

atom of deuterium, and the other from 70 to 98.3% of one atom of deuterium. The standard deuterated material contained 0.983 atom of deuterium per molecule.³ These known mixtures and the unknown mixtures were run consecutively on a Perkin-Elmer Model 421 dual grating spectrophotometer (sodium chloride optics). The samples were run neat in an 0.025-mm. sodium chloride cell at a scan rate of 7 cm.⁻¹ per sec., and were scanned through the region from 900 to 1025 cm.⁻¹. The difference in

absorbance was determined for each standard sample, and this value was plotted against the amount of deuterium in the samples. For the 0 to 30% deuterium samples, the difference in absorbance of the 980 cm.⁻¹ band was used; for the 70-98.3% deuterium samples, the 958 cm.⁻¹ band was employed. For both the lower and upper ranges, a straight line plot was obtained, the average deviation being $\pm 0.5\%$. The amounts of deuterium in the unknowns were determined with an error estimated at $\pm 1\%$.

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY OF THE UNIVERSITY OF DELAWARE, NEWARK, DELAWARE]

Observations Regarding the Mechanism and Steric Course of the α -Bromination of Carboxylic Acid Derivatives. An Electrophilic Substitution Reaction in Nonpolar Media

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Evidence is presented which supports a mechanism involving rate-determining electrophilic displacement by halogen on a cationic complex (II) which, in turn, is formed *via* acid-catalyzed bridging of the α -proton to the carbonyl center in a nonrate-determining step. In agreement with this proposal the following lines of argument have been cited. (1) A linear Hammett plot is obtained with *negative slope* ($\rho = -1.39$), in a hydratropic acid reaction series where the application of σ^+ -values afford only a nonlinear correlation. (2) The polar substituent effect shows negligible implication of kinetic energy terms ($\Delta\Delta S^* \cong 0$). (3) A lack of stereoelectronic effects and any important degree of overlap control or resonance interaction with aromatic substituents is clearly indicated. (4) A direct parallel is demonstrated between 4-substituent effects on the rates of bromination of cyclohexanecarboxylic acid and solvolysis of cyclohexyl tosylates. (5) The magnitude of k_H/k_D is considerably less than half as great as anticipated for a rate-determining enolization mechanism. (6) There is a clear suggestion of the dependence of the rate on bromine concentration. The stereochemistry of both the brominated product and the unreacted acid chloride reagent, after extended heating in SOCl_2 in the presence of HCl, provides strong indication that long range field effects³¹ (charge-dipole and dipole-dipole interactions) exert predominant control over the steric course of electrophilic displacement reactions of such protonated complex ion intermediates (II). Furthermore, the existence of such field effects on equilibrium is demonstrated to parallel the earlier observation³¹ of an analogous influence on the kinetic course of various reactions.

The halogenation of carboxylic acids occurs with random orientation unless one resorts to the so-called Hell-Volhard-Zelinsky procedure,² or some modification thereof. Lapworth³ was the first to recognize that the exclusive α -halogenation achieved by the H.V.Z. method was attributable to the intermediate formation of an enol, formally analogous to that which has been invoked in the acid-catalyzed halogenation of ketones and related carbonyl compounds. General confidence in this interpretation is indicated by its widespread appearance in standard texts and references.⁴

More recent experimental studies of the stereochemistry of bromination⁵ and debromination^{5,6} reactions in carboxylic acid-base systems have not found it necessary to assume that the product-forming step (in either case) involves the rapid attack of an electrophilic reagent (a proton or positive halogen source) on the enolic intermediate. While the kinetic approach has been applied very extensively and is regarded as the classical method for establishing the rate-determining formation of enol in both the base-^{7,8}

and acid-catalyzed^{9,10} halogenation of ketones,^{7,8} such criteria have not been used to evaluate the indications that enolization is the slow step in the H.V.Z. mechanism as it appears to be in the reverse debromination reactions⁶ (with Zn or HI). Against this background, then, we have sought to attain more detailed knowledge of the nature of the α -bromination reaction of carboxylic acids in thionyl chloride media by gathering kinetic information that could be compared with available results on bromination in ketones.

Results

The reaction medium chosen was not unfamiliar to previous investigators.^{6,11} The determination of the relative rates of bromination of a variety of carboxylic acids selected for study was carried out by means of a competition technique,¹² after a series of attempts to accomplish this purpose by more direct methods encountered unsurmountable analytical difficulties. These difficulties were traceable to the nature of the reaction medium (SOCl_2) interfering with the direct determination of bromine concentration; the competition method of measuring relative rates thus held very evident attractions, since we did not wish to alter the reaction medium in which conventionally the H.V.Z. is carried out.

The members of two reaction series were subjected to competition with the unsubstituted case for a de-

(1) Part of the data discussed in this article has been taken from the Ph.D. Thesis of F. V. Scalzi presented in partial fulfillment of the requirements for this degree at the University of Delaware, June, 1963.

(2) C. Hell, *Ber.*, **14**, 891 (1881); C. Hell and J. Sadowski, *ibid.*, **24**, 2388 (1891); N. Zelinsky, *ibid.*, **20**, 2026 (1887); J. Volhard, *Ann.*, **242**, 141 (1887).

(3) A. Lapworth, *J. Chem. Soc.*, **85**, 30 (1904).

(4) See, for examples: (a) J. Hine, "Physical Organic Chemistry," McGraw-Hill Book Co., Inc., New York, N. Y., 1962, Chapter 10; (b) L. Fieser and M. Fieser, "Advanced Organic Chemistry," Reinhold Publishing Corp., New York, N. Y., 1961, p. 367; (c) W. J. Hickinbottom, "Reactions of Organic Compounds," Longman, Green and Co., 1937, London, p. 314.

(5) J. Klein and G. Levin, *J. Am. Chem. Soc.*, **80**, 1707 (1958).

(6) H. E. Zimmerman and T. W. Cutshall, *ibid.*, **81**, 4305 (1959).

(7) R. P. Bell and H. C. Longuet-Higgins, *J. Chem. Soc.*, 636 (1946).

(8) P. D. Bartlett, *J. Am. Chem. Soc.*, **56**, 967 (1934).

(9) I. Zucker and L. P. Hammett, *ibid.*, **61**, 2791 (1939).

(10) P. D. Bartlett and Stauffer, *ibid.*, **57**, 2580 (1935).

(11) (a) C. K. Ingold, *J. Chem. Soc.*, **119**, 316 (1921); (b) E. Schwenk and D. Pappa, *J. Am. Chem. Soc.*, **70**, 3626 (1948).

(12) See, for a full discussion of this approach, G. A. Russell in "Technique of Organic Chemistry," Vol. VIII, Interscience Publishers, Inc., New York, N. Y., 1961.

ficient quantity of bromine in the presence of a large excess of thionyl chloride. The reaction was permitted to proceed for 20–24 hr., well beyond the time required for the bromine to react completely, and quenched in cold methanol for conversion to the methyl ester products and the methyl esters of the unreacted proportions of the competing carboxylic acid reagents. The data obtained on the composition of the resulting mixtures *via* gas chromatographic techniques could be used for computing relative rate constants, as discussed in the Experimental section (see Table I).

TABLE I

RELATIVE RATE CONSTANTS FOR BROMINATION		
Substituent, X =	k_x/k_H	Temp., °C.
A. 4-Substituted cyclohexanecarboxylic acids		
<i>cis-t</i> -Butyl	1.88	75
<i>trans-t</i> -Butyl	0.36	75
<i>cis</i> -Methyl	1.65	75
<i>trans</i> -Methyl	0.68	75
<i>trans</i> -Bromo	0.45	75
<i>cis-t</i> -Butyl (15%)– <i>trans-t</i> -butyl (85%)	} { pre-equilibrated in SOCl ₂ before Br ₂ addn.	75
B. <i>para</i> -Substituted α -methylphenylacetic (hydratropic) acids		
Chloro	0.55	75
Chloro	0.29	100
Methyl	2.31	75
Methoxy	2.59	75
(Phenylacetic acid)	1.04	75
(Cyclohexanecarboxylic acid)	0.62	75
C. α -Deuteriocyclohexanecarboxylic acid		
$k_H/k_D = 1.23 \pm 0.05$		75

We were also able to determine by means of g.l.c. the isomer composition of the product in the case of the cyclohexanecarboxylic acids to ascertain possible directive influences of the 4-substituent. These data are expressed as product ratios in Table II. It was

TABLE II

RATIOS OF α -BROMOCYCLOHEXANECARBOXYLIC ACID ISOMERS FORMED AS A FUNCTION OF 4-SUBSTITUTION

Ratio of products (as methyl esters)	Substituent				
	<i>cis-t</i> -Bu	<i>trans-t</i> -Bu	<i>cis</i> -Me	<i>trans</i> -Me	<i>trans</i> -Br
	48/52	51/49	56/44	51/49	62/38

not possible, however, to establish whether these ratios are *cis/trans* or *trans/cis*.

Finally, the ester isomer composition of the unreacted substances remaining after completion of the bromination reaction was also obtained through g.l.c. analysis. These data listed in Table III are ap-

TABLE III

ISOMER COMPOSITIONS AMONG THE RESIDUAL UNBROMINATED SUBSTRATES RECOVERED FROM THE REACTIONS OF VARIOUS 4-SUBSTITUTED CYCLOHEXANECARBOXYLIC ACID CHLORIDES AT 75°

<i>cis/trans</i> Ratio	4-Substituent		
	<i>t</i> -Butyl	Methyl	Bromo
	16/84	20/80	3/97

parently representative of the equilibrium (*cis-trans*) compositions among the 4-substituted acid chlorides, since the results are unaffected by whether we started with the *cis* or *trans* substrate.

Discussion

Hydratropic Acids.—This reaction series provides an opportunity for testing the nature and magnitude of the charge developed at the seat of the H.V.Z. reaction in the transition state. Where an enolate anion intermediate is being formed in the rate-controlling step at the carbon attached to the aromatic nucleus, we can expect that the net increase in negative charge at the carbon seat of reaction in reaching the transition state would reflect itself in the polar substituent influence on the rate. This expectation has been established for base-catalyzed halogenation of ketones in (largely) aqueous media where $\rho = +1.59$, as calculated by Taft^{13a} from the data of Evans and Gordon¹⁴ on bromination of the series C₆H₅COCHR₁R₂, and by Fischer, Packer, and Vaughn^{13b} reporting $\rho = +1.73$ for the base-catalyzed bromination of substituted benzyl phenyl ketones. On the other hand, in acid-catalyzed bromination of ketones the activated complex is forming a neutral enol from a cationic precursor and experiencing thereby a net reduction in charge character. Consequently, we would anticipate that the reaction constant would be either entirely unbiased or very small in positive or negative magnitude. In agreement with this, Fischer, Packer, and Vaughn¹⁵ have demonstrated that acid-catalyzed brominations of a similar series^{13b} of benzyl phenyl ketones are markedly less sensitive to substituent effects and the observed reaction constant (ρ) has a value of only -0.20 .

From the data given in Table IB on the relative rates of side chain bromination in the analogous series of hydratropic acids we may calculate a Hammett $\rho = -1.39$. Though this relationship encompasses only four experimental rate ratios (Cl-, CH₃-, -OCH₃-, -H), the correlation coefficient, $r = 0.97$, and variance, $\sigma^2 = 0.0046$, provide some confidence in the conclusion that the magnitude of the reaction constant here is much larger than would be anticipated for an acid-catalyzed rate-determining enolization mechanism. Furthermore, a linear relationship is only obtainable with use of Hammett σ -values. The corresponding σ^+ -values of Brown¹⁶ cannot be construed into a linear relationship with the experimental log (k_x/k_H) quantities ($r = 0.87$). This result clearly suggests that, though a very substantial degree of cationic character may have developed at the reaction center in the transition state (as indicated by the sign and magnitude of ρ), direct resonance interaction with appropriate *para* substituents is not a likely possible consequence of structural features of the activated complex. In other words, the positive charge in the transition state either may not reside alone on the side chain carbon, or may be distributed over the reaction centers in such fashion as to prevent resonance overlap with the aro-

(13) (a) R. W. Taft, Jr., in M. Newman, "Steric Effects in Organic Chemistry," John Wiley and Sons, Inc., New York, N. Y., 1956, Chapter 13; (b) A. Fischer, J. Packer, and J. Vaughn, *J. Chem. Soc.*, 226 (1963).

(14) D. P. Evans and J. J. Gordon, *ibid.*, 1434 (1938).

(15) A. Fischer, J. Packer, and V. Vaughn, *ibid.*, 3318 (1962).

(16) H. C. Brown and Y. Okamoto, *J. Am. Chem. Soc.*, **80**, 4979 (1958).

matic ring. The significance of these deductions will be considered in a later section.

Other items of data in Table IB afford further detail regarding the transition state structure. Thus, from the temperature dependence of k_{Cl}/k_H we can compute¹⁷ the activation enthalpy change due to the *para* substitution, $\Delta(\Delta H^*) = 3.4$ kcal., while the corresponding activation entropy change, $\Delta(\Delta S^*)$, is very close to negligible in the temperature range of measurement. The essentially isoentropic nature of the reaction may be interpreted to mean that the polar substituent effect is almost purely inductive in nature and, thus, does not require the fulfillment of a special geometric demand for its conveyance to the reaction center. Any coplanarity requirement which must be satisfied for resonance interaction would be expected to manifest itself in the activation entropy change. We may also cite in full support of this conclusion the rate comparison $k_x/k_H = 1.04$ (see Table IB) of phenylacetic and hydratropic acids. If any form of steric overlap control were a factor in the rate-controlling step of H.V.Z. bromination, as it has been shown to be in a number of reactions involving enolic intermediates,¹⁸ we could have expected a significant rate difference originating from the additional methyl group on the carbon α to the ring in hydratropic acid inhibiting the attainment of coplanarity.

Cyclohexanecarboxylic Acids.—We have here the opportunity to compare the rate response to remote substitution at the 4-position of the cyclohexane ring with what we have observed in this regard for the case in which the reaction center (at the 1-position) on the ring has assumed cationic character in the transition state, namely cyclohexyl tosylate solvolysis.¹⁹ The similarity which will be noted is taken to support the same inference drawn (above) for the charge character of the transition state for hydratropic acid bromination. Thus, for the very polar *trans*-4-bromo substituent, which can exert only a minimal conformational influence on the rate, its field effect transmitted across the ring retards the bromination rate by a factor of about *two*. This is quite consistent with a positively charged transition state with $\rho_I \cong -1 \rightarrow -2$. On the other hand, bulky 4-substituents of very low polarity exercise their rate influence predominantly through their effect on the ring conformational preference. Since the seat of reaction is very much a part of the ring, all influences of a nature which would tend to alter the geometry and/or flexibility of the ring¹⁹ will participate in regulation of the rate. A further parallel to the tosylate solvolysis reaction is also to be found in the fact that *cis*-4-alkyl substituents are (again) noted to be rate enhancing while the same alkyl substituents in the *trans* orientation are rate retarding.¹⁹

In this series, also, we have measured the deuterium kinetic isotope effect in the effort to locate the $\geq C-H$ bond-breaking step along the reaction coordinate. The magnitudes of this effect in mechanisms where enolization is rate determining have been extensively

(17) For this we use the readily derived relation

$$\log (k_{Cl}/k_H = 0.219 \left(-\frac{\Delta(\Delta H^*)}{T} + \Delta(\Delta S^*) \right))$$

(18) H. E. Zimmerman and L. Ahramjean, *J. Am. Chem. Soc.*, **81**, 2086 (1959).

(19) H. Kwart and T. Takeshita, *ibid.*, **86**, 1161 (1964).

catalogued. For example, in the base-catalyzed bromination of acetone Reitz and co-workers²⁰ have reported $k_H/k_D = 7.7$ at 25°. The lowest value previously recorded for the kinetic isotope effect in a base-catalyzed enolization mechanism is $k_H/k_D = 4.6$ at 25° for the case of phenyltolylacetic acid.²¹ This, however, is considerably greater than the result we obtained for the H.V.Z. bromination of cyclohexanecarboxylic acid (see Table IB). Even after we correct²² this value down to 25° for purposes of comparison, the k_H/k_D rate ratio is still more than a factor of two smaller than would be deemed consistent with a reaction mechanism involving any considerable $\geq C-H$ bond ionization in the transition state. It is conceivable that the very small k_H/k_D value indicates a rapid, preliminary equilibrium exchange of the substrate deuterium with the excess hydrogen halide catalyst, this step occurring in the form of some low-lying (energy) intermediate. Whatever the case may be, however, at this juncture in the development of the argument *it is sufficient to infer only that the small k_H/k_D value is clearly inconsistent with a typical enolization mechanism.*^{20, 21}

It will be noted that both the observed relatively large, negative value of the reaction constant ($\rho_I \cong -1.4$) and the near absence of a kinetic isotope effect demand a mechanism of the H.V.Z. reaction in which enolization is *not* the rate-determining step. This is clearly a departure from the kinetic pattern of bromination reactions of carbonyl substrates, where the overall rates in aqueous media at moderate acid concentrations are consistently recorded to be independent of halogen nature and concentration.^{7, 8} From this point of view, the change in medium to the nonpolar solvent thionyl chloride used in the H.V.Z. has eliminated the enol (as such) as an intermediate available for rapid reaction with the bromine and has created a rate dependence on the concentration of this electrophilic reagent.

Several experimental indications exist which strongly suggest that in the H.V.Z. and other halogenation reactions of enolizable carbonyl compounds in non-polar media the halogen does indeed enter the rate-determining step. Thus, it is now evident^{23a} that chlorination of acid chlorides proceeds much more slowly than bromination, in contrast to (so-called) enolization mechanisms where the rate is found to be independent of the halogen nature.³ Furthermore, a very recent report by Cicero and Matthews^{23b} describes the bromination of acetyl bromide in nitrobenzene solution as a bimolecular reaction whose rate is proportional to the concentrations of both bromine and acid bromide.

All the results (discussed above) may be nicely accounted for by taking consideration of the effects to be anticipated on changing from a polar medium (H₂O) to one possessing little proton affinity. In a thionyl chloride solution which is essentially saturated with hydrogen halide any enol (which might tend to be formed) would be by far the strongest base. It would thereby be completely protonated and transformed to a species which is considerably more resistant

(20) O. Reitz, *Z. physik. Chem.*, **A179**, 119 (1937); O. Reitz and J. Kopp, *ibid.*, **A184**, 429 (1939).

(21) D. J. G. Ives and G. C. Wilks, *J. Chem. Soc.*, 1455 (1938).

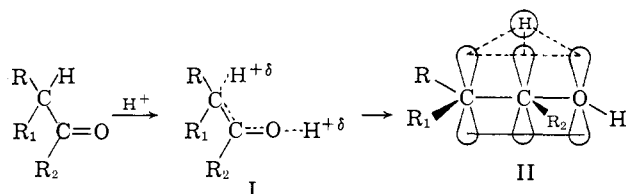
(22) K. Wiberg, *Chem. Rev.*, **55**, 729 (1955).

(23) (a) Unpublished results obtained in these laboratories; (b) C. Cicero and D. Matthews, *J. Phys. Chem.*, **68**, 469 (1964).

to subsequent electrophilic attack by halogen. Under such circumstances the formation of the enol is no longer rate determining; the deuterium kinetic isotope effect does not depend to any significant extent on the ionization of the >C-H bond and the rate-controlling event is shifted along the reaction coordinate to a position representing interaction between two electrophilic species, the proton complexed enol and the halogen.

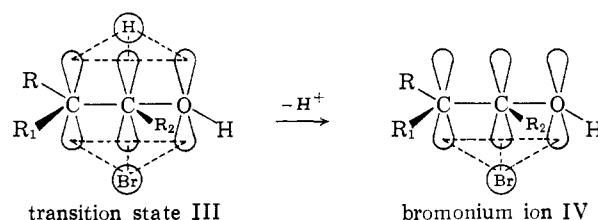
Our data imply that the C-H bond in the substrate (broken in the product) may have been considerably altered prior to the activation step. Thus, if the >C-H bond were already ionized in an intermediate which originates in a step preceding the formation of the activated complex in the bromination reaction, a small kinetic isotope effect becomes understandable. It is therefore necessary to consider the possibility that the enol of the acid chloride (produced by initial reaction of SOCl_2 and RCOOH) is formed rapidly and reversibly, but is only slowly attacked by the electrophilic reagent, Br_2 (or its equivalent in thionyl chloride solution). However, rate data listed in Table IA can be invoked to exclude this premise. Thus, *cis*- and *trans*-*t*-butyl differ by more than a factor of five in reactivity, where we would surmise their rates would be identical if the enol was formed rapidly and reversibly. When, in fact, these geometric isomers are equilibrated by heating in thionyl chloride prior to bromine addition (see Table IA), the resulting rate constant ratio is almost exactly equal to the value computed on the assumption of no further interconversion of substrates (*via* a possible common enol) during reaction with bromine.

The Reaction Intermediate and Transition State.—In keeping with these deductions from our data we are required to describe a relatively low-lying intermediate in which the C-H bond of the conjugate acid I is highly ionized, yet the proton is still associated with the (now) rehybridized α -carbon. It seems likely that stabilization of the developing sp^2 -center is afforded by overlap with the π -orbital of the adjacent carbonyl center. As a consequence, we may regard the (ionized) proton as being imbedded in the resultant molecular orbital much in the manner of a π -complex,²⁴ as depicted in the sequence of structural changes shown, where $\text{R}_2 = \text{Cl}$.



The multicentered π -complex II might be usefully viewed as having been derived from coordination of the electron-rich centers of the enol by a proton. The reaction transition state can be regarded as arising from a rather unusual electrophilic displacement by Br_2 on the complex II. These events may be visualized by means of structures (below) in which the half-reacted state III is converted to a bromonium ion IV

(24) (a) H. Eyring, H. M. Hubert, and R. A. Harman, *Ind. Eng. Chem.*, **35**, 511 (1943); (b) M. J. S. Dewar, *J. Chem. Soc.*, 406 (1946).



bond rearrangement and subsequent product formation.

It must be acknowledged here that a rigorous analogy for such an electrophilic displacement of a proton in a π -complex does not exist in the literature. Most electrophilic substitution reactions (occurring in acidic media) involve the formation of stabilized cationic intermediates or (σ) addition complexes,^{25a} and have been justly classified^{25a} as two-step processes. That is to say, a range of mechanisms are indicated. On one end are to be found nitration reactions, where σ -complex formation is rate determining, and at the other extreme we locate sulfonations, where the intermediate reverts to reactants at a rate comparable to transformation to the observed products. These conclusions are in agreement with the noted^{25d} differences in kinetic deuterium isotope effect. There appears to be no evidence at hand justifying the concerted character of the major transition state in electrophilic aromatic substitution reactions as has been fitted to the H.V.Z. reaction (III) in the preceding discussion.

We conceive the protonated enol structure II to be a π -complex in the sense of the term employed by Dewar.^{25c} This is clearly to be distinguished from the loosely bound HCl -aromatic hydrocarbon complexes that have also been designated by Brown and Brady^{25b} as π -complexes. In the H.V.Z. intermediate II the proton is assumed to be intimately affiliated with all three π -electron centers. However, it experiences no form of covalent bonding such as has been inferred for the σ -complex implicated in aromatic substitution and characterized in special cases by means of direct measurement^{25e,f} or isolation studies.^{25g,h}

While the proposed reaction path is admittedly somewhat lacking in precedence, there appears to be abundant evidence pointing to the existence of an unusual mechanism of α -halogenation under acidic conditions, which are not unlike those prevailing in the H.V.Z. reaction. For example, data taken for a reaction series of *para*-substituted acetophenones undergoing bromination in hydrochloric-acetic acid solution by Watson and co-workers²⁶ has been correlated by Hammett²⁷ in a linear free energy relationship bearing a negative ρ (-0.55) value. Further study of the kinetic features of this and related reactions is presently in progress in these laboratories with the objective of

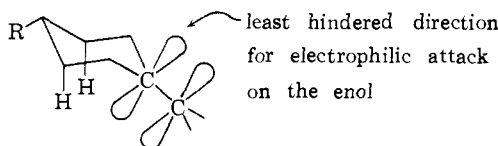
(25) (a) See, for an exhaustive discussion of this subject, C. K. Ingold, "Structure and Mechanism in Organic Chemistry," Cornell University Press, Ithaca, N. Y., 1953, Chapter VI; (b) H. C. Brown and J. D. Brady, *J. Am. Chem. Soc.*, **74**, 3570 (1952); (c) M. J. S. Dewar, "The Electronic Theory of Organic Chemistry," Clarendon Press, Oxford, England 1949; (d) L. Melander, *et al.*, *Nature*, **163**, 599 (1949); *Acta Chem. Scand.*, **3**, 95 (1949); *Arkiv. Kemi*, **2**, 211 (1951); **6**, 219 (1953); (e) D. A. McCaulay and A. P. Lien, *J. Am. Chem. Soc.*, **73**, 2013 (1951); (f) M. Kilpatrick and F. E. Luborski, *ibid.*, **75**, 577 (1953); (g) G. A. Olah, *et al.*, *ibid.*, **80**, 6535, 6541 (1958); (h) W. von E. Doering, *et al.*, *Tetrahedron*, **4**, 178 (1958).

(26) (a) W. S. Nathan and H. B. Watson, *J. Chem. Soc.*, 217 (1933); (b) D. P. Evan, V. G. Morgan, and H. B. Watson, *ibid.*, 1167 (1935).

(27) L. P. Hammett, "Physical Organic Chemistry," New York, N. Y., McGraw-Hill Book Co., Inc., 1940, Chapter 7.

determining the applicability of the electrophilic displacement mechanism of bromination to various types of carbonyl substrates.

Stereochemistry of the H.V.Z. Product.—The reaction applied to 4-substituted cyclohexanecarboxylic acids offers us a unique opportunity for observing some of the factors that regulate the stereochemistry of the bromination reaction. If we were to assume that the product-forming step involves the direct reaction of the enol with an electrophilic reagent, then we may seek the guidance of Zimmerman's work²⁸ establishing the steric course of this step. In view of Zimmerman's model structure of the reaction (V) we are led to anticipate a predominance of the *cis*-acid (*i.e.*, *trans* relationship of Br and R), particularly where R is a large, bulky group.



It is apparent from the product composition data listed in Table II that this type of "steric approach control"^{29,30} is *not* functioning in the H.V.Z. reaction. As mentioned earlier, these data are more indicative of equilibrium or so-called "product development" regulation of the stereochemistry, since the product composition is apparently unaffected by the size of the 4-alkyl group or the geometry of the isomeric acid undergoing reaction. This result, however, may be viewed as nicely in accord with the proposed electrophilic displacement mechanism. The following is a summary of this interpretation and a reasoning of the evidence supporting it.

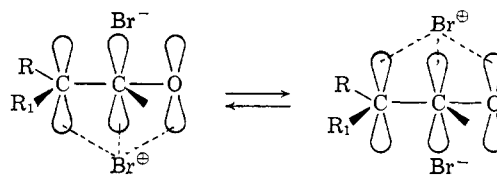
(1) *cis*- and *trans*-cyclohexanecarboxylic acids undergo the H.V.Z. reaction at very different rates. These acids are *not* equilibrated prior to the rate-determining bromination step.

(2) Since these *cis*- and *trans*-acids give exactly the same bromination product composition, their product-forming steps must have a common intermediate or precursor state. If this (intermediate) were the enol, it would have to be formed in an equilibrium process to be in agreement with the rate dependence upon halogen concentration and the substituent effects contributing to rate regulation (as noted earlier in this article).

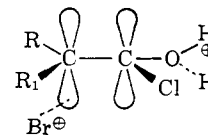
(3) To account for the observed (see (1) above) nonequilibration of the *cis*- and *trans*-acids and the absence of a kinetic isotope effect, we may assume that the acts of protonation and deprotonation of the "enol" occur stereospecifically (a plausible assumption in view of previous work²⁸), and rapidly compared to the slower process by means of which epimeric equilibrium is ultimately attained after long heating of the unreacted acids in the medium (see data, Table III). Again, we conclude that the enol cannot be the common intermediate through which epimeric acids form the same bromination product.

(4) These arguments compel the inference that the *transition state of the bromination step* has the same structure or leads to the same intermediate starting from either of the epimeric acid substrates. Whatever this state or intermediate looks like, it must be symmetrical if it leads to the equilibrium α -bromo acid chloride product.

(5) One likely structure of an intermediate formed from the transition state (proposed earlier in this article) for the H.V.Z. reaction is a consequence of the "ion-pair" nature of the reaction intermediate in the low dielectric solvent; a sort of symmetrical bromonium-bromide as depicted by



(6) Intermediates or transition states resembling the structure



while accounting for the absence of kinetic isotope effect fail to satisfy this essential "symmetry" requirement for product formation.

As a matter of passing interest it should be noted that the more polar 4-bromo substituent has biased the product composition to a significantly greater extent than any of the bulky alkyl groups listed in Table II. A clean analogy for this observation is to be found in the recent report that the dominant influence on both rate and stereochemistry of reduction of 4-substituted cyclohexanones with NaBH_4 may be attributed to a field effect. Electrostatic interaction between the remote 4-substituent dipole and the charges developing at the seat of reaction create preference for formation of one of the two (geometric) alternative transition state structures.³¹ Since the product we are observing in the H.V.Z. bromination is of "equilibrium" nature, the factor of *charge-dipole interaction in the transition state* is obviously not the factor controlling stereochemistry. It seems apparent, however, that *dipole-dipole* interaction between the 4-substituent on the one hand and the bromo and acid chloride groups on the other, occurring through the low dielectric cavity of the cyclohexane ring, *does result in significant differences in stability between the alternative possibilities for product structure*. We can thus identify the operation of a field effect on equilibrium to parallel our earlier observation³¹ of the importance of this effect on the kinetic course of reactions. The influence of such interactions between vicinal as well as remote substituents (compared to steric factors) controlling the *conformational* preferences of cycloalkane rings has been well documented by several investigators.³² In the H.V.Z. reaction we appear to have an instance of relatively long range interactions manifesting an important effect on *configurational* preference.

A final glance at the fate of the unreacted acid chlorides (which form the residue analyzed in the competitive rate experiments) seems to be in order in a complete stereochemical picture of the H.V.Z. reaction. We have pointed out (above) that there is no evidence for equilibration of isomeric acids through rapid reversible formation of a common enol prior to the rate- and product-determining steps. Nevertheless, it is not surprising that continued heating of the acid chlorides (in the absence of bromine) in thionyl chloride medium containing a large excess of HCl will

(31) H. Kwart and T. Takeshita, *J. Am. Chem. Soc.*, **84**, 2833 (1962).

(32) (a) S. Mizushima, "The Structure of Molecules and Internal Rotation," Academic Press, Inc., New York, N. Y., 1954; (b) E. V. Wessels, Ph.D. Thesis, The University of Leiden, Jan. 13, 1960, has presented particularly strong evidence for the existence of such conformationally controlling long range dipole-dipole interactions in the ground state.

(28) See ref. 6 and references cited therein for a full exposition of the principles underlying this excellent work.

(29) W. G. Dauben, G. J. Fonken, and D. S. Noyce, *J. Am. Chem. Soc.*, **78**, 2579 (1956).

(30) W. G. Dauben and R. E. Bozak, *J. Org. Chem.*, **24**, 1596 (1959).

Hydrogenation of *p*-anisic acid (76 g.) was performed at room temperature under 100 lb. of hydrogen pressure for 100 hr. using 5% rhodium-alumina catalyst in dry methanol. Esterification of the isolated acid was carried out in the usual manner with methanol-H₂SO₄. These experiments were repeated so as to accumulate ca. 312 g. of ester which was distilled (b.p. 113° (3 mm.)); g.l.c. analysis showed the ester mixture consisted of 86% *cis*-14% *trans*.

Separation of the *cis*-ester was effected by distillation through a spinning band column (100/1 reflux ratio, 100 mm.). Of 37 fractions collected, the six highest boiling were shown to be a stereochemically pure isomer by g.l.c. The combined high boiling fractions were saponified, acidified, and the acid extracted with ether. Evaporation of the solvent, followed by recrystallization from pentane, gave 34.3 g. of pure *cis*-4-methoxycyclohexanecarboxylic acid, m.p. 53-53.5° (lit.⁴⁴ 54.6-55.6°).

Treatment of the *cis*-methoxy acid with PBr₃ and subsequent hydrolysis afforded a proof of the *cis* stereochemistry of the 4-methoxy acid as well as providing a route to the *trans*-bromo acid desired. The procedure of Noyce and Weingarten⁴⁴ was employed. The pure *trans*-bromo acid, 2.9 g., m.p. 170.5-171.5° (lit.⁴⁴ 169-171°, 170.8-171.4°), was isolated in two crops from benzene-pentane.⁴⁵

α -Deuteriocyclohexanecarboxylic Acid.—Cyclohexanecarboxylic acid (90 g.) was brominated under Hell-Volhard-Zelinsky conditions.⁴⁶ The crude bromo acid thus obtained (142 g., 96% yield) was twice recrystallized from hexane to give 97 g. of pure bromo acid, m.p. 60° (lit.⁴⁷ 63°).

Deuteration was accomplished by heating the bromo acid (20.2 g., 0.1 mole) with zinc powder (0.5 g.-atom)-acetic anhydride (1.4 moles, reagent grade), and deuterium oxide (1.4 moles, 99.5% sample from Gen. Dynamics Corp., San Carlos, Calif.) with stirring for 42 hr. in a dry atmosphere. The usual subsequent procedures of filtration, quenching in water, extraction with ether, washing, and drying gave a liquid which was distilled (b.p. 120° (5 mm.)) giving 9.42 g. (73% yield) of the α -deuterio acid; deuterium analyses of two repeat runs: 6.40 atom % D (77.07% α -deuteration) and 7.36 atom % D (88.35% α -deuteration).

Bromination of Cyclohexanecarboxylic Acid with Bromine in Thionyl Chloride: A Test of Completeness of Reaction under the Conditions of the Kinetic-Competition Measurements.—

Cyclohexanecarboxylic acid (15 g., 0.12 mole) was stirred at 75° under nitrogen atmosphere with thionyl chloride (30 ml.) and bromine (19.2 g., 0.12 mole). After 10 hr. all the bromine color had disappeared. After quenching in ice-water, exhaustively extracting with ether, then washing the ether extracts, and drying over MgSO₄, the solvent was evaporated, leaving a light yellow oil. This oil solidified on cooling, giving the crude bromo acid (23.6 g., 95% yield). One gram of the acid was converted to its methyl ester with diazomethane³⁵ in ether. Evaporation of the ether and analysis of the remaining liquid by g.l.c. gave a single broad peak and a very minor peak (<2%—corresponding to the ester of cyclohexanecarboxylic acid), demonstrating that the reaction was very nearly quantitative. Peak enhancement experiments further demonstrated that the single peak was caused by the bromo ester. Two recrystallizations of the crude bromo acid out of hexane resulted in recovery of 20 g. of pure α -bromocyclohexanecarboxylic acid, m.p. 62-63° (lit.⁴⁷ 63°).

Methyl Esters of All Acids Used in Competitive Rate Studies.—A small amount (ca. 0.005 mole) of each acid prepared was converted to its methyl ester with an excess of diazomethane³⁵ in ether, the ether evaporated, and the residual oil used directly in peak enhancement experiments in g.l.c. analysis.

Method of Analysis. Competitive Rate Experiments.—Approximately 0.00625 mole each of unsubstituted and substituted acids, weighed to the nearest 0.05 mg., were placed in a flask and cooled in ice. An excess (15 ml.) of thionyl chloride (reagent grade) and approximately 0.00625 mole of bromine (ACS reagent) were introduced and the flask was immersed in a thermostat held at 75 ± 0.1°. Each reaction was allowed to proceed for 20 to 24

(44) D. S. Noyce and H. I. Weingarten, *J. Am. Chem. Soc.*, **79**, 3093 (1957).

(45) Complications arising out of the appearance of large amounts of methoxy 3-cyclohexanecarboxylate and equilibration of the stereoisomers involved in the bromination reaction are the subject of unpublished work carried out in these laboratories; to appear in a future article.

(46) A. I. Vogel, "A Textbook of Practical Organic Chemistry," Longmans, Green, and Co., London, 1951, p. 421.

(47) I. Heilbron, ref. 34b, Vol. 1, p. 319.

(48) (a) It was found that accurate results could be achieved if the faster of

hr., well beyond the time for all the bromine to be reacted, and time enough for any subsequent isomerization reactions to attain equilibrium. The reaction mixture was then cooled in ice, and dropped into cold, stirred methanol (40 ml.) in a dry atmosphere. Stirring was continued for 3 to 5 hr. while warming to room temperature.^{48b} The resulting solution was poured into 150 ml. of water and exhaustively extracted with pentane. The extracts were washed with sodium carbonate and with water until neutral, then dried. Evaporation of the pentane left a yellow to colorless oil which was submitted directly to g.l.c. analysis.

All g.l.c. analyses in the relative rate studies were accomplished with a 4-ft. stainless steel column packed with 20% silicone oil on siliconized Chromosorb. Peaks were identified by peak enhancement experiments with pure samples. Relative mole fractions of unreacted substrates were determined from their corresponding peak weights and respective molecular weights.

Manipulations of the g.l.c. instrument variables allowed resolution and determination of weight fractions of the isomer composition of the substituted, unreacted substrates and of the products of the reaction as well (see Tables II and III).

Competitive Rate Experiment with Pre-isomerization of Substituted Acids.—*cis*-4-*t*-Butylcyclohexanecarboxylic acid and the unsubstituted acid (0.00625 mole each) were refluxed in an excess of thionyl chloride for 48 hr. on a steam bath, then cooled, prior to addition of bromine and immersion in the thermostat as described above.

Deuterium Isotope Effect Experiments.—A partially deuterated sample (1.6118 g., 6.14 atom % D) was diluted with pure cyclohexanecarboxylic acid (1.3330 g.) and submitted to reaction with an excess (40 ml.) of thionyl chloride and 0.00115 mole of bromine. The reaction products were separated from the unreacted substrates by g.l.c. using a 10-ft. silicone oil on firebrick preparative column at 145° and the unreacted substrates were collected in a solid CO₂ trap. This colorless liquid was submitted to deuterium analysis.

Procedures in Relative Rate Computations.—The basis of all the computations is the equation (which is derived elsewhere)^{12, 49}

$$k_x/k_H = (\log X_f/X_i)/(\log H_f/H_i)$$

where X_f , X_i , H_f , and H_i are final and initial amounts of the respective substrates expressed as number of moles.

H_i and X_i were computed from the weights of substrates and their respective molecular weights. The total number of moles reacted was then $(H_f + X_f)/2$, assuming 100% consumption^{50a} of bromine in the reaction path under consideration.^{50b}

The mole percentages of unsubstituted and substituted substrates were computed by adding the relative mole fractions of each substrate obtained from g.l.c. analyses of the competitive rate experiments and dividing each value by the sum. Then

$$(\text{mole } \% \text{ unsubst. substrate}) \times (H_i + X_i)/2 = H_i$$

$$(\text{mole } \% \text{ subst. substrate}) \times (H_i + X_i)/2 = X_i$$

The computation of the deuterium isotope effect was completed in an analogous fashion. The equation employed was:

$$k_H/k_D = (\log H_f/H_i)/(\log D_f/D_i)$$

where H_f and H_i denote undeuterated species, and D_f and D_i the deuterated species. H_i and D_i were computed from the deuterium analysis of the samples prepared and the molar amounts of

the competing substrates was allowed to react no more than 90% by limiting the reaction time. The extent of reaction was limited to no more than 50% by using half the amount of bromine necessary to convert both substrates entirely to products. (b) Acylchlorides were thus converted to their methyl esters. Schwenk^{11b} reported a similar conversion in at least 98% yield.

(49) This equation has been employed by previous workers. Since the products of the reaction were not as well resolved as the reagents, the kinetic expression used involved only the amounts of unconverted substrates and the amounts of starting materials: (a) E. Berliner and F. J. Bondhus, *J. Am. Chem. Soc.*, **68**, 2355 (1946); (b) C. K. Ingold and M. S. Smith, *J. Chem. Soc.*, 905 (1938); (c) C. K. Ingold, A. Lapworth, E. Rothstein, and D. Ward, *ibid.*, 1959 (1931).

(50) (a) This assumption is supported by the experiment (see Experimental) in which approximately 95% yield was obtained in treatment of cyclohexanecarboxylic acid with an equimolar amount of bromine in thionyl chloride. Calculations also show that a 90% consumption of bromine produces only a 4% increase in k_x/k_H , while an 80% consumption produces a 10% increase. In any case, the relationship between k_x/k_H values in the rate study series would not be significantly affected by a slightly lower consumption of bromine. (b) Side products were absent, or possibly produced in undetectable amounts, in g.l.c. analysis in all cases.

pure cyclohexanecarboxylic acid added to dilute the sample in the competitive rate runs. The deuterium analysis of the ester recovered from g.l.c. separation allowed computation of the mole fraction of deuterated species (m) in the sample: $m = (\text{atom } - \% \text{ D})/7.14$, where 7.14 is taken as the maximum atom $- \% \text{ D}$ for the α -deuteriocyclohexanecarboxylic acid. The mole fraction of the undeuterated species is then $1 - m$ and

$$m \left(\frac{H_i + D_i}{2} \right) = D_f$$

$$(1 - m) \left(\frac{H_i + D_i}{2} \right) = H_f$$

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[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, PURDUE UNIVERSITY, LAFAYETTE, INDIANA]

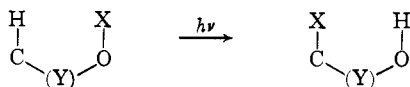
Mechanisms of Substitution at Unactivated Carbon Atoms¹

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Various mechanisms by which substitution at an unactivated carbon atom can occur have been defined. Most of the work has been carried out using the 1,3,3-trimethylcyclohexyl system, I, where X = Br, OH, p -OSO₂C₆H₄CH₃, and p -O₂CC₆H₄NO₂. The bicyclic ether II, 6-oxa-1,5-dimethyl[3.2.1]bicyclooctane, has been shown to be formed by: 1, a free-radical process (I, X = OH $\xrightarrow{\text{Cu}^+}$ II); 2, a radical-pair cage process (I, X = Br $\xrightarrow{h\nu}$ II); 3, a free cation process (I, X = Br $\xrightarrow{\text{Ag}^+}$ II); and 4, an ion-pair process (I, X = OSO₂C₆H₄CH₃ \longrightarrow II).^{8,9} Of all reactions studied only the solvolysis of the p -nitroperbenzoate (I, X = O₂CC₆H₄NO₂) did not give rise to bicyclic ether II, furnishing instead keto alcohols V and VI *via* a Criegee rearrangement.¹³

With a few notable exceptions, organic chemists in the past have focused their attention on reactions which take place because of some form of chemical activation; reactions at unactivated carbon atoms have been largely ignored because of their presumed lack of specificity. It has become increasingly evident, however, that in molecules possessing favorable geometry reactions at unactivated atoms can become quite specific. Examples are the transannular reactions studied extensively by Cope³ and Prelog³ and the reaction which has come to be known as the Barton reaction in which an exchange of various groups, X, for hydrogen is photochemically induced.⁴



The Barton reaction has proved to be an extremely powerful tool in organic synthesis⁴ and as such is deserving of a detailed mechanistic study. In this paper we report the results of experiments undertaken both to determine the scope and limitations of the Barton reaction and related processes as well as to define the various mechanisms by which substitution at a saturated carbon atom can occur.

If one generalization emerges from our work it is that, contrary to the generally held notion that reactions at unactivated atoms are unselective, Barton-type reactions can and do become extremely selective and they take place by a myriad of mechanisms.

(1) Based on the Ph.D. Thesis of N. P. Matheny, Purdue University, 1964. Some of the work described in this paper has appeared in a preliminary communication: R. A. Sneen and N. P. Matheny, *J. Am. Chem. Soc.*, **86**, 3905 (1964).

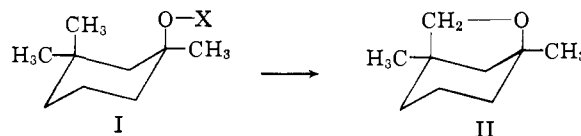
(2) David Ross Fellow, Purdue Research Foundation, 1963–1964.

(3) V. Prelog and J. G. Traynham in "Molecular Rearrangements," P. de Mayo, Ed., Part 1, Interscience Publishers, Inc., New York, N. Y., 1963, p. 593.

(4) O. L. Chapman in "Advances in Photochemistry," W. A. Noyes, Jr., G. S. Hammond, and J. N. Pitts, Jr., Eds., Vol. 1, Interscience Publishers, Inc., New York, N. Y., 1963, p. 399.

Results and Discussion

Most of our work has been carried out using the 1,3,3-trimethylcyclohexyl system,⁵ I, where X = Br, OH, p -OSO₂C₆H₄CH₃, and p -O₂CC₆H₄NO₂. The bicyclic ether, 6-oxa-1,5-dimethyl[3.2.1]bicyclooctane (II), has been shown to be formed by: 1, a free-radical process (I, X = OH $\xrightarrow{\text{Cu}^+}$ II); 2, a radical-pair cage process (I, X = Br $\xrightarrow{h\nu}$ II); 3, a free cation process (I, X = Br $\xrightarrow{\text{Ag}^+}$ II); and 4, an ion-pair process (I, X = OSO₂C₆H₄CH₃ \longrightarrow II).⁸



Free-Radical Decomposition of Hydroperoxide (I, X = OH) to Bicyclic Ether II.—Cuprous chloride catalyzes the decomposition of 1,3,3-trimethylcyclohexyl hydroperoxide (I, X = OH) to bicyclic ether II. The only other apparent organic product is the parent alcohol I (X = H). That the reaction is free radical in nature is suggested by the studies of Kochi¹⁰ and Kharasch¹¹ and is confirmed by the results of studies of the decomposition in the presence of thiophenol, a good radical transfer agent. At low concentrations of added thiophenol (0.0033 *M*, equimolar with hydroperoxide)

(5) Data of Allinger⁶ and of Eliel⁷ suggest that 1,3,3-trimethylcyclohexanol (I, X = H) will exist preferentially (*ca.* 90%) in the conformation shown below with the hydroxyl group oriented in an axial position. A change in the nature of the group, X, would not be expected to affect this conformational preference greatly.

(6) N. L. Allinger and M. A. Miller, *J. Am. Chem. Soc.*, **83**, 2145 (1961).

(7) E. L. Eliel and H. Haubenstock, *J. Org. Chem.*, **26**, 3504 (1961).

(8) This latter process had earlier been reported by Corey and White⁹ who used, however, the p -nitrobenzenepersulfonate.

(9) E. J. Corey and R. W. White, *J. Am. Chem. Soc.*, **80**, 6686 (1958).

(10) J. K. Kochi, *ibid.*, **85**, 1958 (1963), and references cited therein.

(11) M. S. Kharasch, A. Fono, and W. S. Nudenberg, *J. Org. Chem.*, **16**, 113 (1951); M. S. Kharasch and A. Fono, *ibid.*, **24**, 606 (1959), and references cited therein.