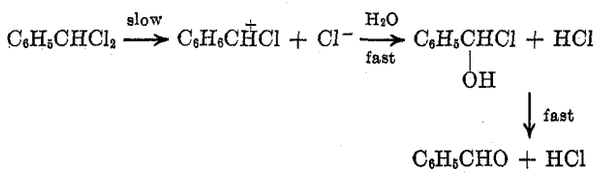
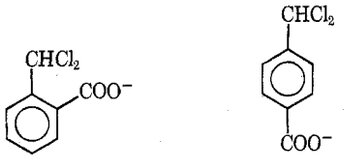
SCHEME I



of m measured in aqueous ethanol solutions for benzal chloride is large (1.31 ± 0.02)[7] indicative of an SN1 transition state.[8]

We have measured the hydrolysis rates of *o*-carboxybenzal chloride (1) and *p*-carboxybenzal chloride (2) in water and mixtures of water and dioxane in the



1

2

presence of excess base and these results are collected in Table I. These results show that in water an ortho

TABLE I

RATES OF HYDROLYSIS OF CARBOXY SUBSTITUTED BENZAL CHLORIDES AT 25.2 ± 0.2° [a]

$10^7 k_{ortho}^{obsd}$, sec^{-1}	$10^7 k_{para}^{obsd}$, sec^{-1}	k_{ortho}/k_{para}	Solvent[b]
2210	2640	0.83	A
563	11.2	50.3	B
276	2.52	110	C

[a] Rate constants were determined by following the increase of absorbance at 257 nm due to the aldehyde product. The slower reactions were studied using an initial rate method and the rate constants thus obtained are considered accurate to ±10%. The results are the average of at least three separate determinations. [b] A, 0.2 *N* NaOH in water; B, 50% dioxane–50% 0.2 *N* NaOH (v/v); C, 60% dioxane–40% 0.2 *N* NaOH (v/v).

carboxylate ion does *not* facilitate the reaction and, in fact, has a slight rate-retarding effect. Presumably in water (a highly polar solvent) the ortho carboxylate ion does not compete effectively with the solvent in stabilizing the ionic transition state. However, increasing the amount of dioxane present in the solvent results in a dramatic increase in k_{ortho}/k_{para} (Table I). Thus, as the solvent becomes less able to stabilize the transition state electrostatic stabilization by the ortho carboxylate ion becomes more pronounced. In fact, extrapolation of the data in Table I give k_{ortho}/k_{para} = 7600 in 90% aqueous dioxane.

An alternative mechanism involving intramolecular nucleophilic displacement by the ortho carboxylate function (Scheme II) cannot rigorously be excluded at the present time.[9]

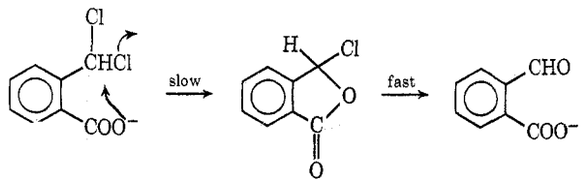
However, if intramolecular displacement was responsible for the high k_{ortho}/k_{para} values in aqueous dioxane solutions, one would expect an even large value of k_{ortho}/k_{para} in aqueous DMSO (*cf.* the large

(7) N. Grossman, unpublished work.

(8) A. Streitweiser, Jr., "Solvolytic Displacement Reactions," Vol. X, McGraw-Hill, New York, N. Y., 1962, pp 45–47.

(9) An additional mechanism suggested by a reviewer involving the intramolecular deprotonation of the dichloromethyl group followed by α elimination to generate a carbene seems unlikely in view of the fact that the rate is independent of the concentration of HO^- (a much stronger base) for both **1** and **2** if pH > pK_A.

SCHEME II



rate accelerations observed[10] for SN2 reactions in DMSO and the increased rate of anhydride formation from phenyl hydrogen phthalate in aqueous DMSO).[11] On the other hand, electrostatic catalysis ought to be favored in media of low dielectric constant and, since DMSO has a higher dielectric constant (~50) than dioxane (~2), a lower value of k_{ortho}/k_{para} is expected in aqueous DMSO. Since k_{ortho}/k_{para} = 12 in 50% aqueous DMSO it would seem that the ortho carboxylate ion enhances the solvolysis rate of benzal chloride by electrostatically stabilizing the ionic transition state rather than effecting an intramolecular nucleophilic displacement.

In conclusion, we feel that the results described in the communication support the suggestion that, under certain conditions, a properly oriented carboxylate ion can stabilize a transition state leading to a resonance stabilized carbonium ion.

Acknowledgment.—We are grateful to the National Science Foundation for financial support of this work (Grant No. GP-29738 X).

(10) J. J. Delpuech, *Bull. Soc. Chim. Fr.*, 1624 (1966).

(11) T. C. Bruice and A. Turner, *J. Amer. Chem. Soc.*, **92**, 3422 (1970).

DEPARTMENT OF CHEMISTRY
UNIVERSITY OF MARYLAND
BALTIMORE COUNTY
BALTIMORE, MARYLAND 21228

V. P. VITULLO*
N. R. GROSSMAN

RECEIVED SEPTEMBER 25, 1972

A Reinvestigation of 3,5′-Anhydro-2′,3′-*O*-isopropylideneinosine

Summary: Nmr studies have shown that 3,5′-anhydro-2′,3′-*O*-isopropylideneinosine (II), previously described, is actually the ring-opened compound 5′,N^5-anhydro-1-(2,3-*O*-isopropylidene-β-D-ribofuranosyl)-5-formamidoimidazole-4-carboxamide (I); the preparation and characterization of authentic II is described.

Sir: The formation of cyclonucleosides from purine nucleoside derivatives is well established.[1] The first reported synthesis[2] of 3,5′-anhydro-2′,3′-*O*-isopropylideneinosine used thermal cyclization of the appropriate 5′-*O*-*p*-toluenesulfonyl derivative in an inert solvent, a procedure first used in the synthesis of 3,5′-anhydro-2′,3′-*O*-isopropylideneadenosine.[3] The inosine cyclonucleoside was isolated as the *p*-toluenesulfonate salt[2] which was converted to a product described as the monohydrate of 3,5′-anhydro-2′,3′-*O*-isopropylideneinosine. Three subsequent reports have described the formation of the same final product by the following

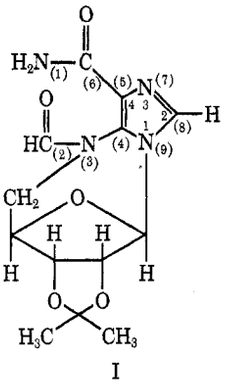
(1) C. A. Dekker and L. Goodman in "The Carbohydrates," Vol. IIA, 2nd ed, W. Pigman and D. Horton, Ed., Academic Press, New York, N. Y., 1970, Chapter 29.

(2) R. E. Holmes and R. K. Robins, *J. Org. Chem.*, **28**, 3483 (1963).

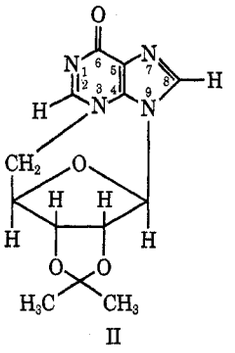
(3) V. M. Clark, A. R. Todd, and J. Zussman, *J. Chem. Soc.*, 2952 (1951).

TABLE I

^1H (PMR) AND ^{13}C (CMR) NUCLEAR MAGNETIC RESONANCE DATA



I



II

A. Pmr[a]

Compd	Chemical shifts, δ								
	H_8	H_2	NH_2	H_1'	H_2'	H_3'	H_4'	$H_5',_5''$	CH_3
I	7.94	8.32	7.34	6.23	4.97	4.54	4.73	4.76	1.48
			7.26					2.93	1.33
II	8.20	8.12		6.56	5.04	4.54	4.94	4.84	1.52
								4.26	1.30

Compd	Vincinal coupling constants, Hz					
	1'–2'	2'–3'	3'–4'	4'–5'	4'–5''	5'–5''
I	<1	6.0	*b*	1.7	2.7	14.0
II	<1	6.0	*b*	2.0	3.0	14.8

B. Cmr[c]

Compd	Chemical shifts, ppm											
	C_2	C_4	C_5	C_6	C_8	C_1'	C_2'	C_3'	C_4'	C_5'	$*C(CH_3)_2$	$*CH_3$
I	−35.7	−4.06	1.40	−35.7	−6.36	37.4	42.8	45.8	42.8	82.6	15.7	101.1
												102.9
II	−20.7	−11.5	2.30	−36.3	−7.95	37.3	43.1	46.9	41.9	71.3	15.1	101.1
												102.8

Compd	C–H coupling constants, Hz				
	$^1J_{C_2-H_2}$	$^1J_{C_8-H_8}$	$^3J_{C_8-H_8}$	$^3J_{C_8-H_2}$	$^3J_{C_8-H_1'}$
I	209	215	*d*	0	*ca.* 3
II	208	*e*	11	11	*ca.* 3

[a] 60-MHz spectra were taken on Perkin-Elmer R20A, probe temperature 34°. Samples were 10% w/v in DMSO-d_6. Shifts were measured in parts per million from internal 2,2-dimethylsilapentanesulfonic acid sodium salt. [b] Not resolved. [c] 22.6-MHz spectra were taken on Bruker HX-90 using the Fourier Transform mode. Samples were 20–40% w/v in DMSO-d_6. Chemical shifts (parts per million) were taken from noise-decoupled spectra (16,000–40,000 accumulation) measured from external hexafluorobenzene and converted to benzene using the experimentally determined relationship $\delta_{C_6H_6} = \delta_{C_6F_6\ (ext)} - 9.9$ ppm. C–H coupling constants (hertz) were taken from undecoupled spectra (40,000–200,000 accumulations). Probe temperature was 40–45° for noise-decoupled spectra and ~30° for undecoupled spectra. [d] Unresolved multiplet. [e] One leg of doublet obscured by C_6F_6.

routes: (1) treatment of 2',3'-*O*-isopropylideneinosine with phosphoryl chloride,[4] (2) interaction of methyltriphenoxyphosphonium iodide with 2',3'-*O*-isopropylideneinosine,[5] and (3) treatment of 5'-deoxy-5'-iodo-2',3'-*O*-isopropylideneinosine with aqueous ammonia.[6] Each of these reports characterizes the inosine cyclonucleoside as a monohydrate identical with the product of Holmes and Robins.[2]

We have recently reexamined the product described as 3,5'-anhydro-2',3'-*O*-isopropylideneinosine by ^1H (pmr) and ^{13}C (cmr) nmr spectroscopy and have determined that this compound is instead the ring-opened derivative 5',N^5-anhydro-1-(2,3-*O*-isopropylidene-β-D-ribofuranosyl)-5-formamidoimidazole-4-carboxamide (I). The preparation of the intact 3,5'-anhydro-2',3'-*O*-isopropylideneinosine (II) was accomplished by careful neutralization of the corresponding *p*-toluenesulfonate salt[2] on a column of Amberlite IR-45 (OH) at 5°. The water was removed from the solution by freeze drying and the product was crystallized from methanol to provide II: mp 314–315° dec; uv max (H_2O) 258 nm (ε 12,000), at pH 1 253 (10,400), at pH 11 250–256 (unstable) (7200). Calcd for $C_{13}H_{14}N_4O_4 \cdot 0.5\ H_2O$: C, 52.17; H, 5.05; N, 18.72. Found: C, 51.98; H, 5.16; N, 18.98. The presence of 0.5 mol of water in the sample was confirmed by the pmr spectrum. The pyrimidine ring of the inosine cyclonucleoside II was readily opened in aqueous solution at room temperature as shown by tlc (silica gel, 4:1 chloroform–methanol). After several days at room temperature, a solution of the inosine cyclonucleoside II in water deposited crystals of the imidazole cyclonucleoside I. Also, tlc of a solution of the *p*-toluenesulfonate salt of II,[2] after neutralization to pH 7, showed the presence of II with the gradual formation of the imidazole cyclonucleoside I.

Pertinent nmr data is contained in Table I. The parenthetical numbering in I is used for data comparison and corresponds to the same positions in II. Important features in the pmr spectra of I are the peaks

(4) K. Kusashio and M. Yoshikawa, *Bull. Chem. Soc. Jap.*, **41**, 142 (1968).

(5) J. P. H. Verheyden and J. G. Moffatt, *J. Org. Chem.*, **35**, 2319 (1970).

(6) A. Hampton, M. Bayer, V. S. Gupta, and S. Y. Chu, *J. Med. Chem.*, **11**, 1229 (1968).

at δ 7.34 and 7.26, characteristic of amide NH_2 protons, and the doublet at high field, 2.93, due to one of the 5′ protons. Contrarily, II displays both 5′ doublets at low field and no exchangeable NH_2 protons. The closely spaced singlets of the purine base protons are arbitrarily assigned with H_8 at lowest field in the spectrum of II.

Natural abundance cmr measurements are even more revealing. The decoupled spectrum of II has one resonance, C_6, in the carbonyl region of inosine at −36.3 ppm.[7] On the other hand, the decoupled spectrum of I contains two peaks superimposed at −35.7 ppm, indicating two carbonyl carbons, C_6 and C_2. In addition, the loss of the conjugated purine ring is noticed in the upfield shift of C_5, from 71.3 in II to 82.6 ppm in I.

Perhaps the most succinct structural information is derived from the undecoupled cmr spectra. The vicinal $^3J_{C_5-H_2}$ of the usual magnitude (~9–12 Hz[8-10]) is observed in II, but is completely absent in I, indicative of no bond between N_1 and C_2.

This report illustrates the utility of cmr in nucleoside structural analysis.

Acknowledgment.—We thank Mr. E. B. Banta for expert technical assistance and Dr. R. Rousseau for helpful discussions.

(7) A. J. Jones, D. M. Grant, M. W. Winkley, and R. K. Robins, *J. Amer. Chem. Soc.*, **92**, 4079 (1970).
(8) F. J. Weigert and J. D. Roberts, *ibid.*, **90**, 3543 (1968).
(9) R. U. Lemieux, T. L. Nagabhushan, and B. Paul, *Can. J. Chem.*, **50**, 773 (1972).
(10) G. P. Kreishman and M. P. Schweizer, unpublished work.

ICN Nucleic Acid Research Institute
Irvine, California 92664

Joseph T. Witkowski*
George P. Kreishman
Martin P. Schweizer
Roland K. Robins

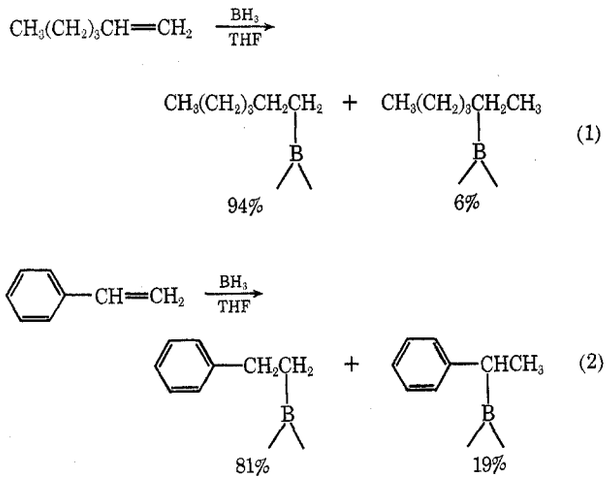
Received October 12, 1972

An Unusually Powerful Directive Effect in the Hydroboration of Representative Olefins with Monochloroborane–Ethyl Etherate

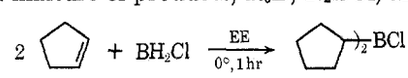
Summary: Hydroboration–oxidation of alkenes with monochloroborane (BH_2Cl) in ethyl ether gives the anti-Markovnikov alcohols in >99.5% isomeric purity, revealing a directive effect in the addition stage far stronger than that exhibited by borane–tetrahydrofuranate itself.

Sir: The hydroboration of representative olefins with monochloroborane–ethyl etherate (BH_2Cl–OEt_2) reveals a powerful directive effect which greatly reduces the yield of the minor isomer formed in hydroborations with borane itself. Consequently, hydroboration with monochloroborane (BH_2Cl) makes possible the synthesis of the major product in purities which often exceed 99.5%.

A difficulty in using hydroboration–oxidation for the anti-Markovnikov hydration of olefins[1] is the formation of significant amounts of the minor isomer in the hydroboration stage (eq 1 and 2). This phenomenon often makes necessary a tedious purification to remove the minor component. Hydroboration with disiamylborane has been recommended as a means of overcoming this difficulty. However, the reagent hydroborates internal and cyclic olefins only very sluggishly.[2] Moreover, here also it is necessary to separate the desired product from the *sec*-isoamyl alcohol resulting from the oxidation of the disiamylborane moiety. We wish to report here a new more readily and generally applied procedure to avoid these difficulties.



We recently discovered that monochloroborane in ethyl ether (EE) in contrast to monochloroborane in tetrahydrofuran (THF) readily hydroborates a wide variety of olefins to give the corresponding dialkylchloroboranes[3] (eq 3). The reaction in THF proceeds to give a mixture of products, R_3B, R_2BCl, and $RBCl_2$.[3]



It has been reported that in THF chloroborane had little, if any, advantage over BH_3 in the directive effects achieved. Thus Zweifel found that the hydroboration–oxidation of 1-hexene gave 94% 1-hexanol with 6% 2-hexanol.[4] Similarly, Pasto and Balasubramaniyan observed a 96:4 distribution of the two products.[5]

We discovered that hydroboration with BH_2Cl in ethyl ether exhibits a far more powerful directive effect. Thus 1-hexene yields >99.5% 1-hexanol with <0.5% 2-hexanol. Styrene (eq 2) gives 96% primary derivative with 4% secondary. Norbornene gives >99.8% exo alcohol. 1-Methylcyclopentene gives >99.8% the *trans*-2-methylcyclopentanol, with no cis isomer and only <0.2% tertiary isomer indicated.

The following procedure for the hydroboration–oxidation of 1-methylcyclopentene with BH_2Cl–OEt_2 is representative. In a dry 50-ml flask under nitrogen was taken 5 mmol of BH_2Cl in ethyl ether[6] (3.7 ml)

(1) (a) H. C. Brown and G. Zweifel, *J. Amer. Chem. Soc.*, **82**, 4708 (1960); (b) H. C. Brown, "Hydroboration," W. A. Benjamin, New York, N. Y., 1962; (c) H. C. Brown and R. L. Sharp, *J. Amer. Chem. Soc.*, **88**, 5851(1966).
(2) H. C. Brown and G. Zweifel, *ibid.*, **83**, 1241 (1961).
(3) H. C. Brown and N. Ravindran, *ibid.*, **94**, 2112 (1972).
(4) G. Zweifel, *Organometal. Chem.*, **9**, 215 (1967).
(5) D. J. Pasto and P. Balasubramaniyan, *J. Amer. Chem. Soc.*, **89**, 295 (1967).
(6) The BH_2Cl solution in ethyl ether was prepared by adding stoichiometric quantity of $LiBH_4$ in ethyl ether solution to a solution of BCl_3 in ethyl ether at 0°, according to eq i.

$$LiBH_4 + BCl_3 + 2Et_2O \xrightarrow{EE} LiCl + 2BH_2Cl\text{–}OEt_2 \quad (i)$$