Acknowledgment.—We are grateful to Professor Henry G. Kuivila for enlightening discussions and to the National Science Foundation for financial support (Grant GP-242).

CHEMISTRY DEPARTMENT   HIROSHI MINATO[18]
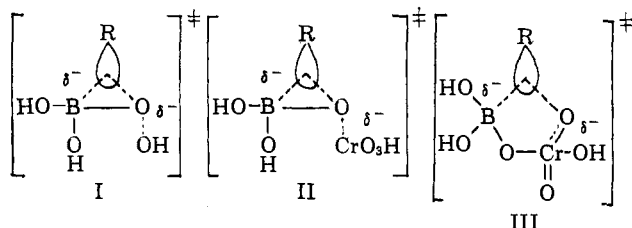UNIVERSITY OF CALIFORNIA, SAN DIEGO   JUDITH C. WARE
LA JOLLA, CALIFORNIA   T. G. TRAYLOR

RECEIVED AUGUST 16, 1963

Electrophilic Substitution.   Chromic Acid Cleavage of Carbon–Boron Bonds

Sir:

In the previous communication[1] we indicated the effect of structure in R on the stability of the three-center transition state I.

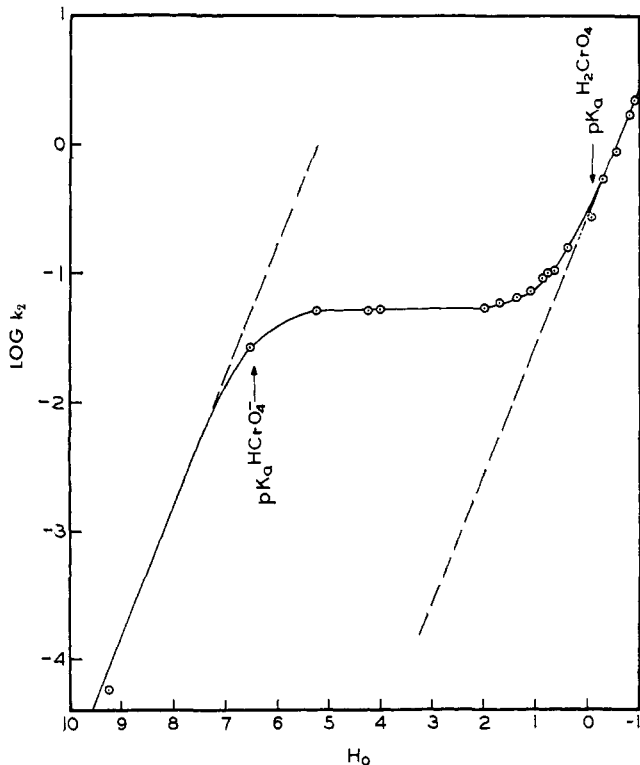The general behavior of chromic acid oxidation of alcohols[2a–f] caused us to believe that chromic acid

cleavage of boronic acids might attain the five-membered transition state III rather than the three-membered II.   Structural effects on transition states such as I (and we imply II) are not strongly dependent on the nature of the leaving group.[1,3]   Therefore, from the effects of the structure of R on the rate of chromic acid cleavage of boronic acids, we might distinguish between II and III.   This is possible only if one mechanism is operating.   However, several species of chromic acid in aqueous solution could bring about oxidation. Among the species $H_3CrO_4{}^+$, H_2CrO_4, $HCrO_4{}^-$, $CrO_4{}^{2-}$, $H_2Cr_2O_7$, $HCr_2O_7{}^-$, and $Cr_2O_7{}^{2-}$, only the first two have been definitely associated with oxidation in dilute solutions and these two usually are in competition. This competition of mechanisms greatly complicates studies of structural effects.[4]

We wish to report an oxidation by $HCrO_4{}^-$ in a reaction which promises important application both in synthesis and in mechanism studies.   This finding also points the way to studies of reactions of the remaining Cr^{VI} species.   The reaction of chromic acid with t-butylboronic acid

$$CrO_3 + t\text{-}BuB(OH)_2 \xrightarrow{H_2O} t\text{-}BuOH + H_3BO_3 + Cr^{3+} \quad (1)$$
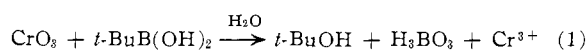
is first order in each reagent over a wide range of pH (-1 to 9) and has a very small salt effect (5% increase at 1.0 M NaClO$_4$) on rate.

$$-\frac{d[Cr^{VI}]}{dt} = k_2[RB(OH)_2][Cr^{VI}] \quad (2)$$

The pH–rate profile is shown in Fig. 1.[5,6]

The shape of this curve has three important implications.   First, the oxidation of boronic acids at pH 3–7 where alcohols are relatively stable to Cr^{VI} makes possible the *synthesis* of alcohols using chromic acid. Thus, oxidation with chromic acid at pH *ca.* 5 will produce alcohols[7] and at higher acidities, *e.g.*, 2 N acid, will produce ketones.[8]   Further, this reagent makes possible selective alkylborane cleavage because its reaction rate is much more sensitive to structure than that of hydrogen peroxide.[1]   Thus, the k_2 values for various R are t-Bu, 7.5×10^{-2}; Et, 6.6×10^{-4}; Me, 2.4×10^{-7} l./mole sec. in 0.114 M perchloric acid at 30.0°.

Secondly, the pH–rate profile is unusually informative about the mechanism of the reaction.   This curve is accurately described by the equation

$$[Cr^{VI}] \times k = 0.054(HCrO_4{}^-) + 0.36(H_2CrO_4) +$$
$$0.32(H_2CrO_4)h_0 \quad (3)$$

using the recorded[9] values of $K_{H_2CrO_4} = 1.21$ and $K_{HCrO_4{}^-} = 3.2 \times 10^{-7}$.   (Dimeric species are precluded by the low Cr^{VI} concentrations.)   Therefore the oxidants in this reaction are $HCrO_4{}^-$ and $H_3CrO_4{}^+$; $CrO_4{}^{2-}$ and H_2CrO_4 are relatively ineffective[10] (*i.e.*, H_2CrO_4

Fig. 1.—Plot of log k_2 at 30.0° *vs.* H_0 (or pH) for the rate expression $d[Cr^{VI}]/dt = k_2[t\text{-}BuB(OH)_2][Cr^{VI}]$.   Circles are experimental points.   The solid line represents eq. 3 and the dashed lines indicate unit slope.   The H_0 values for the perchloric acid solutions were taken from Long and Paul.[6]

(1) H. Minato, J. C. Ware, and T. G. Traylor, *J. Am. Chem. Soc.*, **85**, 3024 (1963).

(2) (a) F. H. Westheimer, *Chem. Rev.*, **45**, 419 (1949); (b) F. Holloway, M. Cohen, and F. H. Westheimer, *J. Am. Chem. Soc.*, **73**, 65 (1951); (c) G. T. E. Graham and F. H. Westheimer, *ibid.*, **80**, 3030 (1958); (d) R. Brownell, A. Leo, Y. W. Chang, and F. H. Westheimer, *ibid.*, **82**, 406 (1960); (e) J. Roček and F. H. Westheimer, *ibid.*, **84**, 2241 (1962); (f) Y. W. Chang and F. H. Westheimer, *ibid.*, **82**, 1401 (1960); (g) H. G. Kuivila and W. J. Becker, *ibid.*, **74**, 5329 (1952); (h) J. Roček and J. Krupicka, *Chem. Listy*, **52**, 1735 (1958); (i) F. H. Westheimer and A. Novick, *J. Chem. Phys.*, **11**, 506 (1943).

(3) H. G. Kuivila, *J. Am. Chem. Soc.*, **77**, 4014 (1955).

(4) H. Kwart and P. S. Francis, *ibid.*, **77**, 4907 (1955).

(5) All rate data were obtained by the spectrophotometric method of Westheimer and Novick.[2i]   Borate buffer was used at pH 9, phosphate at pH 6.5, and acetate at pH 4–5.   At higher acidities perchloric acid was used.   At pH 6.5, the reaction is pseudo first order (RB(OH)₂ in excess) for about one-half life and then acclerates rather sharply.   Similar acceleration was noted with other buffers (except borate) above pH 5.

(6) M. A. Paul and F. A. Long, *Chem. Rev.*, **57**, 1 (1957).

(7) The chromic acid cleavage appears to proceed with the same stereo-chemistry and yield as the hydrogen peroxide cleavage (unpublished results).

(8) H. C. Brown and C. P. Garg, *J. Am. Chem. Soc.*, **83**, 2952 (1961).
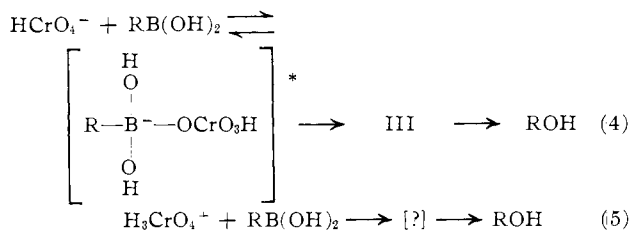
(9) J. T. Long and E. L. King, *ibid.*, **75**, 6180 (1953).

(10) This preference of boronic acids for the anions is seen in other cases. The ¹¹B n.m.r. of ethylboronic acid[11] indicates it to be entirely trigonal[12] in water (*i.e.*, not complexed with water) and tetrahedral in 0.8 N sodium hydroxide.

(11) We are indebted to H. Landesman, J. Ditter, and T. Burns, of the National Engineering Science Co., Pasadena, California, who very generously determined the ¹¹B chemical shifts.

(12) T. P. Onak, H. Landesman, R. E. Williams, and I. Shapiro, *J. Phys. Chem.*, **63**, 1533 (1959).

contributes only at pH values near its pK). That H_2CrO_4 is not an effective oxidant is not surprising considering the previous conclusions[1,3] that OOH^- and $H_3O_2^+$ but not H_2O_2 readily oxidize boronic acids. That the reaction of $HCrO_4^-$ with boronic acids is much more sensitive to structure than is the reaction of HOO^- or $H_3O_2^+$ argues against its having the transition state II. We are therefore tentatively proposing the mechanisms shown.

$$HCrO_4^- + RB(OH)_2 \rightleftharpoons$$

$$\begin{bmatrix} & H & \\ & O & \\ & | & \\ R{-}B^-{-}{-}OCrO_3H & \\ & | & \\ & O & \\ & H & \end{bmatrix}^* \longrightarrow III \longrightarrow ROH \quad (4)$$

$$H_3CrO_4^+ + RB(OH)_2 \longrightarrow [?] \longrightarrow ROH \quad (5)$$

The third application of this reaction in the acid-independent region is in the study of the large solvent and specific ion effects previously observed in chromic acid oxidations.[2a–d] Other chromic acid reactions involve high acidity dependencies.[2a–g] Consequently factors such as solvent and specific ion effects could not be quantitatively separated.[2b] With the discovery of an acid independent Cr^{VI} oxidation, this separation can now be made. Such studies are in progress.

Acknowledgment.—We are grateful to Professors Frank H. Westheimer and Jan Roček for enlightening discussions and most helpful criticism. Financial support by the National Science Foundation is gratefully acknowledged. (Grant GP-242).

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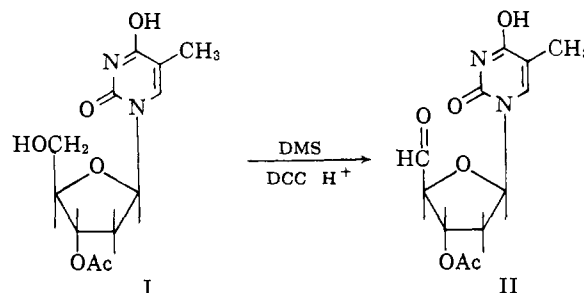
The Synthesis of Nucleoside-5' Aldehydes

Sir:

We have recently observed that the addition of dicyclohexylcarbodiimide to an anhydrous solution of pyridinium thymidine-5' phosphate in dimethyl sulfoxide results in rapid coloration of the reaction mixture and the release of a foul sulfide-like smell. Chromatographic examination of the products showed that within 1 hr. at room temperature the nucleotide had completely disappeared through degradation to thymine and inorganic phosphates, principally trimetaphosphate. Other ribo- and deoxyribonucleotides react in a similar way but at varying rates. A similar release of thymine resulted from P^1,P^2-dithymidine pyrophosphate or from thymidine or 5'-O-acetyl thymidine in the presence of anhydrous orthophosphate. 3'-O-Acetyl thymidine-5' phosphate, 3'-deoxythymidine-5' phosphate[1] (2',3'-dideoxy-β-D-pentofuranosyl thymine 5'-phosphate), or the corresponding nucleosides in the presence of orthophosphate, gave, however, no release of thymine.

Treatment of 3'-O-acetyl thymidine (I) (1 mmole) in anhydrous dimethyl sulfoxide (3 ml.) in the presence of anhydrous orthophosphoric acid (0.5 mmole) and dicyclohexylcarbodiimide (3–5 mmoles) for several hours at room temperature gave no release of thymine. I was, however, converted in roughly 90% yield into a new compound clearly separated from the starting material by paper chromatography and giving a positive carbonyl test with dinitrophenylhydrazine spray. This material has now been shown to be 3'-O-acetyl thymidine-5' aldehyde (II) which was isolated both as the noncrystalline free compound (λ_{max} 267 mμ in

(1) K. E. Pfitzner and J. G. Moffatt, in preparation.

water) or as its crystalline 2,4-dinitrophenylhydrazone (m.p. 233–234°, λ_{max}^{MeOH} 261 and 350 mμ; ϵ_{max} 19,300 and 21,650. *Anal.* Calcd. for $C_{18}H_{18}N_6O_9$: C, 46.76; H, 3.92; N, 18.18; acetyl, 9.31. Found: C, 46.99; H, 4.16; N, 18.37; acetyl, 9.61). The structure of II was proved by reduction with sodium borohydride to thymidine (with concomitant hydrolysis of the acetyl group) and by oxidation with sodium hypoiodite to 3'-O-acetyl thymidine-5' carboxylate, which upon alkaline hydrolysis gave thymidine-5' carboxylate.[2] It is to be emphasized that no acidic nucleoside deriva-

tives could be detected electrophoretically in the final reaction mixture, the method thus being completely selective for oxidation to the aldehyde level. This is to be contrasted with other oxidative techniques which have been applied to nucleosides and have led inevitably to carboxylic acids.[2–4]

The aforesaid release of thymine from thymidine-5' phosphate, which first directed our attention to this oxidation procedure, is clearly the result of quantitative oxidation of the 3'-hydroxyl group to a ketone which spontaneously eliminates both the heterocyclic base and the phosphate moiety under the mildest of conditions. Further experiments designed to utilize this reaction for the stepwise degradation of deoxyoligonucleotides are in progress.

In a similar way, the reaction of 2',3'-O-isopropylidene uridine with dicyclohexylcarbodiimide and 0.5 mole equiv. of pyridinium trifluoroacetate or pyridinium phosphate in anhydrous dimethyl sulfoxide, followed by treatment with 10% acetic acid at 100° for 1 hr., gave a high yield of uridine-5' aldehyde, which has as yet resisted crystallization but which is readily separated from uridine on bisulfite-impregnated paper and gives a positive test for a carbonyl group. Also, a similar reaction on 2',3'-O-isopropylidene adenosine gave, after acidic removal of the isopropylidene group, a major product chromatographically identical with a sample of the adenosine-5' aldehyde isolated by Hogenkamp, *et al.*,[5] by ultraviolet irradiation of coenzyme B_{12}.

Further development of this highly selective and mild oxidation technique will be reported in detail shortly.[6]

(2) J. P. Vizsolyi and G. M. Tener, *Chem. Ind.* (London), 263 (1962).

(3) A. S. Jones and A. R. Williamson, *ibid.*, 1624 (1960).

(4) G. P. Moss, C. B. Reese, K. Schofield, R. Shapiro, and Lord Todd, *J. Chem. Soc.*, 1149 (1963).

(5) H. P. C. Hogenkamp, J. N. Ladd, and H. A. Barker, *J. Biol. Chem.*, **237**, 1950 (1962). We are grateful to Dr. Barker for a sample of their product.

(6) For a preliminary account, see K. E. Pfitzner and J. G. Moffatt, *J. Am. Chem. Soc.*, **85**, 3027 (1963).

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A New and Selective Oxidation of Alcohols

Sir:

We have recently observed that treatment of nucleoside derivatives, substituted such that only the primary