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### Legate Ions. The Use of the Oxibase Scale to Predict Leaving Group Orders from Carbon in SN2 Reactions<sup>1</sup>

Sir:

A fundamental problem of structure-reactivity relationships has been that of the quantitative correlation of leaving group effects from saturated carbon atoms. It is generally stated that the less basic the substituent the more easily it is removed.<sup>2</sup> An empirical relationship has been suggested by Swain and Lohmann<sup>3</sup> using the reaction of methoxide with methyl-X derivatives in methanol at 25°.

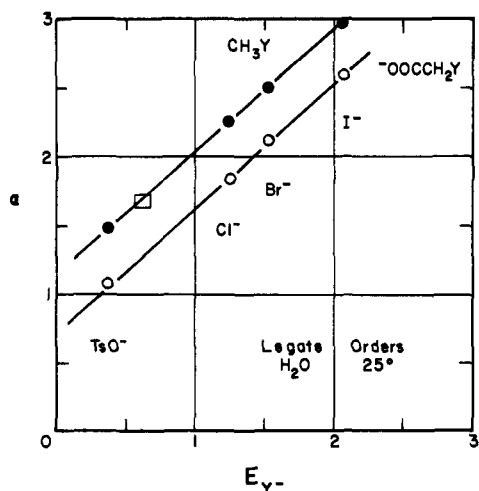


Figure 1. Plot of  $\alpha$  vs. the electrode constant  $E$  of the leaving group,  $Y$ , in water at 25° for a series of alkyl substrates having legate anions of strong acids. Data from ref. 11.  $\square$  represents the value of  $\alpha$  obtained from the rate data with trimethyl phosphate; the  $E$  value of the leaving group, dimethyl phosphate monoanion, can then be estimated.

We wish to suggest that a leaving group is a nucleophile regressing or leaving the reaction center rather than approaching the electrophilic center. The leaving group then can be correlated with nucleophilic constants of oxidation and basicity.

Foss<sup>4</sup> first suggested the use of oxidation potentials to predict reactivity of various nucleophiles in SN2 reactions. Edwards<sup>5</sup> then made the quantitative cor-

(1) Paper VI on Displacement Reactions. Paper V: R. E. Davis and A. Cohen, *J. Am. Chem. Soc.*, **86**, 440 (1964). A qualitative use of the oxibase scale to predict which group will leave in a complex reaction is discussed in this paper.

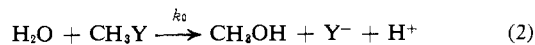
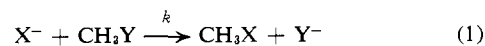
(2) E. S. Gould, "Mechanism and Structure in Organic Chemistry," Henry Holt and Co., New York, N. Y., 1959, pp. 258-263.

(3) C. G. Swain and K. H. Lohmann, unpublished data reported by E. R. Thornton in "Solvolysis Mechanisms," The Ronald Press, New York, N. Y., 1964, pp. 163-166.

(4) O. Foss, *Acta Chem. Scand.*, **1**, 8, 307 (1947).

(5) J. O. Edwards, *J. Am. Chem. Soc.*, **76**, 1540 (1954); **78**, 1889 (1956); J. O. Edwards and R. G. Pearson, *ibid.*, **84**, 16 (1962).

relation (3) between the oxidative dimerization (6) and its basicity toward a proton (5)



with

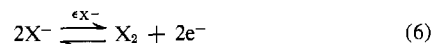
$$\log k/k_0 = \alpha E + \beta H \quad (3a)$$

or

$$\frac{\log k/k_0}{E} = \alpha + \beta \left[ \frac{H}{E} \right] \quad (3b)$$

$$E = \epsilon_{X^-} + 2.60 \text{ v.} \quad (4)$$

$$H = pK_{aX^-} + 1.74 \quad (5)$$



all in water at 25.0°. We wish to suggest that eq. 3 be called the *oxibase scale*.

In keeping with the symmetry of the two model systems used to define (3), we wish to suggest that  $\alpha$  is a *reduction term* and  $\beta$  is an *acidity term* of the substrate. By the rigorous application of nonequilibrium thermodynamics to (1) and (2), it can be shown that  $\alpha$  for carbon substrates ought to be linearly related to the electrode potential of the legate ion,<sup>6</sup>  $Y^-$ , of *strong acids*. Thus leaving group orders ought to be correlated with the same model systems used to correlate the nucleophiles in water at 25°. The data (all in  $H_2O$  at 25°) are presented<sup>7</sup> in Figure 1. The slopes are unity as predicted by theory.

The  $\beta$  of the alkyl substrate is claimed to be an acidity term which is a measure of the amount of partial charge on the carbon. Application of a *free energy cycle*<sup>8</sup> shows that  $\beta$  is related to the square of the electronegativity difference between the legate ion and the carbon. In more simple terms, the more positive the carbon the more positive is  $\beta$ . The values of  $\beta$  and  $\alpha$  have been computed by multiple regression analysis using the experimental data of ref. 11.

$\downarrow$ C-I $\downarrow$ C-Br $\downarrow$ C-Cl $\downarrow$ C-OTs more positive C	$\beta$	$\downarrow$ -0.0134 $\downarrow$ +0.002 $\downarrow$ +0.008 $\downarrow$ +0.013 more positive $\beta$
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Application of the data presented in Figure 1 allows estimation of nucleophilic constants  $E$  for very poor

(6) Derived from *legare*, to send out.

(7) Bunnett (J. F. Bunnett, *J. Am. Chem. Soc.*, **79**, 5969 (1957)) in this interesting paper uses Edwards' polarizability,  $P$ , to estimate  $E$ . Then  $\beta$  was assumed equal to zero and a test made of

$$\log \left[ \frac{k_{C_2H_5I}}{k_{C_2H_5Br}} \right]_{X^-} = (\alpha_{C_2H_5I} - \alpha_{C_2H_5Br}) P_{X^-} + \log \left[ \frac{k_{C_2H_5I}}{k_{C_2H_5Br}} \right]_{H_2O}$$

This equation or one like it derived from (5) tests the validity of the constancy of  $\alpha$  and the nucleophilic parameter,  $P$ , of the nucleophile. It does not relate  $\alpha$  to the legate potential. In a following paper in this series the use of  $P$  will be discussed. Unfortunately kinetic data have not been always measured in the same solvent as that used to calculate  $P$ . Bunnett tested his equation with rate data obtained in acetone using  $P$  values determined in water.

(8) D. H. McDaniel and A. Yingst, *ibid.*, **86**, 1334 (1964). These authors report an interesting thermodynamic cycle and have used the *enthalpies* to derive group electronegativities. The present work has used the *free energies* of the McDaniel cycles since the application of statistical mechanics can allow one to compute the necessary terms.

nucleophiles. Hudson<sup>9</sup> reported kinetic data on trimethyl phosphate with a series of nucleophilic reagents. From these data the  $\alpha$  has been calculated. From this  $\alpha$  of  $1.77 \pm 0.05$ , a value of  $E$  of 0.62 v. for  $(\text{CH}_3\text{O})_2\text{P}(\text{O})\text{O}^-$  has been computed. The value is reasonable and indicates that the phosphate, tosylate, and sulfate ions have rather similar and poor nucleophilic properties.

In further papers in the series the use of the oxibase scale will be extended.

**Acknowledgments.** The author wishes to thank the National Institutes of Health (RH 00279-02) and the Walter Reed Army Institute of Research (DA 49-193) for grants supporting these investigations.

(9) R. F. Hudson and D. C. Harper, *J. Chem. Soc.*, 1356 (1958). An interesting paper by Hudson (*Chimia*, 16, 173 (1962) reports his views on the  $\text{S}_{\text{N}}2$  reaction and a justification of the use of linear free-energy equations as (3). Another approach is reported (R. E. Davis, "Survey of Progress in Chemistry," Vol. 2, A. F. Scott, Ed., Academic Press Inc., 1964, pp. 189-238).

(10) Alfred P. Sloan Fellow, 1962-1966.

(11) The kinetic data used to compute  $\alpha$  and  $\beta$  are (either from the literature or as a result of this study on  $\text{CH}_3\text{OTs}$  and  $\text{TsOCH}_2\text{COONa}$ ): (a) bromoacetate: V. K. La Mer and M. E. Kammer, *J. Am. Chem. Soc.*, 57, 2662 (1935); H. J. Backer and W. H. Van Mels, *Rec. trav. chim.*, 49, 177, 363 (1930); see also ref. 5; (b) chloroacetate: *Rec. trav. chim.*, 49, 457 (1930); H. M. Dawson and E. R. Pycocok, *J. Chem. Soc.*, 153 (1936); A. Slator and D. F. Twiss, *ibid.*, 95, 93 (1909); (c) iodoacetate: C. Wagner, *Z. physik. Chem.*, A115, 121 (1925); H. J. Backer and W. H. Van Mels, *Rec. trav. chim.*, 49, 177, 363, 457 (1930); (d) methyl bromide: A. Slator and D. F. Twiss, *J. Chem. Soc.*, 95, 93 (1909); E. A. Moelwyn-Hughes, *Trans. Faraday Soc.*, 45, 167, (1949); A. Slator, *J. Chem. Soc.*, 85, 1286 (1904); (e) methyl iodide: E. A. Moelwyn-Hughes, ref. 11d; (f) methyl tosylate: A. Praetorius, *Monatsh.*, 26, 1 (1905); R. E. Robertson, *Can. J. Chem.*, 31, 589 (1953); C. G. Swain and C. R. Morgan, *J. Org. Chem.*, 29, 2097 (1964); this study with  $\log k/k_0 = 3.110$  for  $\text{N}_3^-$ , 2.774 for  $\text{SCN}^-$ , 3.873 for  $\text{S}_2\text{O}_8^{2-}$ , and 3.038 for  $\text{OH}^-$  in water at 25°. The values of  $\alpha$  and  $\beta$  of methyl tosylate are nearly identical with those of ethyl tosylate (data of Dr. Nehring of this laboratory), also in water at 25°. The data on sodium tosylacetate,  $\text{TsOCH}_2\text{COONa}$ , were measured spectrophotometrically at 272  $\mu$  in dilute aqueous solution by Mr. William Blume at 35° and 50°, by R. E. D. at 25°. At 25°  $\log k/k_0 = 2.247$  for  $\text{I}^-$ , 1.643 for  $\text{Br}^-$ , 1.711 for  $\text{OH}^-$ , 1.991 for  $\text{SCN}^-$ , 2.703 for  $\text{S}_2\text{O}_8^{2-}$ , and 2.810 for  $\text{SO}_3^{2-}$ . All of the data have been handled on the IBM 7094 using a multiple regression method assuming errors in all the values and the parameters. Errors in the log terms are  $\pm 0.005$  average. Enough data have been obtained at four or more ionic strengths to extrapolate the rate data to infinite dilution. This affects the tosylacetate data (an anion-anion reaction) much more than with methyl tosylate.

The  $E$  value of tosylate ion ( $0.49 \pm 0.02$  v.) can be estimated and compared with 0.59 v. for sulfate<sup>6</sup> anion by the solubility product of silver sulfate and silver tosylate in water at 25°. Kinetically the two legate potentials of tosylate are consistent. Defining  $E$  with the methyl tosylate data places the  $\alpha$  of tosylacetate on the line for  $-\text{OOCCH}_2\text{-Y}$  derivatives.

Since one referee has expressed interest, we have made arrangements that the raw data of this paper and those in following papers and computer programs be microfilmed and placed in the Bureau of Documentation.

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Received May 3, 1965

## On the Incorporation of Oxygen in the Conversion of 8,11,14-Eicosatrienoic Acid to Prostaglandin E<sub>1</sub>

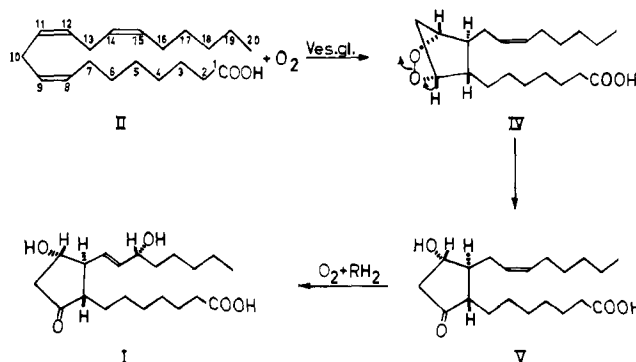
Sir:

The biosynthesis of prostaglandin E<sub>1</sub> (I) from 8,11,14-eicosatrienoic acid (II) involves incorporation of 3 atoms of oxygen.<sup>1,2</sup> Two of these oxygens appear in

(1) D. A. van Dorp, R. K. Beerthuis, D. H. Nugteren, and H. Vonkeman, *Biochim. Biophys. Acta*, 90, 204 (1964).

(2) S. Bergström, H. Danielsson, and B. Samuelsson, *Biochim. Biophys. Acta*, 90, 207 (1964).

the hydroxyl groups at C-15 and C-11 and 1 in the keto group at C-9. Recent experiments demonstrated that the oxygens of the 2 hydroxyl groups are derived from molecular oxygen. However, the origin of the keto oxygen could not be established because of exchange of this oxygen with the aqueous media used for the incubation and isolation.<sup>3</sup>



The experiments described in this communication show that the oxygen atom of the keto group also originates in molecular oxygen and that it is in fact derived from the same molecule of oxygen as the oxygen atom of the hydroxyl group at C-11. These results indicate that a novel biological reaction is involved in the formation and oxygenation of the five-membered ring of the prostaglandins.

For the biosynthesis of prostaglandin E<sub>1</sub>, [2-<sup>14</sup>C]8,11,14-eicosatrienoic acid was incubated with a preparation of vesicular gland for 10 min. in an atmosphere of <sup>18</sup>O-labeled oxygen.<sup>3</sup> Ice-cold ethanol containing NaBH<sub>4</sub> was then immediately added to the incubation mixture. In this way the oxygen of the keto group was protected from exchange by reduction to an alcohol.<sup>4</sup> The ethyl ester of the resulting trihydroxy acid was converted into the trimethoxy derivative<sup>5</sup> in order to minimize elimination of the oxygen functions during the electron impact. For determination of the origin of the oxygens of the ring, this derivative was oxidized by permanganate-periodate.<sup>5</sup> The product was finally converted to the diethyl ester (III in Figure 1) so that, in the mass spectrometric analysis, eliminations involving the methoxy groups and the ester groups could be distinguished.

The upper  $m/e$  region of the mass spectrum<sup>6</sup> of the reference sample of III, and of III formed in an atmosphere of <sup>16</sup>O<sup>16</sup>O (43%), <sup>16</sup>O<sup>18</sup>O (1%), and <sup>18</sup>O<sup>18</sup>O (56%), is shown in Figure 1A and 1B, respectively. There were three fragments, which retained both oxygen atoms in the ring. These appeared at  $m/e$  343 ( $M - 15$  ( $\text{CH}_3$ )), 313 ( $M - 45$  ( $\text{OCH}_2\text{CH}_3$ )), and 297 ( $M - (45 + 1 + 15)$  ( $\text{OCH}_2\text{CH}_3 + \text{H} + \text{CH}_3$ )). In the spectrum of III derived from prostaglandin E<sub>1</sub> formed in the <sup>18</sup>O atmosphere peaks were also seen at  $m/e$  347

(3) R. Ryhage and B. Samuelsson, *Biochem. Biophys. Res. Commun.*, 19, 279 (1965).

(4) The reduction gave mainly the 9 $\beta$ -epimer (PGF<sub>1 $\beta$</sub> ); cf. S. Bergström, L. Krabich, B. Samuelsson, and J. Sjövall, *Acta Chem. Scand.*, 16, 969 (1962). This epimer was isolated and used in the following experiments.

(5) S. Bergström, R. Ryhage, B. Samuelsson, and J. Sjövall, *ibid.*, 17, 2271 (1963).

(6) The mass spectrometric analyses were carried out in conjunction with gas chromatography using the instrument described by R. Ryhage, *Anal. Chem.*, 36, 759 (1964). The column (1% SE-30 on Gas Chrom P) was operated at 165° and about 5  $\mu$ g. of material was injected.