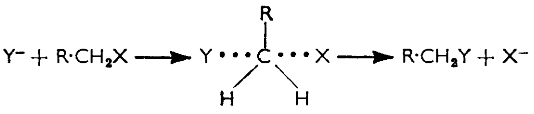
733. *Nucleophilic Substitution at a Metal-bearing Carbon Atom.*

By A. LEDWITH and L. PHILLIPS.

Nucleophilic substitution by iodide ion on chloromethylethylmercury proceeds at a rate which is faster even than related Finkelstein substitution on α-halogeno-ketones. The accelerating influence of the mercury atom is thought to occur *via* a halogen-bridged transition state, and the observed low, negative entropy of activation suggests that the reactant organomercurial also has a halogen-bridged structure. Solvolysis of butylchloromethylmercury in aqueous ethanol is of the second order in organomercurial, and the rate-determining ionisation is therefore considered to occur by a reaction in which one molecule of organomercurial acts as an electrophilic catalyst for ionisation of another.

NUCLEOPHILIC substitutions (replacements) are usefully and conventionally classified as S_N1 or S_N2 depending on the molecularity of the rate-determining step.[1] For primary alkyl halides $R\cdot CH_2X$ in dry acetone, reaction with halide ion (Finkelstein substitution) is usually of S_N2 type and the overall reaction can be represented as:



$$Y^- + R\cdot CH_2X \longrightarrow Y\cdots\overset{R}{\underset{H\quad H}{C}}\cdots X \longrightarrow R\cdot CH_2Y + X^-$$

The effect of changes in R on the rate constants for this type of reaction has been extensively studied[2] and, in particular, it has been shown that when R contains an α-carbonyl or nitrile group, there is a very large increase in the second-order rate constant compared with that of a simple primary alkyl halide.[3] *E.g.*, for reaction with potassium iodide in dry acetone at 50° the observed second-order rate constant for chloroacetone is 33,000 times greater than that for propyl chloride. Phenacyl halides react faster still[4]

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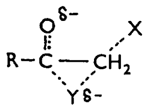
[1] Hughes, *Trans. Faraday Soc.*, 1938, **34**, 185; *Quart. Rev.*, 1951, **5**, 245.

[2] Ingold, " Structure and Mechanism in Organic Chemistry," Cornell Univ. Press, Ithaca, 1953; Gould, " Mechanism and Structure in Organic Chemistry," Holt, Rinehart, and Watson, New York, 1959; Hine, " Physical Organic Chemistry," McGraw Hill, New York, 1956; Streitwieser, *Chem. Rev.*, 1956, **56**, 571.

[3] Conant, Kirner, and Hussey, *J. Amer. Chem. Soc.*, 1925, **47**, 488.

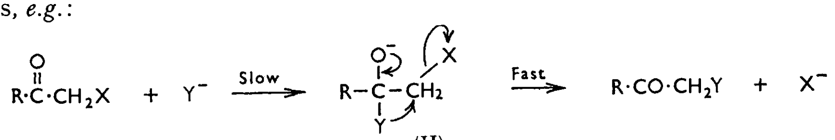
[4] Baker. *J.*, 1938, 445; *Trans. Faraday Soc.*, 1941, **37**, 643.

and it is clear that the transition state for this type of reaction involves some kind of interaction between the attacking halide ion and the carbonyl carbon atom. Dewar suggested[5] that the π-orbitals of the unsaturated group overlap with the p-orbital accommodating the entering and the leaving halide ions, and a similar idea, in valence-bond terminology, has been suggested by Winstein[6,7] who acknowledges that the relative electropositive nature of the carbonyl-carbon atom is likely to be the site for interaction with the ingoing halide ion and that this will yield a transition state (I).



(I)

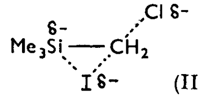
The occurrence of a transition state such as (I) is also indicated by the relatively slow rates of S_N2 reactions of phenacyl derivatives in which the carbonyl group is unable to adopt the necessary conformation. A further possibility, which has been virtually eliminated for phenacyl derivatives,[7] involves rate-determining attack on the α-carbon atom leading to an unstable intermediate (II) which rapidly rearranges to the reaction products, *e.g.*:



(II)

It seemed likely that the above postulates would be equally significant for nucleophilic substitution (replacement) at a metal-bearing carbon atom if the metal had suitable electrophilic character.

Eaborn and Jeffrey,[8] and Cooper and Prober,[9] independently studied the reaction between compounds of the type $R_3Si{\cdot}CH_2Cl$ and potassium iodide in dry acetone. The reaction was uniformly bimolecular and the second-order rate constants were about thirty times faster than for n-butyl chloride. This enhanced reactivity was explained by assuming a transition state (III) which is formally analogous to that proposed by Winstein[6] for reaction of α-halogeno-carbonyl compounds (I), and presumably involves the vacant $3d$-orbitals of silicon.



(III)

In the present work it was decided to investigate the effect of α-mercury atoms on nucleophilic substitution (replacement) since mercury has a well-established ability to expand its valency shell by co-ordination with a halide ion, this being mainly responsible for the frequent use of mercuric derivatives as electrophilic catalysts for ionisation reaction of organic halides.[2,10] Compounds of the type $R{\cdot}Hg{\cdot}CH_2X$ are readily available by reaction between alkylmercuric halides and diazomethane in ethereal solution,[11,12] *e.g.*, $EtHgCl + CH_2N_2 \longrightarrow EtHg{\cdot}CH_2Cl + N_2$. Chloromethylethylmercury was used throughout the present work, and in order to avoid any complication from either a reverse reaction or incomplete dissociation of metal halide[13] the chosen system involves reaction with potassium iodide in dry acetone. In this solvent potassium chloride is virtually insoluble and is precipitated during the reaction.

For the reaction between chloromethylethylmercury and potassium iodide in dry acetone at several temperatures, the reaction is uniformly bimolecular, it proceeds to

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[5] Dewar, " Electronic Theory of Organic Chemistry," Oxford Univ. Press, London, 1949, p. 73.

[6] Winstein, quoted by Bartlett, in Gilman's " Organic Chemistry," Wiley, New York, 1953, Vol. III, p. 35.

[7] Eliel, " Steric Effects in Organic Chemistry," ed. Newman, Chapman and Hall, London, 1956, pp. 103 *et seq.*

[8] Eaborn and Jeffrey, *J.*, 1954, 4266.

[9] Cooper and Prober, *J. Amer. Chem. Soc.*, 1954, **76**, 3943.

[10] Ledwith, Hojo, and Winstein, *Proc. Chem. Soc.*, 1961, 241.

[11] Ledwith and Whittleston, unpublished work.

[12] Hellerman and Newman, *J. Amer. Chem. Soc.*, 1932, **54**, 2859.

[13] Winstein, Savedoff, Smith, Stevens, and Gall, *Tetrahedron Letters*, 1960, No. 9, 24.

completion, and ethyliodomethylmercury can be recovered at the end of the reaction. The rate of reaction is given by:

$$-\mathrm{d}[\mathrm{I}^-]/\mathrm{d}t = -\mathrm{d}[\mathrm{EtHg{\cdot}CH_2Cl}]/\mathrm{d}t = k_2[\mathrm{EtHg{\cdot}CH_2Cl}][\mathrm{KI}].$$

Representative mean values of the second-order rate constant, k_2, are given in Table 1.

TABLE 1.

Reaction of chloromethylethylmercury with potassium iodide in dry acetone.

[EtHg·CH$_2$Cl] (10^{-2}M)	[KI] (10^{-2}M)	Temp.	10^2k_2 (l. mole^{-1} sec.$^{-1}$)
1·79	2·06	−9·25°	1·43 ± 0·04
1·47	2·06	0	4·17 ± 0·08
1·62	2·06	+4·5	7·07 ± 0·10

Table 2 shows the relative rates and Arrhenius parameters of the related reactions for a series of primary alkyl chlorides R·CH$_2$Cl, where R is a substituent likely to interact with the attacking nucleophile. Benzyl chloride and butyl chloride are included for comparison.

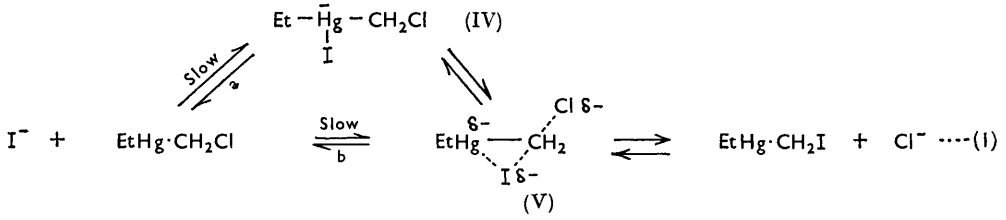
TABLE 2.

Reaction of primary alkyl chlorides with potassium iodide in dry acetone at 0°.

Compound	k_2 (l. mole^{-1} sec.$^{-1}$)	ΔH‡ (kcal./mole)	ΔS‡ (cal./deg.)	Relative rate
C_2H_5·Hg·CH$_2$Cl	$4·17 \times 10^{-2}$	16·3	−4·5	$1·0 \times 10^{6}$
CH$_3$·CO·CH$_2$Cl *	$2·12 \times 10^{-3}$	19·5	+1·5	$5·2 \times 10^{4}$
Ph·CH$_2$Cl *†	$1·4 \times 10^{-5}$	17·0	−26·9	$3·5 \times 10^{2}$
Me$_3$Si·CH$_2$Cl *†	$1·5 \times 10^{-6}$	20·1	−19·9	37·0
Bu^{n}Cl *†	$4·1 \times 10^{-8}$	19·0	−29·4	1

* Data from ref. 3. † Extrapolated from data at higher temperatures. ‡ Data from refs. 8 and 9.

The specific rate of the reaction of chloromethylethylmercury with iodide ion is about 10^6 times faster than that for n-butyl chloride and approximately 20 times faster than that for chloroacetone. This enormous enhancement can readily be understood by assuming a transition state (V) which is analogous to that (III) proposed for the silicon derivative. The great affinity of mercury for halide ion would be expected to facilitate formation of state (V). However, in this case it is perhaps equally likely that there is rate-determining formation of an intermediate (IV), similar to (II), which rapidly rearranges to products. The probability of intermediates such as (IV) is, of course, much higher than for halogenoketones.



In dry acetone it is not possible to differentiate between these alternatives on the basis of the present kinetic work but when water is added to the reaction system the kinetic behaviour changes. Table 3 shows the effect of water on the rate of the reaction with iodide ion, and, as shown in the Experimental section, the reaction becomes uniformly of first order in chloromethylethylmercury and apparently independent of iodide ion when the solvent is changed from dry acetone to ~80% aqueous acetone.

The change from dry acetone to 80% aqueous acetone causes a considerable increase in the ionising power of the solvent [2,14] and many cases are known in which a typical

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[14] Smith, Fainberg, and Winstein, *J. Amer. Chem. Soc.*, 1961, **83**, 618.

S_N2 reaction in dry acetone becomes ionisation-limited, *i.e.*, S_N1, in 80% aqueous acetone.[2,15] In the case of chloromethylethylmercury an ionisation-limited reaction could inolve the steps:

$$\mathrm{EtHg{\cdot}CH_2Cl} \overset{\text{Slow}}{\rightleftharpoons} \mathrm{EtHg{\cdot}CH_2{}^+Cl^-} \xrightarrow[\text{Fast}]{\text{KI}} \mathrm{EtHg{\cdot}CH_2I + KCl} \quad . \; . \; . \; . \; . \quad (2)$$

Reaction (2) would be expected to become faster as the solvent becomes more aqueous [14] and experimentally it is found that increasing the water content of the solvent from 16·7% to 20% lowers the first-order rate constant by 11% (Table 3).

TABLE 3.

Effect of water on the reaction between potassium iodide and chloromethylethylmercury in acetone at 0°.

$[\mathrm{EtHg{\cdot}CH_2Cl}]$ $(10^{-2}\mathrm{M})$	[KI] $(10^{-2}\mathrm{M})$	$[\mathrm{H_2O}]$ (M)	$\mathrm{H_2O}$, vol. % in solvent	10^2k_2 (l. mole^{-1} sec.$^{-1}$)	10^4k_1 (sec.$^{-1}$)
1·47	2·06	0	0	4·17	
1·66	2·06	0·02	0·036	4·16	
0·76	1·88	9·25	16·7		5·55
1·18	1·65	13·88	20·0		4·95

In addition, the observed first-order rate constant in 80% aqueous acetone at 0° ($4{\cdot}95 \times 10^{-4}$ sec.$^{-1}$) is much larger than can be expected in view of the results for solvolysis in 80% aqueous ethanol (see below), which is a much better ionising solvent as measured by the corresponding Winstein–Grunwald Y-values [2] ($Y = 0{\cdot}00$ and $-0{\cdot}67$ for 80% aqueous ethanol and 80% aqueous acetone, respectively).

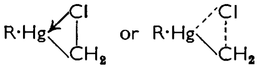
Consequently it is possible that in aqueous acetone the mechanism of the reaction with iodide ion involves rapid and complete formation of an intermediate (IV) which is slowly converted into products, so that the overall rate of disappearance of iodide ion would be of first order in $\mathrm{EtHg{\cdot}CH_2Cl}$ and independent of iodide ion, as observed experimentally.

Even in dry acetone a similar mechanism could be operating, as discussed above, but the observed reaction kinetics would then require either that the intermediate (IV) has insignificant stability in dry acetone or that iodide ion is a much better nucleophile in 80% aqueous acetone than in dry acetone (a premise which is unacceptable [13]).

Finally, if a reaction such as (2) occurred in dry acetone addition of small amounts of water should accelerate it and this is not the case (Table 3).

It appears therefore that whereas intermediates such as (IV) might occur in the reaction between chloromethylethylmercury and iodide ion in aqueous acetone (reaction 1a), the corresponding reaction in dry acetone is more likely to involve direct formation of a transition state similar to that encountered in the reaction of α halogeno-ketones with iodide ion, this type being especially favoured for organomercury derivatives (reaction 1b).

It has been assumed above that the structure of $\mathrm{EtHg{\cdot}CH_2Cl}$ is essentially linear, with mercury forming two *sp*-hybrid bonds to carbon. It is possible, however, that in these halogenomethyl derivatives the C–Hg–C bond angle may be distorted by interaction of the halogen with the mercury atom. Thus the structure might be better represented:



Some evidence for this type of structure can be deduced from the absorption spectra and general properties of these compounds [11] and it is conceivable that the observed low negative entropy of activation for the reaction with iodide ion is in part due to the occurrence of such a structure. This follows since the transition state for reaction would also possess a halogen-bridge structure similar to the reactant organomercury compound.

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[15] Winstein, Hojo, and Smith, *Tetrahedron Letters*, **1960**, No. 22, 12; Winstein, Ledwith, and Hojo, *ibid.*, 1961, No. 10, 341.

Although the estimation of Arrhenius parameters based on rate studies over a small temperature range may lead to erroneous conclusions, it seems clear that there is a very favourable entropy of activation for the reaction of iodide ion with chloromethylethylmercury. As shown in Table 2, this favourable entropy factor is the main cause of the large increase in rate over that for the corresponding reaction of the chloromethyl silicon compound. Since the transition states (III) and (V) for these two reactions are very similar, the entropies of activation should also be fairly close and the large difference observed lends considerable support to the suggestion that the organomercury derivatives have a halogen-bridged structure.

Solvolysis in Aqueous Ethanol.—In a preliminary investigation of the solvolysis of butylchloromethylmercury the reaction was of the second order in organomercury derivative up to about 40% reaction. The reaction was not studied for longer periods because decomposition of the organomercury derivative would then have been appreciable and also the hydrogen chloride formed could begin to attack such of it as was unchanged. Representative second-order rate constants for reaction of a 0·07811M-solution at 25° were: in 4 : 1 ethanol–water $9{\cdot}8 \times 10^{-5}$; and in 3 : 2 ethanol–water $15{\cdot}4 \times 10^{-5}$ l. mole^{-1} sec.$^{-1}$. The 58% increase on changing from 80% to the more ionising 60% aqueous ethanol suggests that the rate-determining step is here an ionisation. Accordingly the observed kinetic order can best be understood if it is assumed that the organomercurial is behaving as an electrophilic catalyst [2,10] for solvolysis of a second molecule of organomercurial, *i.e.*:

$$2\mathrm{BuHg{\cdot}CH_2Cl} \rightleftharpoons \mathrm{BuHg{\cdot}CH_2{}^+[Bu\overset{-}{Hg}Cl{\cdot}CH_2Cl]} \xrightarrow{\mathrm{H_2O}} \mathrm{BuHg{\cdot}CH_2{\cdot}OH} + \mathrm{BuHg{\cdot}CH_2Cl} + \mathrm{HCl}$$

and the reaction rate is given by:

$$\mathrm{d[HCl]}/\mathrm{d}t = -\mathrm{d[BuHg{\cdot}CH_2Cl]}/\mathrm{d}t = k_2\mathrm{[BuHg{\cdot}CH_2Cl]}^2.$$

It is likely that carbonium ions such as $\mathrm{BuHg{\cdot}CH_2{}^+}$ would be stabilised by overlap of the filled and penultimate 5*d*-orbitals of the mercury atom. Interaction of metal *d*-orbitals with adjacent carbonium ion structures has been characterised by Hill and Richards [16] for ferrocenylmethyl derivatives, and d_π–p_π overlap of the kind proposed here is comparable with that proposed for some transition-metal carbonyl and nitrile derivatives and has been treated theoretically for many elements.[17]

Although there are several obvious ways in which this work could be extended or clarified, all further work has been discontinued because, apart from toxicity, the halogenomethylmercury compounds are extremely unpleasant lachrymators and vesicants, contact with them causing immediate blistering.

EXPERIMENTAL

Organomercurials.—Chloromethylethylmercury and butylchloromethylmercury were prepared from the appropriate alkylmercuric chloride by reaction with diazomethane in diethyl ether.[11,12] The compounds were purified by repeated fractionation through a small Vigreux column. They had b. p. 57—58°/1 mm. and 81°/1 mm., respectively.

All handling of them (including kinetic runs) must be carried out under a fume-hood and protective gloves should be worn at all times.

Acetone.—" AnalaR " acetone was dried by slow passage down a 2-ft. column of Linde molecular sieve type 4A, followed by distillation from a small amount of powdered molecular sieve. A middle fraction of constant b. p. 56·0°/760 mm. was used.

Potassium Iodide.—" AnalaR " material was recrystallised from distilled water and dried at 120° for 3 hr. before use.

Ethanol.—Absolute ethanol was purified by Lund and Bjerrum's method.[18]

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[16] Hill and Richards, *J. Amer. Chem. Soc.*, 1961, **83**, 4216.

[17] Craig, Maccoll, Nyholm, Orgel, and Sutton, *J.*, 1954, 332.

[18] Lund and Bjerrum, *Ber.*, 1931, **64**, 210.

Constant-temperature Baths.—Since the total reaction times were always very short, it was convenient to use baths of diethylene glycol and benzene for the runs at −9·25° and +4·5°, respectively. These temperatures were measured with a calibrated thermometer and were constant throughout the runs. Ice–water baths were used for the reaction at 0° and the solvolysis of butylchloromethylmercury was studied at 25·0° in a conventional water-thermostat bath.

Kinetic Measurements.—The reaction was followed by the conventional sampling technique, aliquot parts of the reaction mixture being withdrawn by pipette at appropriate intervals and quenched in ice-cold pentane–water. The pentane layer re-extracted with water. The iodide ion content of the total aqueous solutions was estimated by potentiometric titration with silver nitrate solution in the presence of a 10% acetic acid–sodium acetate buffer. A typical run is shown in Table 4.

TABLE 4.

Typical kinetic run in dry acetone.

Temp. = −9·25°. Initially: [KI] = 0·02062M; [EtHg·CH$_2$Cl] = 0·01798M; also [AgNO$_3$] = 2·123 × 10^{-3}M.

Time (min.)	$AgNO_3$ titre (ml.)	[EtHg·CH$_2$Cl] (10^{-3}M)	[KI] (10^{-3}M)	10^2k_2 (l. mole^{-1} sec.$^{-1}$)
0	48·60	17·98	20·62	—
3·08	44·00	16·02	18·67	1·47
9·58	40·55	14·56	17·22	1·43
20·42	35·75	12·51	15·16	1·45
26·67	33·70	11·64	14·31	1·42
35·25	31·30	10·62	13·28	1·39

Time (min.)	$AgNO_3$ titre (ml.)	[EtHg·CH$_2$Cl] (10^{-3}M)	[KI] (10^{-3}M)	10^2k_2 (l. mole^{-1} sec.$^{-1}$)
49·92	27·70	9·09	11·76	1·37
62·25	25·05	7·97	10·63	1·43
73·05	23·15	7·16	9·83	1·46
87·20	21·65	6·53	9·19	1·40
99·53	20·10	5·86	8·53	1·43
			Mean	1·43

TABLE 5.

Typical kinetic run in 80% aqueous acetone.

Temp. = 0°. Initially: [KI] = 0·01650M; [EtHg·CH$_2$Cl] = 0·01116M; also [AgNO$_3$] = 1·013 × 10^{-3}M.

Time (min.)	$AgNO_3$ (ml.)	Reaction (%)	10^2k_2 (l. mole^{-1} sec.$^{-1}$)	10^4k_1 (sec.$^{-1}$)
2·25	77·85	6·5	2·77	5·09
5·00	73·90	13·7	2·88	4·96
8·50	69·05	22·5	3·34	5·03
13·17	63·40	32·8	3·44	5·04

Time (min.)	$AgNO_3$ (ml.)	Reaction (%)	10^2k_2 (l. mole^{-1} sec.$^{-1}$)	10^4k_1 (sec.$^{-1}$)
18·85	58·20	42·2	3·52	4·86
27·17	52·15	54·9	4·02	4·88
38·25	44·70	66·7	4·09	4·80
			Average	4·95

TABLE 6.

Typical solvolysis in 80% aqueous ethanol at 25° of 0·07811M-Bu^{n}Hg·CH$_2$Cl.

Time (hr.)	20·13	23·44	91·00	114·75	141·00
Reaction (%)	12·2	14·2	36·6	41·8	47·3
10^4k_2 (l. mole^{-1} sec.$^{-1}$)	1·06	1·04	0·98	0·96	0·98

When the reaction was carried out in 80% aqueous acetone, the kinetic order appeared to change as shown for a representative run in Table 5.

For the solvolytic study with butylchloromethylmercury in 80% aqueous ethanol, aliquot parts were removed at appropriate intervals, and titrated directly with a standard solution of sodium hydroxide to B.D.H. 4·5 Indicator. Some results are given in Table 6.

In no reaction in aqueous solvents were the products recovered quantitatively apparently because of the thermal instability of compounds containing mercury and oxygen attached to the same carbon atom.[11]

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DEPARTMENT OF INORGANIC AND PHYSICAL CHEMISTRY,
THE UNIVERSITY, LIVERPOOL, 7.

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