drolysis to the acid using sodium hydroxide solution, and isolation of the corresponding benzylthiouronium derivative. Recrystallization from aqueous alcohol gave pure $CH_3(CF_3)C{=}CFCOO^-$ $^+NH_2{=}C(OH_2)SCH_2C_6H_5$, 181–183°.

Anal. Calcd. for $C_{18}H_{14}F_4N_2O_2S$: C, 46.15; H, 4.14. Found: C, 45.85; H, 4.20.

Acknowledgment.—The authors gratefully acknowledge the financial support of this research by the Quartermaster Research and Engineering Command, U. S. Army, Natick, Massachusetts, with Dr. J. C. Montermoso and Mr. C. B. Griffis as the project officers.

Electrophilic Substitution at the Carbon–Lead Bond

G. C. ROBINSON

Ethyl Corporation, Baton Rouge, Louisiana

Received July 27, 1962

The rates of acetolysis of tetramethyllead, tetraethyllead, tetra-*n*-propyllead, tetra-*n*-butyllead, and tetraisoamyllead were determined at 24.9, 49.8, and 60.0°. A reactivity series methyl > ethyl > *n*-propyl ≅ *n*-butyl ≅ isoamyl was found. The entropies and enthalpies of activation were very similar for all these compounds. The rate of acetolysis of tetra-*n*-butyllead was, surprisingly, almost identical with that of di-*n*-butylmercury. Perchloric acid cleavage in acetic acid solvent gave a reactivity series similar to that in acetolysis.

Few quantitative data on rates of electrophilic substitution at saturated carbon atoms are available. Data on cleavage by protonic acids of a metal–alkyl bond are particularly limited. We report here the rates of acetolysis at three temperatures of a series of tetra-*n*-alkyllead compounds.

$$R_4Pb + HOAc \longrightarrow RH + R_3PbOAc$$

The rate of cleavage of these same compounds by perchloric acid in acetic acid solvent was also determined.

$$R_4Pb + HClO_4 \longrightarrow RH + R_3PbClO_4$$

The only directly comparable data in the literature were obtained by Winstein and Traylor[1] on organomercury compounds. Dessy and his co-workers[2] have also studied rates of hydrogen chloride cleavage of organomercury compounds. This latter work was largely in mixed solvents, and the data obtained are not directly comparable to those in this paper.

Results

Table I summarizes the acetolysis data obtained during this work, together with the derived entropies and enthalpies of activation. Table II shows detailed data for a typical acetolysis run. In Table III are collected the data on rates of perchloric acid cleavage in acetic acid solvent. A typical perchloric acid cleavage run is presented in detail in Table IV. The required control experiments are described in the Experimental.

Discussion

We have used the kinetic data to calculate relative reactivities in electrophilic substitution at the primary carbon atoms in this series. The results are summarized in Table V. For these relative reactivities to be meaningful it must be shown that special steric effects due to the quaternary lead atom are not affecting the rate constants. It must be assumed also that the change in trialkyllead cation formed on cleavage as one proceeds through the series of tetraalkyllead compounds does not substantially alter the reactivity of the lead–alkyl bonds.

Inspection of the enthalpies and entropies of activation in Table I makes it clear that no large steric effects are present, for the enthalpies and entropies of activation are all very similar. Such steric effects would not be expected *a priori* since a lead atom has twice the radius of a carbon atom. It is unlikely that variable inductive stabilization of the incipient trialkyllead cations affects our reactivity sequence; the large size of the lead atom should attenuate to insignificance this secondary inductive effect. Support for this view is obtained from recent work in silicon chemistry. Russel and Napgal have studied the rates of cleavage of alkyltrimethylsilanes with hydrogen bromide and aluminum bromide.[3] They find a reactivity sequence CH_3 >> C_2H_5 (1.0) > *n*-C_3H_7 (0.13) ≅ *n*-C_4H_9- (0.17) with a constant trimethylsilyl leaving group. This reactivity series is similar to those reported in Table V and indicates that the reactivity order may be general in electrophilic substitution. A similar qualitative order was found by Whitmore and Bernstein[4] for the cleavage of alkyl groups from organomercury compounds.

The relative rate data from acetolysis at 25, 50, and 60° are self-consistent within the limits of error. The perchloric acid cleavage data show the same reactivity order as acetolysis but with a wider spread between methyl and ethyl. These reactivity orders are not those one would predict for simple inductive effects on SE2 reactions.[5] In fact, the relative rates resemble those observed in SN2 reactions.[6]

A point of similarity between SN2 and SE2 reactions is the presence of five-coördinate carbon in the transition state in each. The similar reactivities in SN2 and SE2 reactions may arise from some such general feature of the transition states. Russel and Napgal[3] consider that their relative rates of alkyltrimethylsilane cleavage are due to an undefined steric effect. This suggestion seems reasonable but we have no really specific and

(1) (a) S. Winstein and T. G. Traylor, *J. Am. Chem. Soc.*, **77**, 3747 (1955); (b) **78**, 2597 (1956).

(2) (a) R. E. Dessy and J. Y. Kim, *ibid.*, **83**, 1167 (1961); (b) R. E. Dessy, G. F. Reynolds, and J. Y. Kim, *ibid.*, **81**, 2683 9(159).

(3) G. A. Russel and K. L. Napgal, *Tetrahedron Letters*, 421 (1961).

(4) F. C. Whitmore and H. Bernstein, *J. Am. Chem. Soc.*, **60**, 2626 (1938).

(5) E. D. Hughes and C. K. Ingold, *J. Chem. Soc.*, 244 (1935).

(6) L. P. Hammett, "Physical Organic Chemistry," McGraw-Hill Book Co., Inc., New York, N. Y., 1940, p. 154.

TABLE I

RATES OF ACETOLYSIS OF TETRAALKYLLEAD COMPOUNDS

Compound	$k_1 \times 10^5$, sec.$^{-1}$ 24.9°	49.8°	60.0°	ΔH^*, kcal./mole	ΔS^*, e.u.
$(CH_3)_4Pb$	1.16 ± 0.03	16.4 ± 0.2 17.9 ± 1.3	41.2 ± 1.3	20.8	−12
$(C_2H_5)_4Pb$	0.92 ± .06[a] .67 ± .08[a]	11.3 ± 0.6 10.5 ± .7	28.7 ± 1.8 27.7 ± 1.1[b]	20.1	−15
$(CH_3CH_2CH_2)_4Pb$	.225 ± .013	3.1 ± .2	8.2 ± 0.4	20.7	−15
$[CH_3(CH_2)_3]_4Pb$	.311 ± .005 .26 ± .025[a]	4.3 ± .1	10.6 ± .4	21.2	−13
$[(CH_3)_2CHCH_2CH_2)]_4Pb$	.300 ± .015	4.2 ± .3	12.2 ± .5	21.2	−13

[a] At 25.0°. [b] Rate from determination of unchanged tetraethyllead.

TABLE II

RATE OF ACETOLYSIS OF TETRAMETHYLLEAD

(24.9°, calcd. titer 6.56 ml.)

Time, hr.	Titer, ml.	$k_1 \times 10^5$, sec.$^{-1}$
0	0.06	...
3	.80	1.19
6	1.46	1.15
10	2.17	1.11
15.2	3.05	1.14
24.4	4.20	1.16
34	5.12	1.23
120	6.36[a]	

Mean 1.16 ± 0.03

[a] Seven half-lives, 97% of calculated titer.

TABLE III

RATES OF PERCHLORIC ACID CLEAVAGE OF TETRAALKYLLEAD COMPOUNDS

(25.0° in HOAc solvent)

Compound	Initial concentration, moles/l. R_4Pb	$HClO_4$	k_2, l./mole-sec.
$(CH_3)_4Pb$	0.0110	0.0104	0.22 ± 0.01
$(C_2H_5)_4Pb$	.0092	.0104	.024 ± .002
$(CH_3CH_2CH_2)_4Pb$	.0118	.0259	.0089 ± .0003
$[CH_3(CH_2)_3]_4Pb$	.0134	.0134	.0068 ± .0002
$[(CH_3)_2CHCH_2CH_2]_4Pb$	.0133	.0104	.0059 ± .0001

TABLE IV

CLEAVAGE OF TETRAETHYLLEAD BY PERCHLORIC ACID

(25.0° in HOAc solvent)

Time, sec.	Concn., moles/l. $HClO_4$	$(C_2H_5)_4Pb$	k_2, l./mole-sec.
0	0.0104	0.0092	...
180	.0098	.0086	0.037
600	.0091	.0079	.028
1200	.0083	.0071	.024
2100	.0074	.0062	.021
3000	.0065	.0053	.023
4200	.0058	.0046	.022

[a] Value at 180 sec. omitted. Mean 0.024 ± 0.002[a]

TABLE V

RELATIVE CLEAVAGE RATES

Acid	Temp., °C.	CH_3	C_2H_5	n-C_3H_7	n-C_4H_9	i-C_5H_{11}
HOAc	24.9	1.0	0.79	0.19	0.27	0.26
HOAc	49.8	1.0	.65	.18	.25	.25
HOAc	60.0	1.0	.68	.20	.26	.30
$HClO_4$	25.0	1.0	.11	.04	.03	.03

TABLE VI

COMPARISON OF TETRA-n-BUTYLLEAD WITH DI-n-BUTYLMERCURY[a] IN ACETOLYSIS

(50°)

Compound	$10^5 k_1$, sec.$^{-1}$	ΔH^*, kcal./mole	ΔS^* cal./mole °C.
$(n$-$C_4H_9)_4Pb$	4.3	21.2	−13
$(n$-$C_4H_9)_2Hg$	3.8	20.4	−16

[a] Data from ref. 1.

verifiable hypothesis to present at present as an explanation of these unexpected relative reactivities.

The data of Winstein and Traylor[1] permit a direct comparison of their data on the acetolysis of dibutylmercury with our data on acetolysis of tetrabutyllead. These data are summarized in Table VI. The similarities are striking. It is likely that these similarities between lead and mercury alkyls are general in the normal alkyl series. Comparative data on thallium and bismuth alkyls would be of interest since bismuth and thallium are adjacent to lead and mercury in the periodic table. If the rates of cleavage of these metal alkyls are similar to those of lead and mercury, it will demonstrate that at high atomic numbers bond characteristics are little affected by bond type.

Experimental

Materials.—A single supply of acetic acid was used. Its water content was determined as 0.2 wt. % by Karl Fischer titration. Tetramethyllead, tetraethyllead, tetra-n-butyllead, and tetraisoamyllead were supplied by the Ethyl Corp. Tetra-n-propyllead was prepared by the procedure of Grüttner and Krause.[7] A standard 0.0100 M solution of sodium acetate in acetic acid was prepared from sodium carbonate and glacial acetic acid. Approximately 0.01 M and 0.05 M solutions of perchloric acid in glacial acetic acid were prepared from 70% aqueous perchloric acid. The 0.05 M solution was dried with acetic anhydride. These solutions were standardized against the sodium acetate solution using a saturated solution of bromocresol green (National Aniline) as indicator.

Rates of Acetolysis.—Rates of acetolysis were followed by a sealed ampoule technique.[1a] The rate of formation of trialkyllead acetate was followed by titration with 0.01 M perchloric acid in acetic acid. Reaction solutions were *ca.* 0.01 M to minimize acid cleavage during titration. This low concentration also minimized disproportionation of trialkyllead acetate to tetraalkyllead and dialkyllead diacetate.

First-order rate constants were computed using a calculated initial concentration. Experimental infinities were within 5% of the calculated infinities. No systematic trends were noted in any of the rate constants. Reactions were followed to 80% completion or more. It was shown that, at 60.0°, 0.01 M solutions of trimethyllead acetate and triethyllead acetate did not observably change in titer during 32 half-lives of the parent lead alkyls. A similar stability was assumed for the other trialkyllead acetates.

A check on the analytical procedure used for following the rate of acetolysis was devised. It involved determination of unchanged tetraalkyllead rather than titration of the acetate ion formed. This method was applied to acetolysis of tetraethyllead at 60.0°. The individual samples (10 ml.) were prepared for analysis of unchanged tetraethyllead by partition between 10 ml. of benzene and 25 ml. of water containing 10 g. of sodium hydroxide. The aqueous layer was separated and extracted with 5 ml. more benzene. The benzene extracts were combined and analyzed for tetraethyllead by iodometric titration.[8] The rate constant obtained agreed well with that derived using titration of acetate ion.

Rates of Perchloric Acid Cleavage.—The perchloric acid solution used in this study was 0.0519 M. The reaction mixtures were prepared by weighing out the tetraalkyllead compound to

(7) G. Grüttner and E. Krause, *Ber.*, **50**, 278 (1917).

(8) Fr. Hein, A. Klein, and H. J. Mesée, *Z. anal. Chem.*, **115**, 177 (1939).

the nearest 0.1 mg. and adding the requisite amount of acetic acid at 25.0° with an automatic pipet. Then the desired amount of perchloric acid solution was added to the magnetically stirred solution of lead alkyl, using the same automatic pipet. The reaction mixture was immediately immersed in a constant temperature bath at 25.0°. Aliquot samples were removed periodically and titrated for acid content using a 0.0100 *M* solution of sodium acetate in acetic acid. The reactions were followed to at least 50% completion. Rate constants were calculated using an integrated form of the second-order rate equation, assuming the reaction to be first order in perchloric acid and first order in tetraalkyllead compound. The form assumed for this reaction was verified by the constancy and freedom from drift of the rate constants obtained.

Thiosugars. II. Rearrangement of 2-(3,4,6-Tri-*O*-acetyl-2-amino-2-deoxy-β-D-glucopyranosyl)-2-thiopseudourea[1a,b]

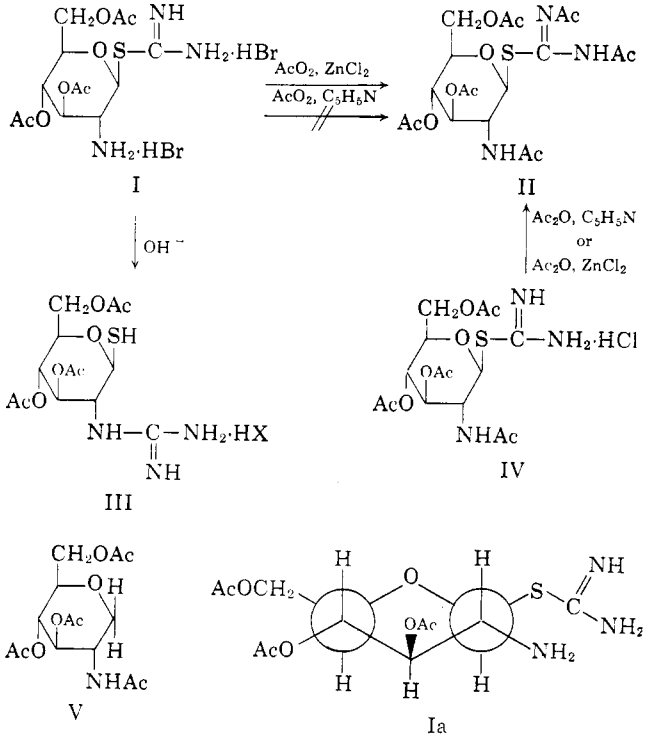
M. L. WOLFROM, D. HORTON, AND D. H. HUTSON[2]

Department of Chemistry, The Ohio State University, Columbus 10, Ohio

Received October 23, 1962

In neutral solution 2-(3,4,6-tri-*O*-acetyl-2-amino-2-deoxy-β-D-glucopyranosyl)-2-thiopseudourea dihydrobromide (I) undergoes rearrangement to form 3,4,6-tri-*O*-acetyl-2-deoxy-2-guanidino-1-thio-D-glucose (III). A product from the acetylation of I in acidic solution was identical with 1,3-di-*N*-acetyl-2-(2-acetamido-3,4,6-tri-*O*-acetyl-2-deoxy-β-D-glucopyranosyl)-2-thiopseudourea (II) which had been prepared by acetylation of 2-(2-acetamido-3,4,6-tri-*O*-acetyl-2-deoxy-β-D-glucopyranosyl)-2-thiopseudourea hydrochloride (IV). The behavior of I and related derivatives on desulfurization is discussed.

The condensation of 3,4,6-tri-*O*-acetyl-2-amino-2-deoxy-α-D-glucopyranosyl bromide hydrobromide with thiourea was described in part I,[1a] and the product was formulated as 2-(3,4,6-tri-*O*-acetyl-2-amino-2-deoxy-β-D-glucopyranosyl)-2-thiopseudourea dihydrobromide (I) by analogy with the products formed by condensation of other glycosyl halide derivatives with thiourea. Optical rotatory data supported a β-D anomeric configuration. In the case of the *N*-acetyl hydrochloride analog of I, 2-(2-acetamido-3,4,6-tri-*O*-acetyl-2-deoxy-β-D-glucopyranosyl)-2-thiopseudourea hydrochloride (IV), the C-1 to S linkage was established by reductive desulfurization.[1a] The present work establishes a direct correlation between I and IV by acetylation to the same derivative, and firmly establishes the existence of a C-1 to S bond in I. Acetylation of IV in pyridine with acetic anhydride gave a crystalline product, containing two more acetyl groups, formulated as 1,3-di-*N*-acetyl-2-(2-acetamido-3,4,6-tri-*O*-acetyl-2-deoxy-β-D-glucopyranosyl)-2-thiopseudourea (II). The possibility of anomerization in this reaction is very improbable. Under the same conditions, acetylation of I gave no trace of II, although the thin layer chromatographic procedure used would have revealed this product in very low concentration in the reaction mixture. This is to be expected in view of the readiness with which I rearranges in neutral or basic media, as described below. Acetylation with acidic catalysts permits reversible anomerization,[3] and the thermodynamically more stable anomer preponderates in the product at equilibrium. Acetylation of either I or IV with acetic anhydride and zinc chloride under the same conditions gave a mixture of two principal products in each case, with identical R_f values and intensities on thin layer chromatograms. The product formed in lesser amount was isolated from each reaction mixture and was shown to be identical with II; the other product was probably the α-D anomer of II.



Compound I was synthesized as a carbohydrate analog of 2-(2-aminoethyl)-2-thiopseudourea (AET) hydrobromide, which is one of the best known agents for protection of mammals against ionizing radiation.[4] It was hoped that a carbohydrate analog might retain this protective ability while exhibiting reduced toxicity.

It has been shown[5] that the protective ability of 2-(2-aminoethyl)-2-thiopseudourea is retained in the propyl analog 2-(3-aminopropyl)-2-thiopseudourea (APT) hydrobromide, but that activity falls off rapidly as the length of the alkyl chain is extended further. The protective activity of these two thiopseudourea derivatives

(1)(a) Part I of this series: D. Horton and M. L. Wolfrom, *J. Org. Chem.*, **27**, 1794 (1962); (b) Supported by contract no. DA-49-193-MD-2143 (R. F. Proj. 1187) from the Walter Reed Army Institute of Research, Washington, D. C. The opinions expressed in this article are those of the authors, and not necessarily those of the sponsoring agency.

(2) D. H. Hutson gratefully acknowledges a travel grant from the Wellcome Trust, 52 Queen Anne Street, London, W. 1.

(3) R. U. Lemieux, *Advan. Carbohydrate Chem.*, **9**, 1 (1954); B. Capon and W. G. Overend, *ibid.*, **15**, 11 (1960).

(4) A. Hollaender, ed., "Radiation Protection and Recovery," Pergamon Press, London, 1960.

(5) J. X. Khym, D. G. Doherty, and R. Shapira, *J. Am. Chem. Soc.*, **80**, 3342 (1958).