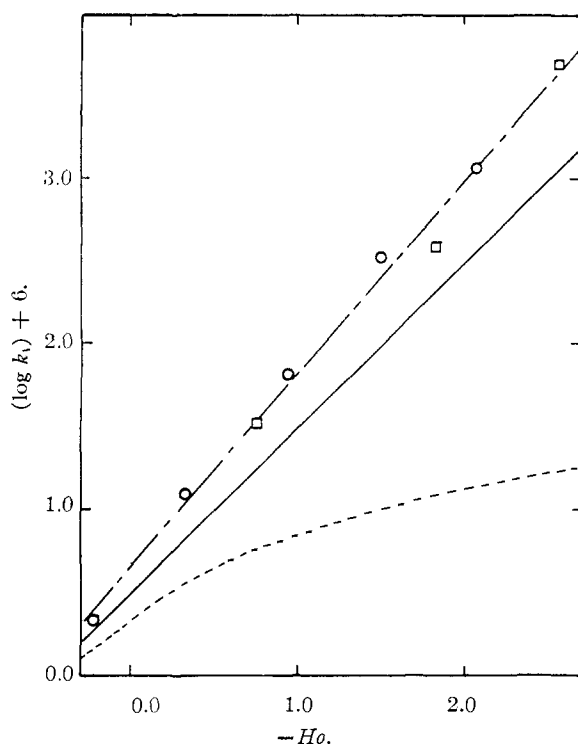


Fig. 1.—A plot of $\log k_1$ for II vs. $-H_0$ in perchloric acid, O, and sulfuric acid, \square : — is the line of unit slope; - - - is the best line through the points and has a slope of 1.17; is the non-linear curve that would have been obtained if k_1 were a linear function of the hydronium ion concentration.

Rate constants for I were determined in two aqueous acetic acid-acetate buffers at 25°. With 0.105 M acetic acid and 0.0243 M sodium acetate, k_1 was $6.06 \pm 0.10 \times 10^{-4} \text{ sec.}^{-1}$. With 0.525 M acetic acid and 0.122 M sodium acetate, k_1 was $7.65 \pm 0.27 \times 10^{-4} \text{ sec.}^{-1}$. Hydronium ion concentrations were evaluated as before² using the ionization constants⁶ and Debye-Hückel parameters^{7,8} of Harned and co-workers. Both buffers gave $6.11 \text{ mole}^{-1}\text{sec.}^{-1}$ for k_2 .

These values verify the constancy of k_2 and preclude "catalysis"⁹ by molecular acetic acid.

Measurements of k_2 at 25° were also made with perchloric acid in a solvent containing 96% methanol and 4% water by volume. For acid concentrations ranging between 4.4×10^{-4} and 2.2×10^{-3} , k_2 had a value of $1.68 \pm 0.10 \text{ l. mole}^{-1} \text{ sec.}^{-1}$ and showed no systematic variation with acid concentration.

Dependence of Rate on Acidity, II.—At 60°, k_1 was determined for II in water at a series of perchloric acid concentrations. Table I gives these values along with the corresponding k_2 values and the acid concentrations. It is clear that k_2 is constant at the lower acid concentrations and the

value $4.16 \pm 0.21 \times 10^{-4} \text{ l. mole}^{-1} \text{ sec.}^{-1}$ was obtained by averaging the values corresponding to the three lowest acid concentrations. As the acid concentration leaves the dilute solution range, k_2 begins to rise.

TABLE I
DEPENDENCE OF RATE ON PERCHLORIC ACID CONCENTRATION AT 60°

(HClO ₄), mole/l.	$10^6 k_1$, sec. ⁻¹	$10^4 k_2$, l. mole ⁻¹ sec. ⁻¹
0.0257	1.12	4.35
.0770	3.30	4.29
.1284	4.94	3.85
.257	12.2	4.75
.474	29.8	6.29

At 25°, k_1 was determined for II at a series of perchloric and sulfuric acid concentrations ranging from about 0.5 M to nearly 6 M. In this range of acid concentrations, $\log k_1$ is an approximately linear function of $-H_0$, the Hammett acidity function,¹⁰⁻¹² with a slope of 1.17. Figure 1 shows a plot of $\log k_1$ vs. $-H_0$. The theoretical unit slope^{10,12} is also shown, along with the hypothetical curve that would have been produced if k_1 were a linear function of the hydronium ion concentration.

Solvent Isotope Effect.—Four determinations of k_2 for I in an aqueous solvent containing 98.3 atom per cent. deuterium and $3.64 \times 10^{-4} \text{ M}$ perchloric acid gave a value of $19.4 \pm 0.3 \text{ l. mole}^{-1} \text{ sec.}^{-1}$. Combining this with the value of k_2 previously obtained in H₂O, a value of 3.2 is obtained for $k_2^{\text{D}}/k_2^{\text{H}}$, with a probable uncertainty of 0.1.¹³ This can be compared with the ratio 2.8, previously obtained for III.²

Four determinations of k_1 for II in an aqueous solvent containing 90.1 atom per cent. deuterium and 1.870 M sulfuric acid gave a value of $8.38 \pm 0.28 \times 10^{-5} \text{ sec.}^{-1}$. For k_1 , similarly determined in 1.870 M sulfuric acid in H₂O, a value of $3.21 \pm 0.18 \times 10^{-5} \text{ sec.}^{-1}$ was obtained. The ratio $k_1^{90.1}/k_1^{\text{H}}$ therefore has a value of 2.61 with a probable uncertainty of 0.11.¹³ Considering the shape of the plot of rate vs. isotopic composition of the solvent for III,² $k_1^{\text{D}}/k_1^{\text{H}}$ for II is very probably between 3.0 and 3.4. Since it seems quite unlikely that the solvent isotope effect is strongly dependent on the acid concentration, $k_2^{\text{D}}/k_2^{\text{H}}$ for II is also presumably around 3.2.

Thermodynamic Quantities of Activation.—For both I and II, rates were studied at six temperatures over a 60° range. For I this range extended from 0 to 60°, and rates were measured in aqueous acetic acid-acetate buffers. At each temperature the buffer ratio was adjusted to give a convenient rate. Hydronium ion concentrations were obtained using ionization constants and parameters suitable to the particular temperatures.⁶⁻⁸ A plot of $\log (k_2/T)$ vs. $1/T$ is linear within the experimental accuracy. The Eyring enthalpy of activation, ΔH^\ddagger , was $17.75 \pm 0.19 \text{ kcal. mole}^{-1}$ calculated by the method of least squares from eq.

(10) L. P. Hammett, "Physical Organic Chemistry," McGraw-Hill Book Co., Inc., New York, N. Y., 1940, Chap. IX.

(11) M. A. Paul and F. A. Long, *Chem. Revs.*, **57**, 1 (1957).

(12) F. A. Long and M. A. Paul, *ibid.*, **57**, 935 (1957).

(13) R. Livingston, "Physico Chemical Experiments," The Macmillan Co., New York, N. Y., 1948, pp. 29-30.

(6) H. S. Harned and R. W. Ehlers, *THIS JOURNAL*, **55**, 652 (1932).

(7) H. S. Harned and B. B. Owen, "The Physical Chemistry of Electrolytic Solutions," Reinhold Publ. Corp., New York, N. Y., 1958, pp. 34-37.

(8) H. S. Harned, *J. Phys. Chem.*, **43**, 275 (1938).

(9) This reaction is not truly acid-catalyzed because acid is consumed in the course of the reaction, but the vocabulary of acid catalysis has its usual significance otherwise.

4. The average difference between measured and calculated rates (using equation 4 and the $R \ln(k_2/T) = \Delta H^\ddagger/T + \{\Delta H^\ddagger/T_0 - R \ln(T_0/k_0)\}$ (4) least-squares parameters) was 5%, which is about the reproducibility of the data. The entropy of activation for I, ΔS^\ddagger , was 4.6 ± 0.6 cal. mole⁻¹ deg.⁻¹. It was determined from equations 5 and 6, using the measured k_2 at 25°. In equation 5, k is the Boltzmann constant and h is Planck's constant.

$$\Delta F^\ddagger = RT \ln(kT/hk_2) \quad (5)$$

$$\Delta S^\ddagger = \frac{\Delta H^\ddagger - \Delta F^\ddagger}{T} \quad (6)$$

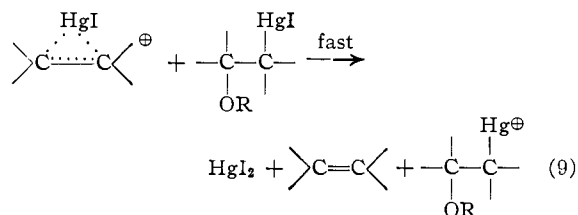
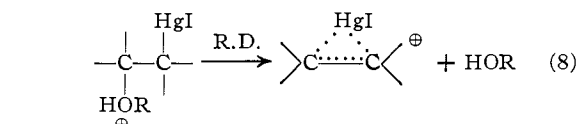
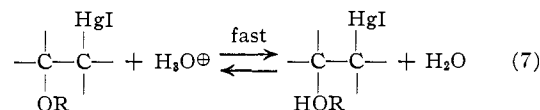
For II, the temperature range extended from 15 to 75°. Rates were measured at a constant acid concentration—0.474 *M* perchloric acid. Table I shows that at such an acid concentration k_2 has a value somewhat above its value in infinitely dilute acid, k_2^∞ . It is very unlikely, however, that the ratio $k_2^{0.474}/k_2^\infty$ is a sharp function of temperature. Because of the slow rates involved, it was not possible to go to lower acid concentrations at the lower temperatures. A plot of $\log(k_2/T)$ vs. $1/T$ was linear for II, also. For II, ΔH^\ddagger was 26.2 ± 0.7 kcal. mole⁻¹, determined from equation 4 by the method of least squares. The average difference between measured and calculated rates was 11%. This is a little larger than that observed for I, probably because the acid concentration could not be adjusted to give convenient rates at all temperatures. Equations 5 and 6 give a value of 4.5 ± 2.0 cal. mole⁻¹ deg.⁻¹ to ΔS^\ddagger for II, using k_2^∞ determined at 60° to obtain ΔF^\ddagger . It will be noted that ΔS^\ddagger for I and II are identical within their uncertainties.

Discussion

In addition to accommodating the facts presented above, a mechanism of deoxymercuration with pretensions to completeness also must explain the great ease with which deoxymercuration takes place. For example, 1-iodomercuri-2-propanol (IV) is deoxymercurated by acid with a second-order rate constant of 2.11 l. mole⁻¹ sec.⁻¹.² This is about 10¹¹ faster than the acid-catalyzed dehydration of 2-propanol.¹⁴ We believe that mechanism A, shown in equations 7–9, is such a mechanism. (Equation 9 may actually require a number of steps. Since it follows the rate-determining step, information pertaining to it is not easily available.)

It has been shown already that a rapid, prototropic equilibrium precedes the rate-determining step in the deoxymercuration of III and IV.² The rate-determining step then proceeds without the formation of covalent bonds to the solvent.² The structure of I is very similar to that of III, and it has a rate of deoxymercuration only one power of ten faster, so it is not surprising to find that deoxymercuration of I also involves a prototropic equilibrium followed by a rate-determining step that does not involve the formation of covalent bonds to the solvent. The absence of catalysis by molecular acetic acid and the solvent isotope effect of about 3 are both comparable to the results

(14) R. W. Taft, Jr., private communication.



obtained with III and interpreted in the same way.² The entropy of activation was not obtained for III. For II it has a small, positive value. For acid-catalyzed reactions in aqueous solution a small, positive ΔS^\ddagger is additional evidence for a fast, prototropic equilibrium followed by a rate-determining step which does not involve the formation of covalent bonds to the solvent.¹⁵

Deoxymercuration of II is over 10⁻⁶ slower than that of III at 25° and over 10⁻⁶ slower than that of I. The solvent isotope effect, k_2^D/k_2^H , is still about 3, however, and the observed, linear dependence of $\log k_1$ on $-H_0$ is thought to suggest that the transition state composition differs from that of the substrate only by the addition of a proton.^{10,12} Entropy is a sensitive function of molecular composition and structure. Since the starting states for deoxymercuration of I and II have similar structures, they probably have similar entropies. The fact that the entropies of activation are identical within a rather small experimental uncertainty, therefore, suggests that the transition state structures are very similar. Finally, deoxymercuration of II is still substantially faster than cleavage of simple aliphatic ethers.¹⁶ All these things suggest that whatever mechanism permits the very facile deoxymercuration of I is still operative for II, although additional energy is required.

Mechanism A provides an effective rationale for all of these facts. Equation 7 provides a fast, prototropic equilibrium which can be used by both I and II. It is undoubtedly analogous to the first step in the acid cleavage of ethers.

The product of the rate-determining step is the mercury-olefin complex first suggested by Lucas, Hepner and Winstein¹⁷ as an intermediate in the oxymercuration reaction. Lucas, Hepner and Winstein demonstrated that mercuric salts do form moderately stable complexes with olefins, and Dewar has discussed their electronic structure.¹⁸ In these complexes, a mercury 6sp-hybrid orbital (the exact state of hybridization probably depends

(15) F. A. Long, J. G. Pritchard and F. E. Stafford, *THIS JOURNAL*, **79**, 2362 (1957).

(16) C. K. Ingold, "Structure and Mechanism in Organic Chemistry," Cornell University Press, Ithaca, N. Y., 1953, p. 334.

(17) H. J. Lucas, F. R. Hepner and S. Winstein, *THIS JOURNAL*, **61**, 3102 (1939).

(18) M. J. S. Dewar, *Bull. soc. chim. France*, **18**, C79 (1951).

on what else is bound to the mercury atom) overlaps both carbon 2p-orbitals equally so that a system is obtained which approximates one of the Hückel aromatic systems¹⁹—a three-orbital, two-electron system in which each of the orbitals has substantial overlap with the other two.

The mercury-olefin complex also derives some additional stabilization by donation of electrons from the filled, 5d-orbitals of the mercury into the empty, anti-bonding, molecular π -orbital of the olefin,¹⁸ but the exact importance of this is hard to assess.

In the rate-determining step for I it is postulated that the protonated methoxy group and the carbon to which it is bound separate, breaking the carbon-oxygen bond and liberating a molecule of methanol. Simultaneously, the hybridization of the carbon bearing the protonated methoxy group changes from sp^3 to sp^2 so that the incipient "empty" orbital is a p-orbital. This orbital is never left completely empty, however, because the carbon-carbon-mercury angle simultaneously contracts from $\sim 109^\circ$ to less than 90° . The hybridization of the carbon bearing the mercury atom changes from sp^3 to sp^2 , the orbital bearing the mercury changing to a p-orbital. In order for the new bonds to form as the old bonds are broken, the mercury atom, the oxygen atom and the two carbon atoms must be coplanar. The postulated atomic motions are shown in Fig. 2. If the mercury atom is

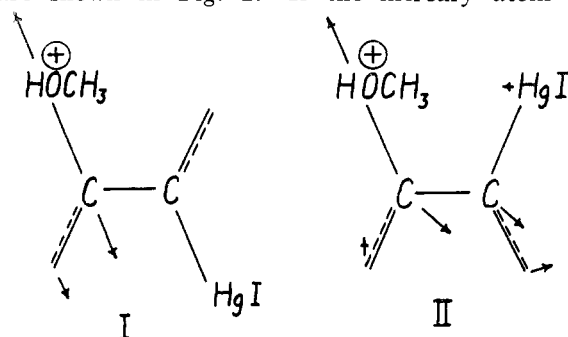


Fig. 2.—A rough pictorial representation of the reaction coordinates for I and II. The arrows are vectors representing the direction and, crudely, the relative size of the atomic motions.

trans to the oxygen atom, the transitions postulated can take place in a completely synchronized fashion without any great increase in the repulsions between non-bonded atoms. The required diaxial conformation probably can be achieved by the *trans* isomer with little or no distortion of carbocyclic bond angles and only a slight expenditure of energy.²⁰ On the other hand, the *cis* isomer could only approximate the diaxial conformation at the expense of a gross distortion of the carbocyclic

(19) E. Hückel, *Z. Elektrochem.*, **61**, 866 (1957); this paper also contains references to Hückel's earlier work.

(20) The most stable conformation of I is probably that with both substituents in equatorial positions, as with *trans*-1,2-dimethylcyclohexane, but the energy difference between the diequatorial conformer and the diaxial conformer of *trans*-1,2-dimethylcyclohexane is thought to be less than 3 kcal./mole. The energy required to obtain the diaxial conformer of the oxymercurial is probably of the same order of magnitude.

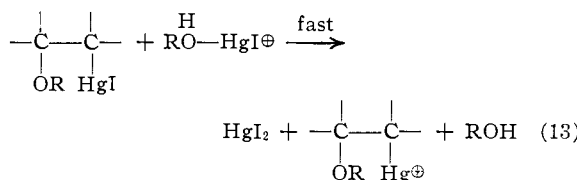
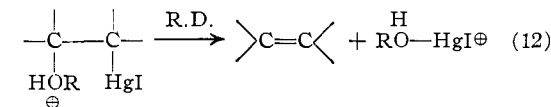
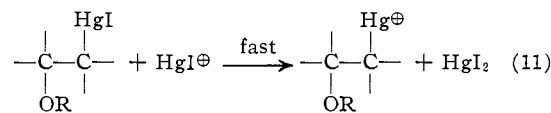
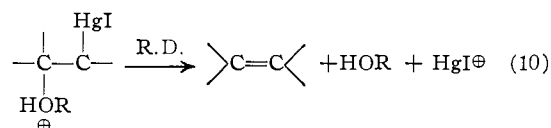
(21) W. G. Dauben and K. S. Pitzer, "Steric Effects in Organic Chemistry," M. S. Newman, ed., John Wiley and Sons, Inc., New York, N. Y., 1956, p. 19.

bonds. This would require a great deal of energy and so it probably does not take place. Instead, in the *cis* isomer, a nearly coplanar arrangement for the two carbon atoms, the oxygen atom, and the mercury atom, is obtained with the two substituents on the same side of the carbocyclic ring. With this arrangement, it is still possible to form the three-membered carbon-carbon-mercury ring as the protonated methoxyl group leaves but perfect synchronization is not possible. The carbon-oxygen bond which is being broken must be substantially lengthened before the carbon-carbon-mercury angle can be reduced without increasing the repulsions between the mercury atom (and its associated solvent molecules) and the oxygen atom. The transition state for the *cis* isomer undoubtedly achieves the lowest possible energy with a carbon-carbon-mercury bond angle larger than that in the transition state for the *trans* isomer but small enough to get some stabilization from three-membered ring formation. This would be done at the expense of a certain amount of repulsion between non-bonded atoms. The carbon-oxygen bond in the transition state for the *cis* isomer would be longer than that in the transition state for the *trans* isomer. The lengthened carbon-oxygen bond, the larger carbon-carbon-mercury angle and the repulsions would all contribute to making the energy of the transition state for the *cis* isomer larger than that of the transition state for the *trans* isomer, making ΔH^\ddagger for the *cis* much higher than ΔH^\ddagger for the *trans*. On the other hand, the solvation and the freedom of internal motions would be about the same in the two transition states, giving them similar ΔS^\ddagger values. It is clear from the foregoing that mechanism A will accommodate all of the data on deoxymercuration by non-halogen acids if I is assigned the *trans* configuration and II the *cis*.²²

For a fairly complex reaction it is not possible to prove that a given mechanism is correct. It can only be shown that certain alternative mechanisms cannot be correct. In the present case, however, no substantially different mechanism comes to mind which is not ruled out by the data.

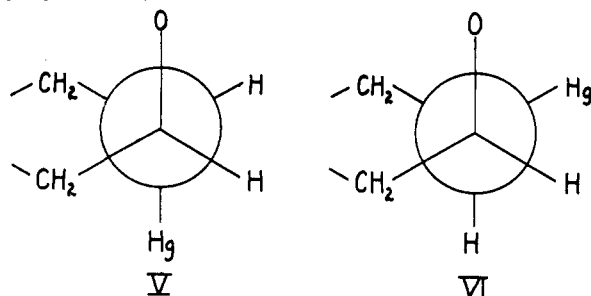
Both mechanisms B (eqs. 10 and 11) and C (eqs. 12 and 13) provide the required prototropic equilibrium. In mechanism B it is postulated that the carbon-oxygen and carbon-mercury bonds are broken simultaneously. In the transition state the oxygen atom and the mercury atom both have partial positive charges, and electrostatic repulsions are responsible for the observed stereospecificity. Again the α -isomer is assigned the *trans* configuration and the β -isomer the *cis*. In mechanism C it is postulated that the carbon-oxygen bond and the carbon-mercury bond break in one step, but that the timing is different enough so that the oxygen atom and the mercury atom do not both have a substantial positive charge at the same time. (Presumably the carbon-oxygen bond breaking would lead.) The alcohol molecule is then in a

(22) This assignment of configurations is consistent with an X-ray crystal study of *cis*- and *trans*-2-methoxycyclohexylmercuric chloride (ref. 24). The crystal structure determination is not completely definitive, however, because of the small scattering power of carbon and oxygen as compared to mercury and chlorine (G. F. Wright, ref. 3).



favorable position to take the place of a solvent molecule in the *cis* isomer, which must be considered alpha.

Mechanism B depends for its stereospecificity on the electrostatic repulsions between the oxygen atom and the mercury atom in the transition state. These repulsions are maximized if each atom is assumed to carry one-half of the unit charge and if they are assumed to act through a hydrocarbon-like medium with a dielectric constant of 2. Both isomers would presumably assume conformations that would maximize the oxygen-mercury distance. These conformations are illustrated in Newman projection by V for the *trans* and VI for the *cis*.



The energy difference between V and VI was calculated under the assumptions given above, using tetrahedral bond angles and bond lengths as follows: 1.54 Å. for the carbon-carbon bond,²³ 1.42 Å. for the carbon-oxygen bond²³ and 2.34 Å. for the carbon-mercury bond.²⁴ The calculated energy difference is only 3 kcal./mole, so mechanism B cannot possibly account for the degree of stereospecificity found.

Mechanism C is essentially that proposed by Berg, Lay, Rodgman and Wright²⁵ for deoxymercuration by halogen acids, modified to accommodate a prototropic equilibrium preceding the rate-determining step. It depends for its stereospecificity on the replacement of a water molecule by the methanol molecule which is already a part of the

substrate. It does not seem likely that the methanol molecule is energetically a better solvator than a water molecule, so the chief gain, free-energy wise, from this substitution would be that a water molecule which would be immobilized in the transition state for the *trans* isomer would retain its freedom in the *cis* isomer. But such an effect would appear in the entropy of activation, rather than the enthalpy of activation. In addition, since the total entropy of water in the liquid state at 25° is only 16.75 cal./mole deg.,²⁶ the maximum difference in ΔF^\ddagger between *cis* and *trans* isomers attributable to this source is less than 5 kcal./mole. Mechanism C, therefore, fails to explain both the degree of stereospecificity and the fact that it appears in ΔH^\ddagger .

Although the evidence presented in this paper, strictly speaking, applies only to deoxymercuration induced by non-halogen acids, mechanism A, with minor modifications, is probably applicable to a rather wide variety of reactions, and its inverse explains most of the facts about oxymercuration quite nicely. Since Wright and co-workers have suggested that these facts favor mechanism C,³ their interpretation in terms of mechanism A is shown.

The deoxymercuration of I by hydrogen iodide in a medium containing 96% methanol and 4% water has been reported to have a second-order rate constant of 0.71 l. mole⁻¹ sec.⁻¹.²⁵ This rate constant is smaller than k_2 , determined with perchloric acid in the same solvent, by a factor of 2.4. The origin of this difference is unexplained but k_2 for the hydrogen iodide-induced reaction is invariant under a fourfold change in hydrogen iodide concentration, so it seems likely that iodide ion at very low concentration does not participate in the reaction except by furnishing an iodide ion to HgI^\oplus after the rate-determining step has been passed. If so, mechanism A can be assigned to deoxymercurations by dilute halogen acids except that the halide ion required in equation 9 need not come from a second mole of substrate. Mechanism A accounts for the fact that β -2-methoxycyclohexylmercuric chloride is deoxymercured by HCl much more slowly than the α -isomer.²⁵ Mechanism A is consistent with the finding that α -alkoxycyclohexylmercuric chlorides are deoxymercured more rapidly as the alkyl part of the alkoxy group becomes more electron donating.²⁷ Mechanism A is also consistent with the finding that the rate of deoxymercuration in anhydrous solvents is decreased by the addition of small increments of water.²⁵ The tendency of HCl solutions in anhydrous solvents to protonate neutral bases is markedly decreased by the addition of small increments of water.¹¹ This probably results from the conversion of whatever acidic species is present in anhydrous solution to the more weakly acidic hydronium ion on addition of water.

Mechanism A provides a satisfying rationale for the fact the β -2-methoxy-1-chloromercuri-1,2-diphenylethane (VII)—derived from *trans*-stilbene—

(23) V. Schomaker and D. P. Stevenson, *THIS JOURNAL*, **63**, 37 (1941).

(24) A. G. Brook and G. F. Wright, *Acta Cryst.*, **4**, 50 (1951).

(25) O. W. Berg, W. P. Lay, A. Rodgman and G. F. Wright, *Can. J. Chem.*, **36**, 358 (1958).

(26) I. Kirshenbaum, "Physical Properties and Analysis of Heavy Water," McGraw-Hill Book Co., Inc., New York, N. Y., 1951, p. 32.

(27) A. Rodgman, D. A. Shearer and G. F. Wright, *Can. J. Chem.*, **35**, 1377 (1957).

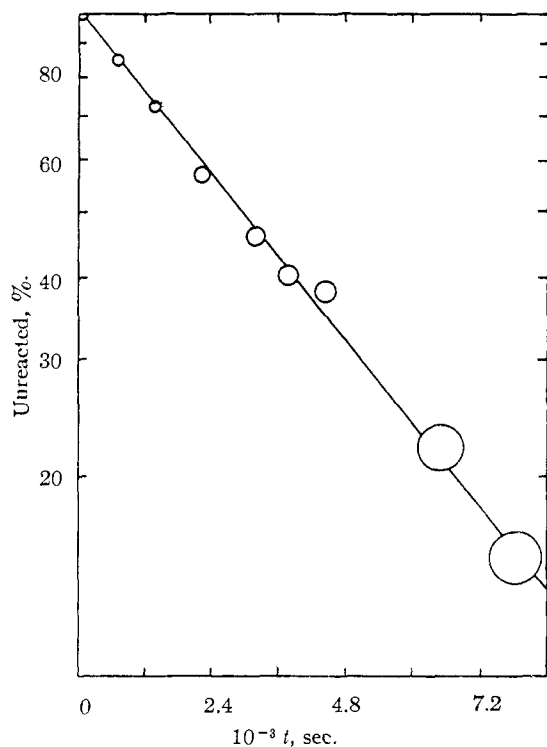


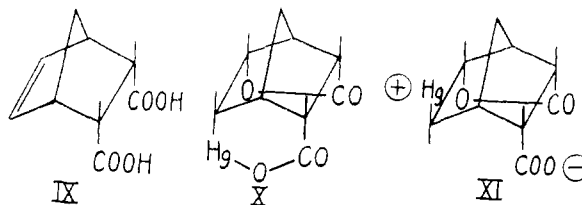
Fig. 3.—A typical semi-log plot of percentage unreacted substrate vs. time for reactions followed by intermittent withdrawal of samples.

is less stable toward deoxymercuration by HCl than the α -isomer VIII.^{3,23} Equilibrium constants for *trans-gauche* isomerizations seem to be determined primarily by electrostatic considerations.^{28,29} The direction of the carbon-oxygen and carbon-mercury dipole moments suggest that the most stable conformer of VII has *gauche* phenyl groups, while the most stable conformer of VIII has *trans* phenyl groups so that the starting state for VII is less stable than the starting state for VIII. Exactly the reverse is true of the conformations required for the protonated substrates to enter reaction 8. As a result, the activation energy for deoxymercuration of VII should be substantially less than that required to deoxymercurate VIII.

Brook and Wright³⁰ have shown that the Lucas, Hepner and Winstein¹⁷ evidence for the mercury-olefin complex as an intermediate in oxymercuration is unconvincing. They have not ruled it out, however, and the present results make it seem very attractive. The inverse of equations 7 and 8, with acetate substituted for iodide, would certainly explain the stereospecificity of the reaction. The tendency of the oxygen to add to the more highly substituted carbon of the double bond^{3,4} is explained if it is assumed that the carbon atom to which the oxygen is being attached has slightly more carbonium ion character than the other. The failure of butadiene to give 1,4-methoxymercuration³¹ is very neatly explained. A cyclic system of

three orbitals containing two electrons will have substantially more resonance energy than a cyclic system of five orbitals containing four electrons.¹⁹

The results obtained by McNeely, Rodgman and Wright on bridged cycloolefin dicarboxylic acids^{3,32} remain somewhat troublesome. The product of the addition of mercuric acetate to *endo*-norbornene-2,3-dicarboxylic acid (IX) in methanol was assigned the structure X. The *endo* configuration of the mercury atom was assigned largely on the basis of its composition and molecular weight.³² Compound X would be the product of *cis* addition rather than the *trans* addition postulated above. Of the several possible explanations, the most attractive seems to be that the product in question actually has the zwitterionic structure XI. This



explanation is supported by the recent finding that the products of the oxymercuration of a number of unsaturated carboxylic acids are zwitterionic.³³

Traylor and Winstein³⁴ have shown that deoxymercuration of I by iodide ion is also much faster than deoxymercuration of II. Since the postulated mercury-olefin complex requires only one of the mercury atom's empty orbitals, it may also be an intermediate in the iodide ion-catalyzed deoxymercuration.

Acid-catalyzed olefin formation from 1-trimethylsilyl-2-propanol is about 10^{-2} slower than deoxymercuration of IV, but still some 10^9 faster than the acid-catalyzed dehydration of 2-propanol.³⁵ An attractive explanation is offered by equations 7 and 8, with the trimethylsilyl group taking the place of the iodomercury group. It will be noted, however, that the silicon atom has no filled d orbitals. If equations 7 and 8 do represent the mechanism of cleavage for the silyl alcohol, the importance of electron donation from a filled d-orbital into the anti-bonding orbital of the olefin in the transition states for deoxymetalation can only be marginal.

House and Ro³⁶ have recently found that deoxyhalogenation by metals is non-stereospecific. Dehalogenation of vicinal dihalides, on the other hand, is specifically *trans*.³⁶ It seems quite likely that both these reactions proceed through the for-

(31) K. H. McNeely and G. F. Wright, *THIS JOURNAL*, **77**, 2553 (1955).

(32) K. H. McNeely, A. Rodgman and G. F. Wright, *J. Org. Chem.*, **20**, 714 (1955).

(33) C. W. Whitehead, *THIS JOURNAL*, **80**, 2178 (1958). NOTE ADDED IN PROOF.—The present authors do not consider that these conclusions are disturbed by the recently reported findings of D. D. K. Chin and G. F. Wright (*Can. J. Chem.*, **37**, 1425 (1959)).

(34) T. C. Traylor and S. Winstein, paper presented before the Division of Organic Chemistry, 135th Meeting of the American Chemical Society, Boston, Mass., April, 1959; Abstracts, p. 82-O.

(35) R. A. Miller, Ph.D. Thesis, Pennsylvania State University, University Park, Pa., 1957, p. 56.

(36) H. O. House and R. S. Ro, *THIS JOURNAL*, **80**, 182 (1958), and references cited therein.

(28) S. Mizushima, "Structure of Molecules and Internal Rotation," Academic Press, Inc., New York, N. Y., 1954, p. 64.

(29) M. M. Kreevoy and E. A. Mason, *THIS JOURNAL*, **79**, 4851 (1957).

(30) A. G. Brook and G. F. Wright, *Can. J. Chem.*, **29**, 308 (1951).

mation of an organometallic halide.³⁷⁻⁴⁰ The different stereochemical results are understandable if it is recalled that the halide ion is a much better leaving group than the alkoxide ion in the absence of acid. With the halometallic halide the analogs of reaction 8 proceed fast enough to exclude stereochemical rearrangement at the carbon-metal bond. With the alkoxymetallic halides, however, the elimination is slower, giving the carbon-metal bond time to lose its stereochemical identity. Most organometallic compounds probably lose their stereochemical identity with great ease, although they are capable of retaining it for very short periods of time or at very low temperatures.⁴¹

Experimental⁴²

Materials.—Standard acids, buffers and solvents were prepared as before.^{2,43} Compound I was prepared by the method of Romeyn and Wright,⁴⁴ and had m.p. 81.5–82.0°. Compound II was prepared in 50% yield from the corresponding chloromercurial. β -2-Methoxycyclohexylmercuric chloride (1.8 g., 0.0051 mole) was dissolved in 50 ml. of methanol and treated with 50 ml. of 0.10 *M* NaI in water. The resulting precipitate was filtered off, redissolved in 50 ml. of methanol, and the procedure repeated. The product was recrystallized from a 50% aqueous methanol solution, to obtain 1.1 g. of II, m.p. 95–96°. The melting point of II was unchanged on resolidification and remelting. β -2-Methoxycyclohexylmercuric chloride was prepared from the α -isomer in 12% yield by the "benzoyl peroxide" method

(37) D. R. James, R. W. Rees and C. W. Shoppee, *J. Chem. Soc.*, 1370 (1955).

(38) L. C. Swallen and C. E. Boord, *THIS JOURNAL*, **52**, 651 (1930).

(39) R. Paul, *Bull. soc. chim. France*, [4] **53**, 421 (1933).

(40) M. Tallman, *THIS JOURNAL*, **56**, 129 (1934).

(41) R. L. Letsinger, *ibid.*, **72**, 4842 (1950).

(42) All melting points are corrected.

(43) Maurice M. Kreevoy, *THIS JOURNAL*, **81**, 1099 (1958).

(44) J. Romeyn and G. F. Wright, *ibid.*, **69**, 697 (1947).

of Romeyn and Wright.⁴⁴ It had a m.p. of 111–112° and a mixed m.p. with the α -isomer of 90–105°. The infrared spectra of I, the α -chloromercurial, and the β -chloromercurial in carbon tetrachloride are very similar, and are what would be expected of aliphatic ethers.

Kinetic Procedures.—Kinetic procedures for reactions carried out at 25° already have been described.² At other temperatures the reaction mixture was held at constant temperature in a thermostat of conventional design² and the optical density of periodically withdrawn samples was measured. The sort of data obtained by the second method is illustrated in Fig. 3.

Products.—The ultraviolet spectra of reaction mixtures from both I and II were determined on a Beckman DU spectrophotometer after the reactions were completed (after more than 10 half-lives had passed). The spectra were essentially identical with those expected if each mole of substrate yielded one-half mole of mercuric iodide.²

To identify other products, 0.50 g. of substrate was treated with 50 ml. of 11.86 *M* perchloric acid. After five minutes of stirring, 50 ml. of water was added with constant cooling and stirring. A solution of 40 g. of KOH in 100 ml. of water then was added, again accompanied by stirring and ice cooling to prevent overheating. A large precipitate of potassium perchlorate appeared during the addition of base and was filtered off; 50 ml. of water then was distilled out of the filtrate. This water was thoroughly extracted with 1 ml. of carbon tetrachloride. The carbon tetrachloride layer was separated, dried over anhydrous calcium sulfate, and its infrared spectrum determined by means of a Perkin-Elmer Infracord. For both I and II the resulting spectrum was essentially identical with that of a solution of methanol in carbon tetrachloride. The failure to observe cyclohexene may be due to hydration and/or polymerization, or the fact that it has a less intense spectrum than methanol.

Acknowledgment.—The authors are pleased to acknowledge the financial support of the National Science Foundation through grant No. N.S.F.-G5434 during part of the period when this work was in progress.

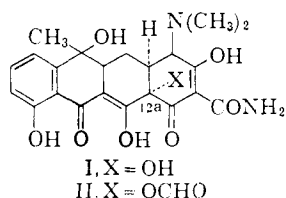
MINNEAPOLIS 14, MINN.

COMMUNICATIONS TO THE EDITOR

SOME TRANSFORMATIONS AT THE 12a-POSITION OF THE TETRACYCLINES

Sir:

Recent publications¹⁻³ concerning transformations at the 12a-position in the tetracycline series prompt us to report certain of our own results in this area.



Treatment of tetracycline (I) in pyridine with acetoformic acid reagent⁴ in the cold yields O^{12a}-

(1) H. Muxfeldt and A. Kreutzer, *Naturwissenschaften*, **46**, 204 (1959).

(2) C. E. Holmlund, W. W. Andres and A. J. Shay, *THIS JOURNAL*, **81**, 4748 and 4750 (1959).

(3) Belgian Patent 572,382. We have been advised that a paper by Drs. A. Green and J. H. Booth describing substance IV is in press in *THIS JOURNAL*.

(4) A mixture of acetic-formic anhydride and acetic acid, *cf.* V. C.

formyltetracycline (II) [m.p., 163° (dec.); ultraviolet spectrum⁵ (solution preacidified to avoid rapid solvolysis), λ_{\max} 267 and 360 μ , $\log \epsilon$ 4.29 and 4.07; infrared peak (KBr pellet), 5.84 μ ; *Anal.* Found for C₂₃H₂₄N₂O₉: C, 58.12; H, 5.30; N, 6.10; CHO, 4.6]. O^{12a}-Formyltetracycline shows essentially the same antimicrobial activity *in vitro* and *in vivo* as tetracycline.⁶ By following the rate of change of ultraviolet absorption of II in aqueous buffers, approximate half-lives for hydrolysis to tetracycline at pH 2.0, 4.0, 6.0 and 7.5 were indicated to be 6 hours, 4 hours, 30 minutes and 5 minutes, respectively.

Refluxing O^{12a}-formyltetracycline in toluene yields formic acid (presumably *via cis*-elimination) and 4a,12a-anhydrotetracycline (III). [Ultraviolet spectrum⁵ (after 30 minutes to achieve tautomeric equilibrium): λ_{\max} 247, 329, 405 and 426 μ , $\log \epsilon$ 4.29, 3.82, 4.33, 4.35. *Anal.* Found for

Mehlenbacher in "Organic Analyses," Vol. I, Interscience Publishers, Inc., New York, N. Y., 1953, p. 37.

(5) Solvent was methanol, 0.01 *N* in hydrochloric acid.

(6) We are indebted to Drs. A. R. English and T. J. McBride for antimicrobial investigations.