

[CONTRIBUTION OF THE CHEMISTRY DEPARTMENT, OHIO UNIVERSITY, ATHENS, OHIO]

## The Role of Hydrogen as a Migrating Group in the Pinacol Rearrangement

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RECEIVED OCTOBER 22, 1960

The rates of rearrangement of 2-methyl-1,2-propanediol, 2-methyl-1,2-propanediol-1-*d*<sub>2</sub>, 2-methoxy-2-methyl-1-propanol, 2-methoxy-2-methyl-1-propanol-1-*d*<sub>2</sub>, 2-methoxy-2-methyl-3-butanol and 2-methoxy-2-methyl-3-butanol-3-*d*, have been measured in aqueous perchloric acid. The initial ratio of hydrolysis to glycol and rearrangement of the methoxyalcohols has been determined. This information coupled with the kinetic isotope effects leads to a firm kinetic argument for the participation of hydrogen as a neighboring group and non-classical ion formation during the rearrangement.

In a previous study of the role of hydrogen as a migrating group in the pinacol rearrangement the rates of rearrangement of 2-methyl-2,3-butanediol and 2-methyl-2,3-butanediol-3-*d* were reported under various conditions of acidity and temperature.<sup>1</sup> Kinetic isotope effects of 1.6 to 1.8 were found, and it was shown that these values were independent of the acidity of the reaction medium but did decrease slightly with an increase of reaction temperature. Utilizing the kinetic expression for the pinacol rearrangement given by Bunton and co-workers<sup>2</sup> and other data taken from the literature, a case was built for the participation of hydrogen as a neighboring group in the ion-forming process, a non-classical hydrogen-bridged ion acting as the reaction intermediate.

In extending the above study we have now made a similar kinetic study of the rearrangement of 2-methyl-1,2-propanediol and 2-methyl-1,2-propanediol-1-*d*<sub>2</sub>. While the results of this study are presented in detail later on, it may be noted here that the isotope effect in this system is somewhat greater than that previously reported. Since the conclusions drawn in the original study necessitated certain assumptions regarding the relationships of various terms in the complex kinetic expression, this finding made it imperative that an experimental evaluation of these terms be carried out. To this end we have now made measurements on the rates of hydrolysis and rearrangement of 2-methoxy-2-methyl-1-propanol, 2-methoxy-2-methyl-1-propanol-1-*d*<sub>2</sub>, 2-methoxy-2-methyl-3-butanol and 2-methoxy-2-methyl-3-butanol-3-*d*. The results and conclusions drawn from this study are also presented below.

### Experimental

**Preparation of 2-Methyl-1,2-propanediol and 2-Methyl-1,2-propanediol-1-*d*<sub>2</sub>.**—A solution of 20 g. of 2-hydroxy-2-methylpropionic acid in 150 ml. of ether was reduced with 11 g. of lithium aluminum hydride following the procedure previously given.<sup>1</sup> The yield of 2-methyl-1,2-propanediol was 6.02 g. (34.5%), b.p. 76° (10 mm.) (reported<sup>3</sup> b.p. 74° (10 mm.)).

In a similar fashion, 8.0 g. of the hydroxyacid was reduced with 3.3 g. of lithium aluminum deuteride<sup>4</sup> in 50 ml. of ether; yield 1.05 g. (15%), b.p. 74–75° (10 mm.). The infrared spectrum of this compound showed two bands characteristic of C–D absorption at 2110 and 2210 cm.<sup>-1</sup>.

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(1) W. B. Smith, R. E. Bowman and T. J. Kmet, *J. Am. Chem. Soc.*, **81**, 997 (1959).

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

(3) J. B. Ley and C. A. Vernon, *ibid.*, 2897 (1957).

(4) Metal Hydrides, Inc., Beverly, Mass.

**Preparation of 2-Methoxy-2-methyl-1-propanol and 2-Methoxy-2-methyl-1-propanol-1-*d*<sub>2</sub>.**—Acetone–chloroform was prepared by the method of Weizmann, Bergmann and Schulzbacker<sup>5</sup> and converted to 2-methoxy-2-methylpropionic acid, b.p. 98–99° (20 mm.) (reported<sup>6</sup> b.p. 98–99° (20 mm.)).

The reduction of the methoxyacid was carried out as previously described.<sup>1</sup> From 10 g. of the methoxyacid, reduced with 2 g. of lithium aluminum hydride or deuteride, one could obtain 2.5 g. of 2-methoxy-2-methyl-1-propanol or 2-methoxy-2-methyl-1-propanol-1-*d*<sub>2</sub>, respectively, b.p. 49.5–49.9° (20 mm.). 2-Methoxy-2-methyl-1-propanol was analyzed.

*Anal.*<sup>7</sup> Calcd. for C<sub>5</sub>H<sub>12</sub>O<sub>2</sub>: C, 57.66; H, 11.62. Found: C, 57.95; H, 11.71.

**The Preparation of 2-Methoxy-2-methyl-3-butanol and 2-Methoxy-2-methyl-3-butanol-3-*d*.**—A sample (34 g.) of carefully distilled 2-hydroxy-2-methyl-3-butanone (Air Reduction Co.) was treated with methyl iodide and dilute potassium hydroxide according to the directions of Nazarov and Elizarova.<sup>8</sup> In order to avoid impurities which were carried through later steps and interfered with the kinetic determinations, the product was carefully distilled through a Minical column; b.p. 122°, *n*<sub>D</sub><sup>25</sup> 1.4000 (reported<sup>9</sup> b.p. 124–127°, *n*<sub>D</sub><sup>18</sup> 1.4100).

When 2.7 g. of this material was reduced with lithium aluminum hydride (1 g.) and the product worked up in the usual fashion, one obtained upon distillation through a Minical column 2.6 ml. of 2-methoxy-2-methyl-3-butanol, b.p. 138–141°, *n*<sub>D</sub><sup>25</sup> 1.4200.

*Anal.* Calcd. for C<sub>6</sub>H<sub>14</sub>O<sub>2</sub>: C, 60.98; H, 11.94. Found: C, 60.81; H, 11.72.

Similarly, the reduction of 3.8 g. of 2-methoxy-2-methyl-3-butanone with 1.8 g. of lithium aluminum deuteride gave 2.7 ml. of 2-methoxy-2-methyl-3-butanol-3-*d*, b.p. 140–141°, *n*<sub>D</sub><sup>25</sup> 1.4200.

**Kinetic Runs.**—The kinetics of the rearrangement of the above compounds were determined in 1.2 *M* perchloric acid at 72.9° by the sealed ampoule technique as previously described.<sup>1</sup> The rate of formation of the carbonyl compounds was followed by measuring the absorbance of the 274 mμ band on a Beckman DU spectrophotometer. The  $\epsilon_{\max}$  for isobutyraldehyde was determined as 15.21, and  $\epsilon_{\max}$  for methyl isopropyl ketone was taken as 30.5.<sup>1</sup>

The data for the rate of appearance of the carbonyl compounds from the glycols was fitted to the first-order rate equation by means of the usual least squares method. The theoretical value of the final concentration was used in all calculations. Three or more determinations were made for each glycol. The reaction was followed to 60–90% completion in each case. The rates of rearrangement and the kinetic isotope effect for 2-methyl-1,2-propanediol and 2-methyl-1,2-propanediol-1-*d*<sub>2</sub> are given in Table I.

For the reactions of the methoxyalcohols the material in each ampoule was divided into two portions. The first was analyzed for carbonyl content as described above. An aliquot was taken from the second portion and added to a standard solution of metaperiodic acid in dilute acetic acid. A blank of the reagent was set aside at the same time. After 1 hour in the dark an excess of potassium iodide

(5) C. Weizmann, E. Bergmann and M. Schulzbacker, *J. Am. Chem. Soc.*, **70**, 1189 (1948).

(6) C. Weizmann, M. Schulzbacker and E. Bergmann, *ibid.*, **70**, 1153 (1948).

(7) Microanalysis by Galbraith Laboratories, Knoxville, Tenn.

(8) I. N. Nazarov and A. N. Elizarova, *Bull. acad. U. S. S. R.*, 303 (1940).

solution was added to each and the liberated iodine was titrated with standard sodium thiosulfate. The amount of glycol present was then calculated. Preliminary experiments revealed that the methoxyalcohols did not react with the reagent under these conditions. At least three runs were made for each of methoxyalcohols except for 2-methoxy-2-methyl-3-butanol-3-*d* where only enough starting material was available for two runs. Six to eight points were taken in each run. The reactions were followed to 40–60% completion. Beyond this point the curves for the appearance of glycol and carbonyl compound could not be adequately fitted to the second-order equations given below.

The data for the formation of glycol and carbonyl compounds from each of the methoxyalcohols was fitted by the method of least squares to an equation of the type

$$[\% \text{ compound}] = at + bt^2$$

By virtue of the fact that the same initial concentration was used for each methoxyalcohol, all of the data for a given starting compound could be computed at once. Thus, sixteen to twenty-four points were used in each calculation. The equations for each case were determined in this fashion to be

Compound	[% Glycol]	[% Carbonyl]
III	$5.443t - 0.299t^2$	$2.118t + 0.053t^2$
IV	$3.501t - .083t^2$	$1.364t - .032t^2$
VII	$4.080t - .266t^2$	$3.321t - .061t^2$
VIII	$2.366t - .041t^2$	$2.051t - .082t^2$

The numbers here refer to the compounds as listed in Table I. As set forth in the discussion, the initial rates of formation of the hydrolysis and rearrangement products are given by the values of  $a$  in each case. This can readily be seen by differentiating the equation with respect to  $t$  and setting  $t = 0$ . The quality of the data may be judged by the fact that in no case did the least squares probable error in  $a$  exceed  $\pm 5\%$ .

The rate of disappearance of the methoxyalcohols was determined by computing the concentration of methoxyalcohol at various times from the curves determined above  $[\% \text{ methoxyalcohol}] = 100 - [\% \text{ glycol}] - [\% \text{ carbonyl}]$ . The disappearance of methoxyalcohol, computed in this fashion, was a clean-cut first-order process. The rate constants for the disappearance of the various methoxyalcohols are also given in Table I.

TABLE I  
RATE DATA AND ISOTOPE EFFECTS IN 1.2 M PERCHLORIC ACID AT 72.9°

		$(\text{CH}_3)_2\text{CR}'$   OR				
R	Compound R'	$k \times 10^4$ sec. <sup>-1</sup>	$k^H/k^D$	$k_{-2}/k_1$	$k_1/k_2$ ( $k_{-2}/k_3$ ) +	
I	H CH <sub>2</sub> OH	$40.8 \pm 0.1^a$	2.14	..	..	
II	H CD <sub>2</sub> OH	$19.1 \pm 0.1$	..	..	..	
III	CH <sub>3</sub> CH <sub>2</sub> OH	$83.5^b$	1.52	2.57	0.28	
IV	CH <sub>3</sub> CD <sub>2</sub> OH	$54.8^b$	..	2.24	0.31	
V	H C(OH)HCH <sub>3</sub>	$37.2 \pm 0.2$	1.62 <sup>c</sup>	..	..	
VI	H C(OH)DCH <sub>3</sub>	$22.9^c$	..	..	..	
VII	CH <sub>3</sub> C(OH)HCH <sub>3</sub>	$75.4^b$	1.60	1.23	0.45	
VIII	CH <sub>3</sub> C(OH)DCH <sub>3</sub>	$47.0^b$	..	1.15	0.46	

<sup>a</sup> Average error of three or more runs. <sup>b</sup> Computed as indicated in the Experimental section from the composite date of three or more runs. <sup>c</sup> From the previously determined isotope effect at 75°.<sup>1</sup>

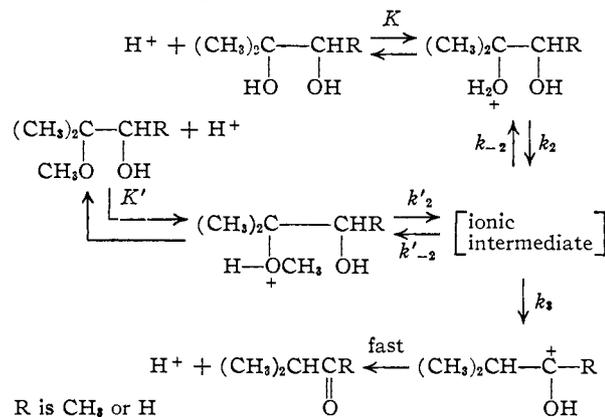
### Discussion

The rate constants and kinetic isotope effects for the pinacol rearrangement of 2-methyl-1,2-propanediol (I), 2-methyl-1,2-propanediol-1-*d*<sub>2</sub> (II), 2-methyl-2,3-butanediol (V) and 2-methyl-2,3-butanediol-3-*d* (VI) in 1.2 M perchloric acid at 72.9° are given in Table I. The observation that the isotope effect in the propanediol system was ca. 30% higher than observed in the butanediol system suggested the possibility that some of the

assumptions which we had made in our earlier study might be at fault.

In order to evaluate several of the unknown terms in the kinetic expression a study of the rates of hydrolysis and rearrangement of the appropriate methoxyalcohols was next undertaken. The behavior of 2-methoxy-2-methyl-1-propanol, as well as the other methoxyalcohols listed in Table I, was typical of a complex reaction sequence where one product is unstable. The methoxyalcohol was hydrolyzed rather rapidly at first to the corresponding glycol. The glycol concentration passed through a broad maximum after two to four hours reaction time and then slowly decreased. Simultaneously, part of the methoxyalcohol underwent a pinacol rearrangement to isobutyraldehyde. The concentration of aldehyde increased throughout the reaction until finally it was the sole product. The rates of appearance of the glycol and the aldehyde were related through equations of the type  $y = at + bt^2$ , where  $y$  is the concentration of either the glycol or the aldehyde. The values of  $a$  and  $b$  for the various methoxyalcohols utilized in this study are given in the Experimental section. From these curves the disappearance of the methoxyalcohols as a function of time was computed. The reactions of the methoxyalcohols in all cases followed clean-cut first-order kinetics. The rate constants for the disappearance of 2-methoxy-2-methyl-1-propanol (III), 2-methoxy-2-methyl-1-propanol-1-*d*<sub>2</sub> (IV), 2-methoxy-2-methyl-3-butanol (VII) and 2-methoxy-2-methyl-3-butanol-3-*d* (VIII) are given in Table I.

The kinetic scheme which may be applied both to the pinacol rearrangement of the glycols and to the hydrolysis and rearrangement of the methoxyalcohols may be generalized as



R is CH<sub>3</sub> or H

The terms here are the same as those used in the previous publication.<sup>1</sup>

The question of importance here is whether or not the ionic intermediate in the above scheme should be represented by a classical open carbonium ion or by a non-classical hydrogen-bridged ion.

The expressions for the experimental rate constant and the experimental isotope effect, in terms given in the above scheme, are

$$k_{\text{exp}} = \frac{Kk_0k_2k_3}{(k_{-2} + k_3)} \\
 \frac{k_{\text{exp}}^H}{k_{\text{exp}}^D} = \frac{k_2^H k_3^H}{(k_{-2}^H + k_3^H)} \cdot \frac{(k_{-2}^D + k_3^D)}{k_2^D k_3^D}$$

In the original work<sup>1</sup> the values of the  $k_3/(k_{-2} + k_3)$  terms were assigned on the basis of reasonable assumptions coupled with data available in the literature. The conclusion was then reached that the isotope effect occurred solely in the ion-forming step ( $k_2$ ) and was consistent with hydrogen participation in this step.

The data from the hydrolysis and rearrangement of the methoxyalcohols now makes these terms directly accessible. Consideration of the reaction scheme for the methoxyalcohols reveals that the ratio of  $k_{-2}/k_3$  can be determined from the initial rates of formation of glycol and carbonyl product. It can also be seen that these values are simply the ratios of the appropriate values of  $a$  from the equations relating the percentage of each compound formed as a function of time. The values of  $k_{-2}/k_3$  and  $k_3/(k_{-2} + k_3)$  for the two methoxyalcohol systems are given in Table I.

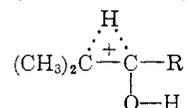
The postulation of an open carbonium ion as the reaction intermediate allows one to make a reasonable calculation for the experimental isotope effect in the pinacol rearrangement. One may assign the following values to each discrete step in the above scheme:  $k_2^H/k_2^D = 1.2$ , a normal value for hyperconjugative stabilization of a carbonium ion<sup>9</sup>;  $k_{-2}^H/k_{-2}^D = 1.2$ , as demanded by the principle of microscopic reversibility;  $k_3^H/k_3^D = 3$ , a reasonable value for the hydride shift<sup>10</sup>; and  $k_{-2}^H/k_3^H = 2.6$ , from our experimental determination. Using the equation for the experimental isotope effect and these values, an over-all isotope effect of *ca.* 2.5 may be calculated for the rearrangement of 2-methyl-1,2-propanediol and its deuterated analog. This value is not far from the observed value of 2.1. The calculation is instructive as it shows that the experimental isotope effect would arise

(9) K. B. Wiberg, *Chem. Revs.*, **55**, 713 (1955).

(10) C. J. Collins, W. T. Rainey, W. B. Smith and L. A. Kaye, *J. Am. Chem. Soc.*, **81**, 460 (1959).

mainly due to differences in the  $k_{-2}/k_3$  terms. Based on the open ion postulate a value of  $k_{-2}^D/k_3^D$  of about 6.5 is demanded, a value contrary to our data.

Quite plainly the open ion postulate leads to a conclusion contrary to the experimental facts. In Table I it may be seen that in both methoxyalcohol systems the terms  $k_{-2}/k_3$  are nearly insensitive to isotopic substitution. The clear implication is that there must be a substantial isotope effect in the ion-forming process (step 2). Thus, our original contention of hydrogen participation is confirmed. Since the rearrangement occurs through an internal hydrogen migration, it is logical to conclude that the ionic intermediate is best written as a hydrogen-bridged ion of the type



The relative magnitudes of the values for the  $k_{-2}/k_3$  terms in the systems III-IV and VII-VIII are also consistent with the postulate of a non-classical intermediate. Bearing in mind that the statistical factor of two migrating hydrogens or deuteriums in III-IV must be included in any comparison of these systems, it is seen that the process of hydrogen or deuterium migration is favored over reaction with water by nearly a factor of four in VII-VIII as compared to III-IV. This clearly reflects the driving force for hydrogen migration provided by the substitution of a methyl group on the  $\beta$ -carbon.

**Acknowledgment.**—The authors wish to acknowledge gratefully the support of this work by the U. S. Atomic Energy Commission under Contract No. AT (11-1)-555. We also wish to thank Mr. Hans-Georg Gilde for preparing some of the compounds used in this study.

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

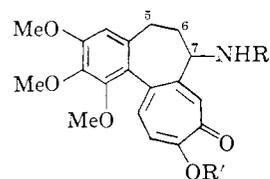
## The Biogenesis of the Alkaloids of *Colchicum*. II. Tracer Studies with Acetate-1-C<sup>14</sup> and Methionine-methyl-C<sup>14</sup>

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RECEIVED NOVEMBER 12, 1960

The administration of sodium acetate-1-C<sup>14</sup> to *Colchicum byzantinum* corms led to the formation of radioactive colchicine which was labeled on the N-acetyl group, negligible activity being found in the rest of the molecule. Demecolcine isolated from the same plants was essentially inactive. Radioactive colchicine and demecolcine labeled on their O- and N-methyl groups were obtained when L-methionine-methyl-C<sup>14</sup> was fed to the *Colchicum* plants.

In our first paper on the biogenesis of colchicine<sup>2</sup> we found that the administration of phenylalanine-3-C<sup>14</sup> to *C. byzantinum* corms led to the formation of colchicine (I) labeled at C-5. There was no activity in the rest of the molecule, and we speculated that the tropolone ring was formed in part from acetic acid especially since it has been shown that six of



I R = COMe, R' = Me      IV R = COMe, R' = H  
 II R = R' = Me            V R = Me, R' = H  
 III R = R' = H

(1) This work was presented in part at the I.U.P.A.C. symposium on the chemistry of natural products, Australia, August, 1960. This investigation was supported by a research grant MY-2662, from the National Institute of Mental Health, Public Health Service.

(2) E. Leete and P. E. Németh, *J. Am. Chem. Soc.*, **82**, 6055 (1960).

the carbons of the tropolone ring of the mold metabolite puberulic acid are derived from acetic acid.<sup>3</sup>