[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY OF THE UNIVERSITY OF MICHIGAN]

Rearrangement of Alkyl Groups. Kinetic and Tracer Studies in the Pinacol Rearrangement[1]

BY MARTIN STILES AND RAYMOND P. MAYER[2]

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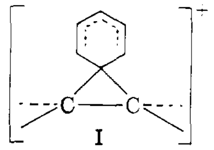
The rearrangement of 2,3-dimethyl-2,3-pentanediol (IIb) in aqueous sulfuric acid yielded 83% methyl *t*-amyl ketone and 17% ethyl *t*-butyl ketone. Isotopic labeling showed that the methyl ketone arose both by ethyl migration (69%) and methyl migration (31%). Similar rearrangement of 2,3,4,4-tetramethyl-2,3-pentanediol (IIc) led to 98.6% methyl triptyl ketone and 1.4% hexamethylacetone. In this case the methyl ketone was shown to result entirely from *t*-butyl migration. The relative rates of rearrangement of pinacol (IIa), IIb and IIc were 1.0:7.2:>10^3. The tendencies of alkyl groups to migrate in this rearrangement are expressed in terms of partial rates, which are in the ratio >4000:17:1 for *t*-butyl, ethyl and methyl, respectively. A reaction mechanism is discussed in the light of these and other recent results.

Rearrangements which involve the 1,2-shift of an aryl group to an electrophilic carbon atom are generally believed to pass through an intermediate or transition state of the phenonium ion[3] type (I). In this process the C-1 of the aromatic ring has increased its coördination number from 3 to 4 and has altered its hybridization in the direction of the tetrahedral arrangement. So far as the migrating group is concerned the process is analogous to normal aromatic substitution, the similarity of the intermediates[4] and substituent effects for the two processes being generally recognized.

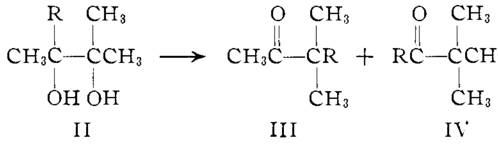


I

The nature of the transition state for the 1,2-shift of a saturated alkyl group is much more obscure. Although such rearrangements are very common, a detailed description of the process has not been attempted. Particularly interesting is the nature of the valence state of the carbon atom undergoing migration, which appears to have a coördination number of 5. If considered as a displacement reaction upon the alkyl group the process involves a charge type (electrophilic) and stereochemistry (retention of configuration) which are uncommon in the chemistry of saturated aliphatic compounds. Only with organometallic derivatives[5] does an analogous process seem likely, and at present the chemistry of this class of compounds is not sufficiently understood to aid in the interpretation of alkyl migration.

Furthermore, no systematic information is available concerning the effect of structural variation upon the migration tendencies of alkyl groups. The results of Meerwein,[6] Nybergh,[7] and Reeve and Karickhoff[8] indicated that ethyl migration predominates over methyl in the pinacol rearrangement, but Cram and Knight[9] found a large preference for methyl migration in the rearrangement which accompanies the solvolysis of 3,4-dimethyl-4-phenyl-3-hexyl *p*-bromobenzenesulfonate.

More precise reactivity data would be a logical starting point in attempting a detailed description of alkyl group rearrangements. The aim of the present work was to evaluate the performance of some simple alkyl groups in the pinacol rearrangement. The system chosen for study was the family of glycols II. Locquin[10] studied the rearrangement of this series



$$\mathrm{CH_3\overset{R}{\underset{OH}{C}}-\overset{CH_3}{\underset{OH}{C}}CH_3 \longrightarrow CH_3\overset{O}{\overset{\|}{C}}-\overset{CH_3}{\underset{CH_3}{C}}R + R\overset{O}{\overset{\|}{C}}-\overset{CH_3}{\underset{CH_3}{C}}CH_3}$$

II III IV

a, R = CH_3; b, R = C_2H_5; c, R = t-C_4H_9

where the dissimilar group R was ethyl, *n*-propyl, isopropyl, *n*-butyl, isobutyl and *t*-butyl, and reported that the chief product in each case was the methyl ketone III. This result was not useful in comparing the migration of methyl and the other alkyl groups, however, since III could arise by either R migration or methyl migration. We have separated the products (III and IV) of the rearrangement of glycols IIb and IIc by vapor-phase chromatography, and have used isotopic labeling to determine the extent to which the methyl ketone III arose by R migration.[11] This information, coupled with the results of a kinetic study of the rearrangement of IIa, IIb and IIc, has allowed a com-

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[1] Presented before the Division of Organic Chemistry, American Chemical Society, Chicago, Ill., September, 1958; Abstracts, p. 9P.

[2] Based upon the Ph.D. thesis of Raymond P. Mayer, University of Michigan, 1958.

[3] D. J. Cram, THIS JOURNAL, **71**, 3863 (1949).

[4] L. Melander, *Arkiv Kemi*, **2**, 211 (1950).

[5] S. Winstein and T. G. Traylor, THIS JOURNAL, **78**, 2597 (1956), and earlier papers.

[6] H. Meerwein, *Ann.*, **419**, 121 (1919).

[7] B. Nybergh, *Ber.*, **55**, 1960 (1922).

[8] W. Reeve and M. Karickhoff, THIS JOURNAL, **78**, 6053 (1956).

[9] D. J. Cram and J. D. Knight, *ibid.*, **74**, 5839 (1952).

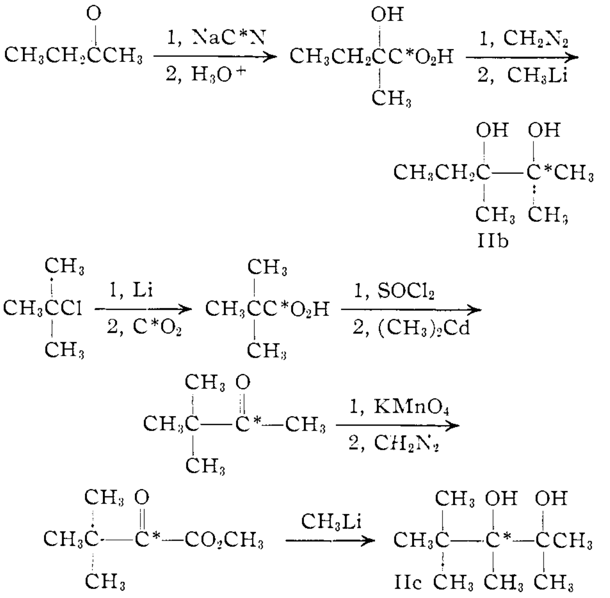
[10] R. Locquin and W. Sung, *Bull. soc. chim.*, [4] **35**, 753 (1924); *Compt. rend.*, **178**, 1179 (1924); R. Locquin and L. Leers, *Bull. soc. chim.*, [4] **39**, 426, 433 (1926).

[11] Kinetic isotope effects were neglected in interpreting the tracer results. Duncan and Lynn [*Austral. J. Chem.*, **10**, 7 (1957)] have reported an extraordinarily large rate difference (more than a factor of two) between pinacol and pinacol containing C^{14} in rearrangements carried out in aqueous acid at 78°, 100° and 113.5°, although no rate difference at 67° was detected. We have found (M. Stiles and R. B. Bernstein, unpublished results) the ratio k_{12}/k_{13} to be less than 1.007 at 100°, where k_{12} is the rate constant for rearrangement of molecules containing only C^{12}, and k_{13} that for molecules containing one C^{13} atom. Since the C^{13} was randomly distributed in the molecule, this isotope effect must be multiplied by a factor of 6, yielding a value of *ca.* 4% for the *maximum* C^{13}-isotope effect for a single carbon atom. This suggests that the C^{12}/C^{14} isotope effect would be only as large as 8–9% even if it were confined to a single carbon atom. NOTE ADDED OCTOBER 6, 1958: V. F. Raaen and C. J. Collins, THIS JOURNAL, **80**, 4432 (1958), have now reinvestigated the C^{14}-isotope effect and have shown that it is less than 1%.

plete evaluation of methyl, ethyl and *t*-butyl as migrating groups in this system.

Results

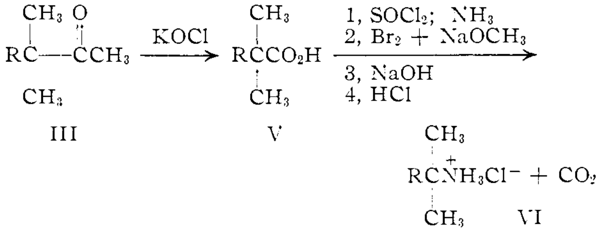
Tracer Study.—The two labeled glycols IIb and IIc were prepared as indicated in the flow diagrams. Each step in the synthesis of both compounds was based on published procedures except the reaction of pivalyl chloride with dimethylcadmium, which gave disappointing yields (*ca.* 10%). The low yield is particularly puzzling in view of the fact that methyl *t*-amyl ketone could be prepared in 61% yield by the same method. The use of methyllithium instead of methyl Grignard reagent in the final step allowed isolation of the glycols without acidification.



The glycol IIb rearranged at room temperature in 50% aqueous sulfuric acid, conditions under which the ketones IIIb and IVb are stable,[12] to give a mixture of ketones in 78% yield. The composition of the mixture was revealed to be 83% methyl *t*-amyl ketone (IIIb) and 17% ethyl *t*-butyl ketone (IVb) by vapor-phase chromatographic separation.

The glycol IIc rearranged completely in a few minutes with 50% sulfuric acid, which does not cause any measurable change[13] in IIIc and IVc, to give a 78% yield of a liquid product whose infrared spectrum was essentially that of IIIc. The product was separated by vapor-phase chromatography into a small fraction (5%) which was probably unsaturated hydrocarbon, and the two ketones IIIc and IVc in a ratio of 72 to 1.

The methyl ketones IIIb and IIIc were degraded by hypochlorite oxidation to the carboxylic acids Vb and Vc, respectively, which were converted to the amides and thence *via* the Hofmann rearrangement to the carbamate esters, which were hydrolyzed and decarboxylated to the amine hydrochlorides VIb and VIc. Since hexamethylacetone (IVc) is inert to hypohalite it did not give rise to any degradation products to contaminate those from the methyl ketone IIIc. Ethyl *t*-alkyl ketones are attacked by hypochlorite,[14] however, and the acid Vb obtained in the oxidation was presumed to be contaminated with a small quantity of pivalic acid (Va). Nevertheless Vb gave a crystalline amide which appeared to be pure dimethyl-*t*-butylacetamide, and the amine hydrochloride obtained in the final degradation was shown to contain only 2.4% *t*-butylamine hydrochloride (VIa) as a contaminant in VIb. The composition was determined by vapor-phase chromatographic separation of the pure amines, using authentic samples for comparison. A correction was applied to the radiochemical assay data to allow for the presence of 2.4% VIa.



a, R = CH_3; b, R = C_2H_5; c, R = *t*-C_4H_9

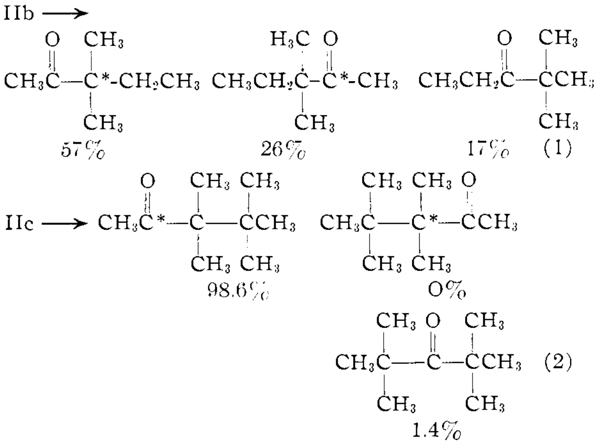
The counting data are given in Table I and the results of the tracer study are expressed in equations 1 and 2. The carbon dioxide was counted as barium carbonate and the amines as the solid hydrochlorides. Various plate thicknesses were used and the results tabulated were obtained by extrapolation to zero thickness.

TABLE I

RADIOCHEMICAL ASSAY OF DEGRADATION PRODUCTS

Starting ketone	Degradation product	Counts/min./mmole
IIIb	Acid Vb	4380[a]
	Amine VIb	2870
	$BaCO_3$	1300
IIIc	Acid Vc	2080
	Amine VIc	0
	$BaCO_3$	2010

[a] Counted as the solid amide.



Kinetic Study.—The rates of rearrangement of IIa-IIc are summarized in Table II. The reactions were followed by infrared analysis of carbon tetrachloride solutions of the quenched reaction

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[12] H. D. Zook, W. E. Smith and J. L. Greene, THIS JOURNAL, **79**, 4436 (1957).

[13] M. Stiles and R. P. Mayer, *Chemistry & Industry*, 1357 (1957).

[14] H. Meerwein, *Ann.*, **396**, 253 (1913).

mixtures. The rates of IIa and IIb were followed to 70–75% completion. Glycol IIc was completely rearranged in 5 minutes at 25° in 49.22% sulfuric acid and accurate rate data could not be obtained. The use of lower acidities or lower temperatures, where the reaction would be slower, was not feasible because of reduced solubility. The figure for the first order rate constant for this compound is a minimum value, calculated from the fact that reaction was at least 99% complete in 5 minutes.

TABLE II

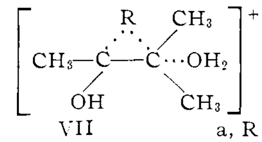
FIRST-ORDER RATE CONSTANTS FOR REARRANGEMENT IN AQUEOUS SULFURIC ACID

	$10^3 k_{\text{obs}}$, sec.$^{-1}$ at 25.0°	
	49.22% H_2SO_4	59.16% H_2SO_4
IIa	0.0150 .0145^a	0.145^a
IIb	.108	0.952
IIc	>15	

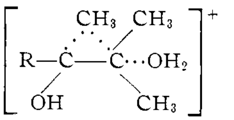
^{a} Interpolated from data of Deno and Perizzolo, ref. (22).

Discussion

Migration Tendencies.—The pattern of rearrangement of pinacols has usually been correlated in terms of migration aptitudes,[15] which expressed the rate of rearrangement of a substituent relative to some standard substituent in the same molecule, such as a phenyl group. This *intramolecular* comparison, when applied to symmetrical aromatic pinacols, yields information useful in predicting the course of some untried rearrangement. However, it does not constitute a theoretically valid description of any property of the migrating group which is independent of other substituents on the pinacol molecule. In the present series, for example, the migration aptitude of the group R would be expressed in terms of its superiority over methyl, by comparing the rate of the processes symbolized by VII and VIII.[16] By this method the migration aptitudes of the ethyl and *t*-butyl groups are determined from the product ratios (eq. 1 and 2) to be 3.4 and 72, respectively. These two processes differ by factors other than those inherent in the migrating group, however, the importance of β-substitution having been amply demonstrated[17] in rearrangements of the Wagner–Meerwein type.



VII



VIII

a, R = CH_3
b, R = C_2H_5
c, R = $t\text{-}C_4H_9$

We propose therefore to utilize *intermolecular* comparisons in describing the migration tendencies of substituents. A comparison of the rates of the process symbolized by VII for a series of pinacols should constitute a valid comparison of the different R groups.[18] In order to make these intermolecular comparisons one has to know the over-all rate of rearrangement of each pinacol, and the fraction (α) of the over-all process which involves migration of the dissimilar group. It is convenient to define a partial rate, k_p,

$$k_p = \alpha k \tag{3}$$

where k is the acidity-independent first-order rate constant,[19] k_{obs} is the observed first-order rate constant at a particular value of the Hammett acidity function h_0, and K_A is the acid dissociation constant of protonated pinacol.

$$k = k_{\text{obs}} K_A / h_0 \tag{4}$$

The migration tendency, M_{CH_3}, of any group R compared to methyl may then be expressed as the ratio of partial rates as in equation 5 where the superscripts identify

$$M_{CH_3} = \frac{k_p^R}{k_p^{CH_3}} = \frac{\alpha^R k_{\text{obs}}^R K_A^R h_0^{CH_3}}{\alpha^{CH_3} k_{\text{obs}}^{CH_3} K_A^{CH_3} h_0^R} \tag{5}$$

the migrating group. All of the quantities necessary to determine M_{CH_3} are readily measured except K_A. If it is assumed that K_A does not vary appreciably for a series of pinacols such as II, the migration tendency M_{CH_3} for the ethyl and *t*-butyl groups may be calculated to have the values shown in Table III. If values for individual dissociation constants, K_A, become available, a refinement in the calculation of M_{CH_3} will be possible.

TABLE III

MIGRATION TENDENCIES OF ALKYL GROUPS

Group	α	$10^5 k_p$, sec.$^{-1}$	M_{CH_3}
CH_3	0.25	0.19 K_A^{Me}	1.0
C_2H_5	0.57	3.2 K_A^{Et}	17
$t\text{-}C_4H_9$	0.99	>700 K_A^{tBu}	>4000

The inapplicability of the older migration aptitude formulation to aliphatic pinacols is illustrated by comparison of the rates of the processes symbolized by VIII. In the present series the relative values of the partial rates, k_p, for pinacols where R is methyl, ethyl and *t*-butyl are 1:4.7:54. Thus a non-migrating ethyl group in the β-position increases the rate of methyl migration by almost 5 times and a β-*t*-butyl group increases it more than 50-fold.

Reaction Mechanism.—The striking rate differences in the series IIa-IIc provide a strong argument for a mechanism in which bond formation between C_α and the migrating group occurs in a

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[15] M. Tiffeneau and A. Orekhoff, *Bull. soc. chim.*, **35**, 1639 (1924).

[16] Structures VII and VIII are intended only as symbols for R- and CH_3-migration and do not attempt to describe the transition state. It should be emphasized that the partial rates, k_p, described in this paper are not dependent upon any assumptions concerning the reaction mechanism except the acidity dependence described by equation 4.

[17] S. Winstein, C. R. Lindegren, H. Marshall and L. L. Ingraham, THIS JOURNAL, **75**, 147 (1953).

[18] It should be pointed out that while this comparison is a much better measure of the migration tendency than the earlier one, it still neglects possible second-order differences between VIIa, b, and c due to variation in the extent of positive character of C_β as R is varied; this variation would result in different degrees of interaction between C_β and the non-migrating group.

[19] This acidity dependence has been demonstrated rigorously only in the rearrangement of pinacol[20–23] in aqueous acids, and benzopinacol in acetic–perchloric acid mixtures.[24] We made no effort to establish this acidity dependence in the present work, but it may be noted that the data for glycol IIb are reasonably consistent ($-\Delta \log k/\Delta H_0 = 0.86$) with this formulation and not with other likely dependences.

[20] J. F. Duncan and K. R. Lynn, *J. Chem. Soc.*, 3512 (1956).

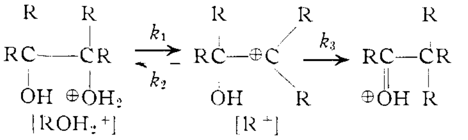
[21] J. B. Ley and C. A. Vernon, *ibid.*, 2987 (1957).

[22] N. C. Deno and C. Perizzolo, *J. Org. Chem.*, **22**, 836 (1957).

[23] C. A. Bunton, T. Hadwick, D. R. Llewellyn and Y. Pocker, *J. Chem. Soc.*, 403 (1958).

[24] H. J. Gebhart, Jr., and K. H. Adams, THIS JOURNAL, **76**, 3925 (1954).

slow step. This conclusion, when considered in the light of the acidity dependence for the rearrangement, indicates that the carbonium ion mechanism (eq. 6) frequently proposed[21,23,25] is inadequate.



(6)

If one assumes a "steady state" concentration of the carbonium ion, the observed rate of rearrangement can be expressed as in equation 7 where the brackets denote concentration, f_i is the activity co-

$$v = \frac{k_1k_3[\mathrm{ROH_2}^+](f_{\mathrm{ROH_2^+}}f_{\mathrm{R^+}}/f_{\mathrm{X_1}}f_{\mathrm{X_2}})}{k_2[\mathrm{H_2O}](f_{\mathrm{R^+}}f_{\mathrm{H_2O}}/f_{\mathrm{X_1}}) + k_3(f_{\mathrm{R^+}}/f_{\mathrm{X_2}})} \qquad (7)$$

efficient of species i, referred to dilute aqueous solution, and X_1 and X_2 refer to the transition states for the formation and decomposition of R^+. The limiting case where $k_2[\mathrm{H_2O}](f_{\mathrm{R+}}f_{\mathrm{H_2O}}/f_{\mathrm{X_1}}) << k_3(f_{\mathrm{R+}}/f_{\mathrm{X_2}})$ is eliminated since the rate equation then reduces to 8, which, though consistent with the de-

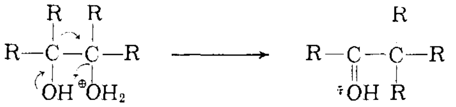
$$v = k_1[\mathrm{ROH_2}^+](f_{\mathrm{ROH_2^+}}/f_{\mathrm{X_1}}) \qquad (8)$$

pendence on H_0, predicts no dependence on the rearrangement step k_3.[26] The other limiting case, where $k_2[\mathrm{H_2O}](f_{\mathrm{R+}}f_{\mathrm{H_2O}}/f_{\mathrm{X_1}}) >> k_3(f_{\mathrm{R+}}/f_{\mathrm{X_2}})$ leads to 9, which predicts[27]

$$v = (k_1k_3/k_2)[\mathrm{ROH_2}^+](f_{\mathrm{ROH_2^+}}/a_{\mathrm{H_2O}}f_{\mathrm{X_2}}) \qquad (9)$$

a dependence of the rate upon C_0 rather than H_0. If the two terms in the denominator of eq. 7 are comparable then the dependence should be intermediate between the two acidity functions. All kinetic results so far reported[20-24] indicate a strict H_0 dependence.[28] It would thus appear that equation 6 fails to account for the data at hand regardless of the relative rates of the various steps.

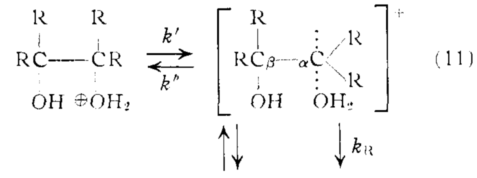
The large rate enhancement provided by groups which are demonstrably more prone to migrate than methyl groups, and the dependence of the the rearrangement upon the stereochemistry of the pinacol,[8,30,31] both point to a mechanism in which the removal of water from the protonated pinacol is anchimerically assisted by the migrating alkyl group.[32] The acidity dependence is consistent with the idea that this process (eq. 10) is the kinetically measurable one.



(10)

However this picture needs modification in view of recent experiments by Bunton, Hadwick, Llewellyn and Pocker.[23] These investigators found that pinacol which was recovered from an interrupted rearrangement reaction had partially exchanged its oxygen with that of the solvent, O^{18}-enriched water. Except for the seemingly remote possibility that the exchange reaction is a bimolecular attack of a water molecule upon the conjugate acid,[33] it would involve intermediates which need to be considered in any mechanism for the rearrangement. The simple carbonium ion, for example, would be expected to rearrange at least as readily as the conjugate acid, and therefore cannot be excluded from the rearrangement mechanism without exclusion from the exchange reaction also.

It is possible that pinacol (IIa) rearranges both by a carbonium ion path (eq. 6) and a concerted path (eq. 10), the former being responsible for the oxygen exchange. The enhanced rates of IIb and IIc would indicate complete dominance by the latter mechanism in these cases. However the importance of anchimeric assistance in ionizations at a tertiary carbon atom remains in doubt at present, and for this reason the mechanism represented by eq. 11 is favored. In this mechanism both rearrangement and oxygen exchange are preceded by the formation of a "carbonium hydrate." This intermediate is pictured as containing the original H_2O bound by a p-orbital to C_α, and is essentially that proposed by Doering and Zeiss[34] for solvolytic reactions. It is structurally analogous to an "intimate ion pair."[35] The rearrangement process (k_R) involves a backside displacement of the water molecule by a neighboring R group, similar to the process of eq. 10, except that the attack is upon a carbon atom whose geometry and hybridization make it considerably more vulnerable to such displacement than the conjugate acid of pinacol would be.



(11)

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[25] F. A. Long and M. A. Paul, *Chem. Revs.*, **57**, 975 (1957).

[26] A referee has pointed out the possibility that k_1 is highly sensitive to steric acceleration, which would increase in the series IIa–IIc, and that equation 8 is the correct rate equation. Steric strain would appear to be more effectively alleviated by the loss of the hydroxyl group from the carbon atom bearing the largest groups, however, and since this path is not observed with IIc and makes a minor (26%) contribution in the case of IIb, we think it unlikely that the observed rate differences are due to steric acceleration in carbonium ion formation. It should be kept in mind, however, that the relief of steric strain may be an important factor in the large migration tendency of the *t*-butyl group.

[27] N. C. Deno, J. J. Jaruzelski and A. Schriesheim, THIS JOURNAL, **77**, 3044 (1955).

[28] Evidence has recently been presented[13,29] to suggest that the applicability of the H_0 and C_0 functions to kinetic data depends on the structure of the intermediate ions and the transition state (X) in rather subtle ways, and that equality of empirical formula between X and $\mathrm{ROH_2}^+$ or R^+ may be only one of several factors. However there seems to be general agreement[25,29] that a reaction such as eq. 7 (where $k_2 > k_3$) should follow C_0 more closely than H_0.

[29] N. C. Deno and C. Perizzolo, THIS JOURNAL, **79**, 1345 (1957).

[30] P. D. Bartlett and R. F. Brown, *ibid.*, **62**, 2927 (1940).

[31] E. R. Alexander and D. C. Dittmer, *ibid.*, **73**, 1665 (1951).

[32] S. Winstein and L. L. Ingraham, *ibid.*, **77**, 1738 (1955), have discussed the various possibilities for anchimeric assistance in the pinacol rearrangement.

[33] Such a mechanism was proposed [N. C. Deno, T. Edwards, and C. Perizzolo, *ibid.*, **79**, 2108 (1957)] for the exchange between tertiary butyl and secondary butyl alcohols and water. In the pinacol case, however, it seems highly unlikely in view of the "neopentyl" character of the carbon undergoing substitution.

[34] W. E. Doering and H. Zeiss, *ibid.*, **75**, 4733 (1953); see also the discussion by A. Streitwieser, *Chem. Revs.*, **56**, 571 (1956).

[35] S. Winstein, E. Clippinger, A. H. Fainberg and G. C. Robinson, THIS JOURNAL, **76**, 2597 (1954).

The dissociation–rearrangement mechanism represented by eq. 11 is analogous to the Wagner Meerwein rearrangements which accompany many solvolytic reactions, but at least one important difference should be mentioned. The driving force for rearrangement is normally much greater in the pinacol case, due to the stabilization provided by the incipient carbonyl group. Thus, even though the dissociation takes place at a tertiary carbon atom, rearrangement occurs at a relatively early stage, while the water molecule is still weakly bonded to C_α.

If one assumes a "steady-state" approximation for the mechanism of eq. 11, the rate is given by

$$v = \frac{k_R k'[ROH_2^+]}{k'' + k_R} \tag{12}$$

provided the Hammett–Zucker hypothesis is assumed to apply to both steps. In order to explain the observed variation of the rate in the series IIa-IIc, k'' must be much larger than k_R, at least for the first two compounds in the series.

The exchange of water between the carbonium hydrate and the solvent might occur either by a direct displacement reaction between a solvent water molecule and the intermediate, which would invert the configuration of C_α, or by participation of the neighboring hydroxyl group to give an intermediate similar to the protonated epoxide. No data are at hand to distinguish between these two possibilities although clarifying stereochemical experiments can be envisaged.

The intervention of carbonium hydrate intermediates similar to the one in eq. 11 serves also to explain several recently investigated reactions which otherwise exhibit contradictory kinetic and stereochemical features. Noteworthy are the exchange of O^{18} between 2-butanol and aqueous acid,[36] which exhibits complete stereochemical inversion, apparently without kinetic dependence upon water, and the acid-catalyzed opening of substituted ethylene oxides[37] which also occurs by inversion without kinetic dependence on the nucleophile. In these two cases the carbonium hydrate must be attacked by a solvent molecule more rapidly than it collapses to form the conjugate acid of the substrate. The ratio of the two processes is thus essentially the inverse of that postulated for the pinacol intermediate. This difference follows from the much greater steric hindrance to backside attack upon the more highly branched intermediate from pinacol.

Experimental

Pivalic Acid-carboxyl-C^{14} was prepared in 63% yield by the carbonation of *t*-butyllithium[38a] (prepared from 0.75 mole of *t*-butyl chloride and 1.64 g. atom of lithium[38b]) with carbon dioxide generated from 2.6 g. (0.0132 mole, 15 microcuries) of labeled barium carbonate-C^{14}. The radioactive carbon dioxide was swept into the reaction flask with ordinary carbon dioxide, and sufficient of the latter was then added until the *t*-butyllithium had reacted completely. The acid distilled at 160–161° and solidified at room temperature (reported[39] b.p. 162–165°, m.p. 34–35°).

Pivalyl Chloride-carbonyl-C^{14}.—Treatment of 10.5 g. (0.103 mole) of labeled pivalic acid with 15 ml. of thionyl chloride under reflux for 3 hr., followed by distillation through a 35-cm. tantalum-spiral column, yielded 6.9 g. (53%) of the acid chloride, b.p. 100–103° (reported[40] b.p. 103–104°).

Pinacolone-Carbonyl-C^{14}.—A solution of dimethylcadmium was prepared by the addition of 20.0 g. (0.11 mole) of cadmium chloride to methylmagnesium iodide prepared from 0.20 mole of magnesium and 0.20 mole of methyl iodide. The solvent ether was replaced by benzene and 6.9 g. (0.057 mole) of labeled pivalyl chloride in 50 ml. of benzene was added during 5 min. After a further 20 min. at reflux the solution was hydrolyzed with dilute hydrochloric acid. The organic layer was washed with 5% sodium hydroxide and dried over sodium sulfate. Removal of most of the solvent yielded a product which was shown by its infrared spectrum to be essentially pure pinacolone. Since the yield was low (*ca.* 10%) and separation from the benzene rather difficult on this small scale, the crude labeled ketone was diluted with 5.0 g. of unlabeled pinacolone and the diluted material was carefully fractionated through a 35-cm. tantalum-spiral column. The purified material weighed 3.0 g., b.p. 100–103° (reported[41] 105° (746 mm.)).

Methyl Trimethylpyruvate-carbonyl-C^{14}.—Labeled pinacolone (3.0 g., 0.030 mole) was oxidized with alkaline permanganate as described by Glucksmann.[42] The crude labeled trimethylpyruvic acid was treated with an etheeral solution of diazomethane, prepared from 8.0 g. (0.078 mole) of nitrosomethylurea.[43] Distillation through a short column gave 2.35 g. (54% based on ketone) of the labeled ester, b.p. 60–64° (16 mm.); ν_{CCl_4} 1740, 1720 (reported[44] b.p. 160–162° (atm.), 69–70° (20 mm.)).

In a larger unlabeled preparation the intermediate trimethylpyruvic acid was purified to give a 50% yield of material, b.p. 70–74° (10 mm.); ν_{CCl_4} 2980 (broad), 1785 and 1715 (reported[42] b.p. 85° (20 mm.)).

2,3,4,4-Tetramethyl-2,3-pentanediol-3-C^{14} (IIc).—An ethereal solution of methyllithium, prepared from 4.5 g. (0.65 mole) of lithium and 62.0 g. (0.43 mole) of methyl iodide, was cooled in an ice-bath and 2.35 g. (0.0162 mole) of labeled methyl trimethylpyruvate in 25 ml. of anhydrous ether was added over a 10-min. period. The solution was refluxed for 2.5 hr. and then hydrolyzed by the slow careful addition of 150 ml. of water. In order to avoid rearrangement, the solution was not acidified. The ether layer was extracted with 100 ml. of water, the combined water layer was extracted with 50 ml. of ether, and the combined ether layer was dried over sodium sulfate. Removal of solvent and distillation of the residue through a short column gave 1.95 g. (75%) of the labeled glycol, b.p. 100–104° (17 mm.); ν_{CCl_4} 3600, 3520, 3440, 2980, 1485, 1385, 1350, 1220, 1180, 1105, 1075, 1015, 960, 910 and 840 cm.$^{-1}$, which solidified in the refrigerator (reported b.p. 98–100° (17 mm.),[45] m.p. 22°,[45] 27°[46]).

Rearrangement of the Labeled Glycol IIc.—A sample of 2,3,4,4-tetramethyl-2,3-pentanediol-3-C^{14} (1.95 g., 0.0121 mole) was added to 20 ml. of 50% sulfuric acid in a separatory funnel and the mixture was shaken intermittently for 10 min. at room temperature. The ketone layer which separated weighed 1.35 g. (78%). The infrared spectrum of the product of rearrangement of an unlabeled sample of the glycol was nearly identical with that of 3,3,4,4-tetramethylpentan-2-one (IIIc) prepared as described previously.[47] However the former sample was shown by vapor-phase chro-

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[36] C. A. Bunton and D. R. Llewellyn, *J. Chem. Soc.*, 3402 (1957).

[37] J. G. Pritchard and F. A. Long, THIS JOURNAL, **78**, 2667 (1956); see the discussion by F. A. Long and M. A. Paul, *Chem. Revs.*, **57**, 961 (1957).

[38] (a) P. D. Bartlett and E. B. Lefferts, THIS JOURNAL, **77**, 2804 (1955). (b) The lithium contained 1–2% sodium, which had been added to the melt in preparing lithium sand. Several attempts to prepare *t*-butyllithium from "sodium-free" lithium failed.

[39] S. V. Puntambeker and E. A. Zoellner, "Organic Syntheses," Coll. Vol. I, John Wiley and Sons, Inc., New York, N. Y., 1941, p. 524.

[40] H. C. Brown, *ibid.*, **60**, 1325 (1938).

[41] F. C. Whitmore, C. I. Noll and V. C. Meunier, *ibid.*, **61**, 683 (1939).

[42] C. Glucksmann, *Monatsh.*, **10**, 770 (1889).

[43] F. Arndt, "Organic Syntheses," Coll. Vol. II, John Wiley and Sons, Inc., New York, N. Y., 1943, p. 461.

[44] A. Richard, *Ann. chim.*, [8] **21**, 360 (1910).

[45] W. J. Hickinbottom, A. A. Hyatt and M. B. Sparke, *J. Chem. Soc.*, 2533 (1954).

[46] R. Locquin and W. Sung, *Compt. rend.*, **176**, 682 (1923).

[47] P. D. Bartlett and R. M. Stiles, THIS JOURNAL, **77**, 2806 (1955).

matographic separation[48] at 106° to contain IIIc and hexamethylacetone (IVc) in a ratio of (73 ± 5) to 1. In addition a small fraction (5%, assuming comparable thermal conductivity), which was assumed to be unsaturated hydrocarbon, was eluted before the ketones.

Oxidation of the Methyl Ketone IIIc.—The crude methyl ketone IIIc (1.35 g.) was added to a potassium hypochlorite solution, prepared from 20.0 g. of calcium hypochlorite, 14.0 g. of potassium carbonate and 4.0 g. of potassium hydroxide. The mixture was stirred and heated at 75° for 38 hr. Ten grams of potassium hydroxide was added and stirring and heating at reflux was continued for 10 hr. more. The aqueous solution was cooled, extracted twice with 25 ml. of ether, and acidified with concentrated hydrochloric acid. The precipitated acid was collected by filtration, dissolved in hot 40–60° petroleum ether, filtered from inorganic salts, and concentrated. Upon cooling there was obtained 0.60 g. (44%) of *t*-butyldimethylacetic acid (Vc), m.p. 194–196° (reported m.p. 198–199°,[47] m.p. 200°[10]). A 6.2-mg. sample of this acid spread over an area of 2 cm.^{2} gave 90 counts per minute above background (14.5 c./min./mg. or 2080 c./min/mmole) measured in a windowless, gas-flow Geiger–Muller counter.

Hofmann Degradation of the Labeled Acid.-A sample (0.55 g.) of the *t*-butyldimethylacetic acid (Vc) obtained in the foregoing experiment was converted to the acid chloride[47] and thence to the amide by treatment of an ethereal solution with anhydrous ammonia. The over-all yield was 0.40 g. (73%) of *t*-butyldimethylacetamide, m.p. 197–199°; ν_{Nujol} (of an unlabeled sample) 3400, 3180, 1675 cm.$^{-1}$ (reported[10] m.p. 200°).

A solution of sodium methoxide (prepared from 0.5 g. of sodium metal) was cooled in ice and 0.40 g. (0.0027 mole) of *t*-butyldimethylacetamide was added, followed by 0.4 ml. of bromine. After standing 5 min. in the ice-bath, the solution was refluxed 15 min. on the steam-bath. The solution was cooled, 25 ml. of water was added, and the mixture was extracted three times with 25-ml. portions of ether. The ether was evaporated, leaving the crude carbamate which solidified upon cooling. It was dissolved in 40–60° petroleum ether and dried, and the solution was concentrated to 1 ml., cooled and filtered, giving 0.38 g. (82%) of labeled **methyl N-(2,3,3-trimethyl-2-butyl)-carbamate**, m.p. 63–65°; ν_{Nujol} (of an unlabeled sample) 3350, 2920, 1735, 1530, 1460, 1405, 1375, 1260, 1220, 1190, 1160, 1090, 970 and 770 cm.$^{-1}$.

Anal. Calcd. for $C_9H_{19}NO_2$: C, 62.39; H, 11.06; N, 8.09. Found (for an unlabeled sample): C, 62.52; H, 11.25; N, 8.17.[49]

A 100-ml. 3-necked flask was swept with nitrogen, 0.38 g. (0.0022 mole) of the labeled carbamate in 10 ml. of methyl alcohol was added, followed by 10 ml. of 50% carbonate-free sodium hydroxide, and the solution was refluxed for 8 hr., while protected from atmospheric carbon dioxide. The solution was cooled in an ice-bath and the top of the reflux condenser was connected to a fritted glass sparger immersed in a 100-ml. solution of *N* carbonate-free sodium hydroxide. Concentrated hydrochloric acid, 35 ml., was added slowly from a dropping funnel to the hydrolysis solution and carbon dioxide-free air was sucked through the system to sweep the liberated carbon dioxide into the alkali. The acidified hydrolysis solution was boiled and flushed in this way for 10 min. The sodium hydroxide solution was then treated with 5.35 g. (0.1 mole) of ammonium chloride followed by 25 ml. of a 30% solution of barium chloride (0.0375 mole). After standing 5 min., the solution was filtered through a dry, weighed, sintered-glass funnel and the precipitate was washed 3 times with distilled water and dried 3 hr. at 115°, to give 0.435 g. (100%) of labeled barium carbonate. A 7.6-mg. sample spread over approximately 2 sq. cm., gave 77 c./min. above background or 10.1 c./min./mg. of barium carbonate (2,010 c./min./mmole) (96% of the C^{14} labeling).

The acidified hydrolysis solution was covered with a 50-ml. layer of ether and neutralized with 25% sodium hydroxide. The ether layer was separated and the aqueous solution was extracted twice more with 25-ml. portions of ether. The amine was purified by extraction into aqueous acid, followed by neutralization and re-extraction with ether. The ether solution of the purified material was dried over potassium hydroxide and then treated with hydrogen chloride to precipitate the labeled **2-amino-2,3,3-trimethylbutane hydrochloride (VIc)**. The amine salt was collected and dried at room temperature to give 0.30 g. (90% yield) of material which sublimed at 320°; ν_{Nujol} 2900, 2100, 1630, 1530, 1480, 1425, 1405, 1395, 1295, 1210 and 1170 cm.$^{-1}$.

Anal. Calcd. for $C_7H_{18}NCl$: C, 55.42; H, 11.96; N, 9.24; Cl, 23.38. Found (for an unlabeled sample): C, 55.14; H, 11.86; N, 9.17; Cl, 23.24.[49]

A 21.7-mg. portion spread over approximately 2 sq. cm. gave a total of 74 c./min. compared with the background of 76 c./min., counting both for a 30-min. interval. With a standard deviation of 2 c./min. or 0.09 c./min./mg. of amine hydrochloride (14 c./min./mmole), the C^{14}-labeling of the acid precursor was 0.0± 0.7% in the amine hydrochloride.

2-Methyl-2-hydroxybutanoic acid-1-C^{14} was prepared by the procedure of Young, Dillon and Lucas.[50] An unlabeled batch distilled at 125–128° (17 mm.), m.p. 70–72° (reported b.p. 133–134° (16 mm.),[14] m.p. 72.5°[50]). The labeled material was not distilled but was converted directly to the ester.

Methyl 2-Methyl-2-hydroxybutanoate-1-C^{14}.—The unlabeled acid reacted with ethereal diazomethane to produce the ester, b.p. 146–150° (reported[14] b.p. 151–152°), in 80% yield; ν_{CCl_4} 3520, 2980, 1735, 1470, 1440, 1385, 1250, 1180, 1050, 990 and 940 cm.$^{-1}$. The ether solution of the labeled ester was dried and used directly in the next step.

2,3-Dimethyl-2,3-pentanediol-2-C^{14} (IIb).—An ether solution of methyl 2-methyl-2-hydroxybutanoate-1-C^{14}, prepared from 8 g. (0.0678 mole) of the acid, was treated with an ether solution of methyllithium, prepared from 8.5 g. (1.21 g.-atoms) of lithium and 91 g. (0.65 mole) of methyl iodide, for 3 hr. at reflux. The mixture was worked up without acidification and the product distilled through a 10-cm. Vigreux column to yield 7.1 g. (79%) of the glycol, b.p. 88–91° (16 mm.) (reported[14] 94–95° (21 mm.)); ν_{CCl_4} (of an unlabeled sample) 3440, 2980, 1470, 1390, 1375, 1275, 1150, 1105, 1045, 1005, 955, 920 and 680 cm.$^{-1}$.

Rearrangement of the Glycol IIb.—The labeled glycol, 7.1 g., was added to 100 ml. of 50% sulfuric acid which had been cooled to 5°. The mixture was stirred for 6 hr. at room temperature, added to approximately 100 g. of ice and extracted three times with 50-ml. portions of ether. The organic layer was washed with 50 ml. of 5% sodium carbonate, dried over sodium sulfate, and evaporated to yield 4.8 g. of crude labeled ketones.

Distillation of an unlabeled batch through a 10-cm. Vigreux column gave a fraction, b.p. 125–132°, whose infrared spectrum was nearly identical with that of authentic methyl *t*-amyl ketone (IIIb) containing 15% ethyl *t*-butyl ketone (IVb). Gas chromatographic separation[48] of an unlabeled batch indicated the ratio of IIIb to IVb to be (4.9 ± 0.3) to 1.0. No other compound was found in significant quantity.

Oxidation of the Mixture of Labeled Ketones IIIb and IVb.—The undistilled, labeled ketones, 4.8 g., from the glycol rearrangement were placed in 240 ml. of hypochlorite solution prepared from 40 g. of calcium hypochlorite. The mixture was heated at 75° in a water-bath and stirred for a 12-hr. period. Ten grams of potassium hydroxide was added and the solution was refluxed for 4 hr. The solution was cooled and worked up in the usual manner to yield 3.6 g. of crude labeled ethyldimethylacetic acid (Vb). The small amount of pivalic acid present as a contaminant was not detected in the infrared spectrum.

Hofmann Degradation of the Acid Vb.—The crude labeled ethyldimethylacetic acid was added to 10 ml. of thionyl chloride and the mixture was refluxed for 4 hr. under a cold finger condenser. The mixture was cooled in an ice-bath, 100 ml. of anhydrous ether was added, ammonia gas was bubbled in until the solution was saturated and the mixture was allowed to stand for 2 hr. Ammonium salts and unreacted acid were removed by extraction and the crude amide

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(48) The apparatus used for the separations in this paper is described by K. Burgess, Thesis, University of Michigan, 1957. The ketone mixtures were separated on a column of 30–60 mesh firebrick coated with silicone grease. The amine mixtures were separated on a column of 30–60 mesh Celite which had been coated first with potassium hydroxide, then with mineral oil [*cf.* A. T. James, A. J. Martin and G. H. Smith, *Biochem. J.*, **52**, 238 (1952)]. Helium was used as a carrier and the exit gas was analyzed by thermal conductivity measurements. In every case mixtures of known composition were analyzed to establish retention times and relative thermal conductivities.

(49) Spang Microanalytical Laboratory, Ann Arbor, Mich.

(50) W. G. Young, R. T. Dillon and H. J. Lucas, THIS JOURNAL, **51**, 2528 (1929).

was recrystallized from petroleum ether to yield 0.80 g. of labeled **ethyldimethylacetamide**, m.p. 103–104° (reported[51] m.p. 103–104°).

Plates of varying thickness, spread over a uniform area, were made so that the specific activity could be evaluated for an infinitely thin plate. The amide gave 38.0 c./min./mg. (4380 c./min./mmole) above background of 70 c./min., extrapolated to zero thickness.

The labeled ethyldimethylacetamide, 0.7 g., was rearranged to the carbamate ester using the procedure described for the amide from Vc. In this case the carbamate ester did not crystallize. It was hydrolyzed and decarboxylated as described above to give 0.25 g. (33%) of ***t*-amylamine hydrochloride (VIb)**, m.p. 229–231°, and 0.76 g. (63%) of barium carbonate (yields based on the amide).

Anal. Calcd. for $C_5H_{14}NCl$: C, 48.57; H, 11.42; N, 11.33; Cl, 28.68. Found (unlabeled duplicate sample): C, 48.42; H, 11.57; N, 11.44; Cl, 28.58.[49]

The picrate melted at 180–182° (reported[52] 182–183°).

Anal. Calcd. for $C_{11}H_{16}N_4O_7$: C, 41.77; H, 5.10; N, 17.72. Found (unlabeled duplicate sample): C, 41.76; H, 5.11; N, 17.81.[49]

Both the *t*-amylamine hydrochloride and the barium carbonate were radioactive. Plates of varying thickness were made from portions spread over a uniform area so that the specific activity could be evaluated for an infinitely thin plate. The amine salt gave 23.5 c./min./mg. (2900 c./min./mmole) and the carbonate gave 6.45 c./min./mg. (1270 c./min./mmole) above background of 70 c./min., extrapolated to zero thickness. The results were corrected for the 2.4% *t*-butylamine hydrochloride (*vide infra*), which had all the activity of the ethyl *t*-butyl ketone, and the 2.4% barium carbonate, which had none of the activity of the ethyl *t*-butyl ketone, to give 2870 c./min./mmole for *t*-amylamine hydrochloride and 1300 c./min./mmole for barium carbonate from the methyl *t*-amyl ketone.

Liberation of the labeled *t*-amylamine from its hydrochloride and subjection to vapor-phase chromatography[48] detected the presence of 2.4% *t*-butylamine as a contaminant.

Reference Compounds.—**Hexamethylacetone** (**IVc**) was prepared as described earlier.[47] **Methyl *t*-amyl ketone** (**IIIb**) was prepared in 61% yield by the reaction of ethyldimethylacetyl chloride[53] with dimethylcadmium according to the procedure described above for making pinacolone-carbonyl-C^{14}. The material distilled at 128–130°, n^{25}_D 1.4087 (reported b.p. 131.5–132.5°,[53] n^{20}_D 1.4100[54]); 2,4-dinitrophenylhydrazone, m.p. 111–112° (reported[54] 112°). **Ethyl-*t*-butyl ketone** (**IVb**) was prepared by the method of Whitmore, Noll and Meunier.[41] The product contained some unsaturated material, as indicated by its infrared spectrum. Treatment with dilute permanganate in acetone solution followed by redistillation gave a sample which was homogeneous as determined by vapor-phase chromatography, b.p. 120°, n^{20}_D 1.4025 (reported[41] b.p. 124.5°, n^{20}_D 1.4049–1.4052); 2,4-dinitrophenylhydrazone, m.p. 144–145° (reported[41] m.p. 143.5–144.5°). Pure samples of ***t*-butylamine and *t*-amylamine** were generated from the hydrochlorides which had been prepared by Hofmann degradation of the corresponding amides. The picrates melted at 196–198° (reported[52] 197–198°) and 178–181° (reported[58] 182–183°), respectively.

Kinetic Measurements.—Solutions of the glycols (0.03–0.1 molar) in aqueous sulfuric acid were prepared and stored at 25.0 ± 0.1°. Five-ml. samples were quenched periodically with 5 g. of ice, and extracted with 1.00 ml. of carbon tetrachloride. The carbon tetrachloride solutions were analyzed for total ketone content by infrared analysis, using the carbonyl absorption peak. Known mixtures could be analyzed in this way with an error of less than 5%. The first-order rate constants were determined graphically.

Acknowledgment.—The advice and coöperation of Professor W. W. Meinke in the radiochemical work is gratefully acknowledged.

ANN ARBOR, MICH.

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[51] A. Haller and E. Bauer, *Ann. chim.*, [9] **1**, 5 (1914).

[52] R. Brown and W. E. Jones, *J. Chem. Soc.*, 781 (1946).

[53] A. Wischnegradsky, *Ann.*, **178**, 103 (1875).

[54] F. C. Whitmore and C. E. Lewis, THIS JOURNAL, **64**, 2964 (1942).

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY AND THE LABORATORY FOR NUCLEAR SCIENCE, MASSACHUSETTS INSTITUTE OF TECHNOLOGY]

Cyclic Diacyl Peroxides. IV.[1,2] Phthaloyl Peroxide-*carbonyl*-O^{18}

BY FREDERICK D. GREENE

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Reaction of phthaloyl peroxide-*carbonyl*-O^{18} with *trans*-stilbene in carbon tetrachloride affords cyclic phthalate of *dl*-1,2-diphenylethanediol (I) in which 11% of the excess oxygen-18 is located at alkyl oxygen. The same distribution of oxygen-18 in cyclic phthalate is obtained from phthaloyl peroxide that has been subjected to 80° in carbon tetrachloride for four days prior to reaction with olefin. From these results it is concluded that equilibria between phthaloyl peroxide and any species in which a carbonyl oxygen atom becomes symmetrically located with respect to an oxygen of the oxygen–oxygen link are unimportant. The bearing of the oxygen-18 results on the stability of phthaloyl peroxide and the relationship of the results to the reaction of phthaloyl peroxide with olefins are discussed.

Previous papers in this series[3,4] have focused attention on some of the marked differences between the behavior of the cyclic peroxide, phthaloyl peroxide and acyclic analogs such as benzoyl peroxide. These differences lie in three areas: in thermal stability, in sensitivity of rate to nature of the solvent, and in reactivity toward carbon–carbon unsaturation. This paper reports the results of some experiments utilizing phthaloyl peroxide labeled with oxygen-18 which aid in delineation of the above differences.

Results

Phthaloyl peroxide containing excess oxygen-18 in the carbonyl oxygen atoms was prepared from labeled phthaloyl chloride. Subjection of phthaloyl chloride to water enriched in oxygen-18 (1.4 atom per cent. enrichment) for an extended reflux period afforded phthalic acid of approximately 1.2 atom per cent. oxygen-18 at each oxygen atom.[5] The phthalic acid-O^{18} was converted to phthaloyl chloride-O^{18}, which was con-

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[1] Part III, F. D. Greene and W. W. Rees, THIS JOURNAL, **80**, 3432 (1958).

[2] (a) This work was supported in part by the research program of the Atomic Energy Commission under Contract No. AT(30-1)-905. Reproduction is permitted for any purpose of the United States Government. (b) Presented before the Organic Division at the 134th Meeting of the American Chemical Society, Chicago, Ill., September, 1958.

[3] Part II, F. D. Greene, *ibid.*, **78**, 2250 (1956).

[4] Part I, F. D. Greene, *ibid.*, **78**, 2246 (1956).

[5] See M. L. Bender, R. R. Stone and R. S. Dewey, *ibid.*, **78**, 319 (1956), and D. B. Denney, *ibid.*, **78**, 590 (1956), for evidence on the slowness of the equilibration of carboxyl oxygen with water oxygen-18.