Anal. Calcd. for $C_{20}H_{23}O_3N$: C, 73.82; H, 7.12. Found: C, 74.85; H, 7.43.

Catalytic reduction of 0.45 g. of XXII in ethyl acetate over pre-reduced Adams catalyst resulted in the uptake of 126 ml. (2 molar equivalents) of hydrogen. The recovered product (0.35 g.) reacted with sodium hypoiodite in aqueous dioxane to give a yellow solid, m.p. 121–122°, identified as iodoform (lit.[21] m.p. 119–121°).

[21] "Merck Index," 6th ed., Merck & Co., Inc., Rahway, N. J., 1952, p. 530.

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[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF IOWA STATE COLLEGE]

Ion-Pair Formation in the Reactions of Alkyl Iodides with Silver Salts

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The reactions of silver nitrate and silver perchlorate with methyl, ethyl, isopropyl and neopentyl iodides have been studied. The effects of added salts, the fact that silver nitrate reacts more rapidly than silver perchlorate, and the low reactivity of neopentyl iodide, all indicate that the reactions have some S_N2-character. Third-order kinetics cannot be documented clearly because variations in ionic strength are not controllable. However, the kinetic data are best rationalized by a mechanism in which both silver cations and the accompanying anions participate in the rate-determining step of the reactions. The results, combined with data from the literature, are interpreted in terms of a mechanism in which the first-formed product is an ion pair composed of an anion and a carbonium ion.

Kinetic studies of the reactions of silver nitrate,[2–12] silver perchlorate[13] and other silver salts[14] with alkyl halides, although numerous, have left a rather clouded picture as to the actual mechanism(s) of such reactions. The view that they are "SN1-like" is widely held[15] and is largely due to the familiar sequence of reactivities, tertiary > secondary > primary, which is observed when alkyl halides are treated with an alcoholic solution of silver nitrate.[16] This qualified statement has often been extended to the specification of a mechanism including the intermediate production of a carbonium ion.

$$R\text{-}X + Ag^+ \longrightarrow R^+ + AgX \qquad (1)$$

$$R^+ + Y^- \longrightarrow R\text{-}Y \qquad (2)$$

Kornblum, *et al.*,[14] have argued that SN1-like reactivity cannot be considered as diagnostic for a mechanism involving free carbonium ions. They maintain that the transition states for concerted reactions may, in some instances, involve the development of large amounts of carbonium ion character in the substrate undergoing substitution. This is quite consistent with most modern views of the continuity in mechanism in all nucleophilic displacement reactions.[17] Particular stress is laid on the low reactivity of neopentyl iodide toward silver nitrite since the phenomenon is indicative of a steric barrier to the reaction similar to that observed in displacements, such as halide exchanges in non-hydroxylic solvents, which are classic examples of limiting SN2 reactions.

The study of these reactions by conventional kinetic methods has been regarded as rather difficult and even under the most favorable circumstances is somewhat unsatisfying. Heterogeneity is the greatest problem, although it does not seem to be as universally troublesome as has often been supposed. Most silver salts are but sparingly soluble, especially in organic solvents, so many observations have been made with a reactant in the solid phase. Kornblum, *et al.*, strongly suggest that under such circumstances the reactions are likely to occur on the surface of the solid reactant. If such is the case, kinetic analysis will be complex and is likely to yield little information concerning the molecularity with respect to the reagent except for those conclusions which may be inferred from relative reactivities. The very high solubility of silver salts in acetonitrile and the generally great solubility of silver nitrate and silver perchlorate do provide a means of carrying out kinetic studies in solutions which are, at the outset, homogeneous. Since solid silver halide will always be deposited throughout the reaction, two new problems arise. First, the solid silver halide may provide a surface on which reaction may occur and, second, it is virtually impossible to maintain constant ionic strength throughout the reaction. Catalysis by precipitated silver halide has often been reported.[4,18,19]

Consideration of the details of various investigations leaves many questions as to the actual status of this problem. Donnan and Burke[2] studied the reactions of silver nitrate with various alkyl iodides in alcohol and alcohol–water solutions. Their

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[2] A. K. Burke and F. G. Donnan, *J. Chem. Soc.*, **85**, 555 (1904); F. G. Donnan and A. K. Burke, *Z. physik. Chem.*, **69**, 148 (1909).

[3] A. F. Donnan and H. E. Potts, *J. Chem. Soc.*, **97**, 882 (1910).

[4] G. Senter, *ibid.*, **97**, 346 (1909); **99**, 95 (1911).

[5] H. V. Euler and A. Ölander, *Z. Elektrochem.*, **36**, 506 (1930).

[6] J. W. Baker, *J. Chem. Soc.*, 987 (1934).

[7] E. Gand, *Bull. soc. chim.*, **12**, 203 (1945).

[8] I. Dostrovsky and E. D. Hughes, *J. Chem. Soc.*, 169 (1946).

[9] C. Prevost and H. Martin, *Compt. rend.*, **226**, 1626 (1946).

[10] C. Prevost and E. Singer, *Bull. soc. chim. France*, 1608 (1950).

[11] M. Murakami, S. Oae and S. Takeuchi, *Bull. Chem. Soc. Japan*, **24**, 1 (1951).

[12] J. Landois, *Compt. rend.*, **238**, 1520 (1954).

[13] M. F. Redies and T. Iredale, *J. Phys. Chem.*, **48**, 224 (1944).

[14] For an excellent review of the general subject of reactions of silver salts including a discussion of the mechanistic implications of relative reactivities and products see N. Kornblum, R. A. Smiley, R. K. Blackwood and D. C. Iffland, THIS JOURNAL, **77**, 6269 (1950).

[15] See, for example, C. K. Ingold, "Structure and Mechanism in Organic Chemistry," Cornell University Press, Ithaca, N. Y., 1953, p. 358.

[16] R. F. Shriner, R. C. Fuson and D. Y. Curtin, "The Characterization of Organic Compounds," John Wiley and Sons, Inc., New York, N. Y., 1955.

[17] For an adequate review see J. Hine, "Physical Organic Chemistry," McGraw-Hill Book Co., Inc., New York, N. Y., 1955.

[18] J. W. Baker, *J. Chem. Soc.*, 987 (1934).

[19] E. D. Hughes, C. K. Ingold and S. Masterman, *ibid.*, 1236 (1937).

principal observations may be summarized: (1) the reactions are close to first order with respect to the iodides but are apparently between first and second order with respect to silver nitrate; (2) the addition of ionic nitrate in the form of ammonium or calcium nitrate accelerates the reaction; (3) there is apparently a genuine autocatalytic effect since the specific velocity at a given concentration of reactants is highest in those solutions which have reached that concentration from the highest initial concentrations; (4) addition of the known, soluble reaction products, nitric acid and the alkyl nitrate has no influence on the reaction rate in absolute alcohol; and, (5) if precipitated silver iodide is removed by filtration the reaction continues at the same rate as that found in a similar, but unfiltered, mixture. Furthermore, Donnan and Potts[3] found that in acetonitrile solution the rate of the reaction of ethyl iodide with silver nitrate showed only small autocatalysis. Senter[4] reported that the reactions of methyl iodide and of α-bromoacids with silver nitrate in water were strongly catalyzed by traces of solid silver bromide. However, he also observed that the reactions of α-bromoesters with silver nitrate in ethanol were influenced relatively little by silver bromide. Hughes, Ingold and Masterman[19] have described silver bromide catalysis in the reactions of silver oxide, nitrate and acetate with secondary bromides. One can only conclude that heterogeneous catalysis is particularly significant in aqueous systems and that its importance in other media varies and can, in some instances, become insignificant. One particularly confusing fact is Senter's observation that, despite the heterogeneous catalysis, fresh solutions of the bromoacids gave consistent values for calculated second-order rate constants with different initial concentrations of reactants. This he attributed to some unknown, fortuitous cancellation of effects.

The recent development of the reaction between alkyl iodides and silver nitrate in acetonitrile as a preparative method for alkyl nitrates[20,21] prompted us to reinvestigate the reaction under these conditions.

Results and Discussion

Reactivity Relationships.—Although analysis of the kinetic data is difficult and somewhat unsatisfying, it is possible to compare reactivities semiquantitatively. Table I shows rate data suitable for comparative purposes. Data are expressed as third order rate "constants." Since the constants are concentration dependent (*vide infra*) the comparison is made as nearly as possible at similar initial concentrations of silver salts. The data show that α-branching increases reactivity as is the case in the familiar characterization test[16] with alcoholic silver nitrate. However, the low reactivity of neopentyl iodide shows that steric hindrance, such as is characteristic of SN2 reactions, must also play a role. Further indication of the S$_N$2-like character of the reactions is found in the effects of anions on the reaction rates. Silver nitrate is much more reactive than silver perchlorate. If the only effect of the two ions were regulation of the silver ion activity, as would be expected if reaction 1 were rate-determining, the perchlorate should be the more reactive of the two salts. This conclusion follows from the fact that nitrate is the more nucleophilic of the two anions and should, therefore, bind silver ions the more extensively.

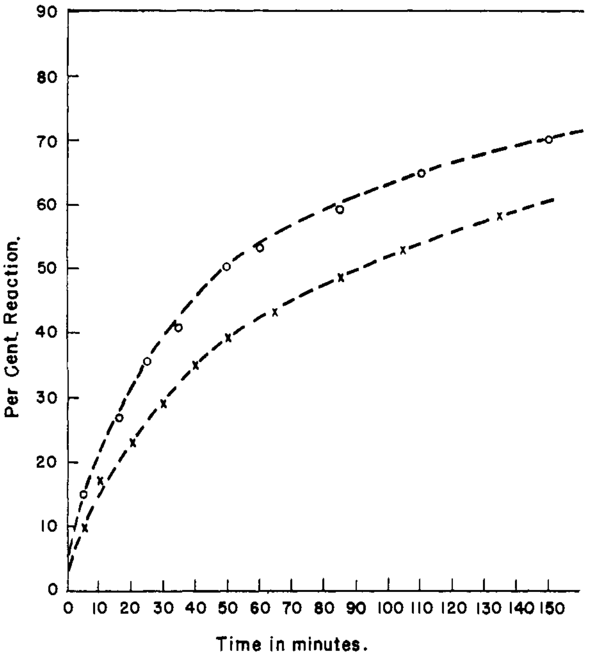

Fig. 1.—Catalytic effect of adding $LiCl_4$; X-X-X, $[i\text{-PrI}]_0 = 0.264$, $[AgClO_4]_0 = 0.266$, $[LiClO_4] = 0$; O-O-O, $[i\text{-PrI}]_0 = 0.220$, $[AgClO_4]_0 = 0.264$, $[LiClO_4] = 0.176$; acetonitrile solvent; 25°.

TABLE I

RATES OF REACTION OF SILVER SALTS WITH ALKYL IODIDES

Alkyl group	T, °C.	Solvent	Silver salt	Init. concn. of silver salt	$k_3 \times 10^2$, l.^{2} mole^{-2} sec.$^{-1}$
Methyl	25	Acetonitrile	Nitrate	0.1357	2.6
Ethyl	25	Acetonitrile	Nitrate	.109	18
Isopropyl	0	Acetonitrile	Nitrate	.1529	3.0
Neopentyl	25	Acetonitrile	Nitrate	.2754	0.064
t-Butyl	0	Acetonitrile	Nitrate	.1	[b]
Methyl	25	Benzonitrile	Nitrate	.0596	18
Isopropyl	25	Acetonitrile	Perchlorate	.1022	0.26
Isopropyl	25	Acetonitrile	Perchlorate	.2662	0.23
Isopropyl	25	Acetonitrile	Perchlorate	.2636 + .2752 $LiClO_4$	0.22[a]
Neopentyl	25	Acetonitrile	Perchlorate	0.266	0.0031
t-Butyl	0	Acetonitrile	Perchlorate	0.2	[b]

[a] Calculated assuming, $[LiClO_4]_0 + [AgClO_4] = [ClO_4^-]$.
[b] Too fast to measure.

That even the weakly nucleophilic perchlorate ion plays a part in the reactions is indicated by the effect of lithium perchlorate on the rates. Addition of the lithium salt increases the rate of reaction of isopropyl iodide substantially and, as is shown in Fig. 1, gives a significant acceleration with even neopentyl iodide. This is contrary to the result that would be expected from a salt effect on a silver ion-assisted S$_N$1 reaction. The same effect was observed when lithium perchlorate was added to

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[20] L. F. Fieser and W. von E. Doering, THIS JOURNAL, **68**, 2252 (1946).

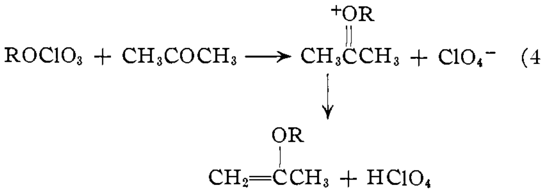
[21] A. F. Ferris, K. J. McLean, I. C. Marks and W. D. Emmons, *ibid.*, **75**, 4078 (1953).

methyl iodide–silver reaction mixtures in acetone solution (*vide infra*). We conclude that anions are regularly included in the rate-determining transition states in the reactions of simple alkyl iodides with silver salts. *t*-Butyl iodide, which is too reactive to permit quantitative measurements, may well be an exception to this generalization.

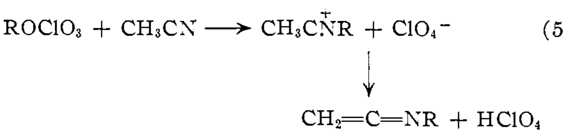
Products and Mechanism.—There is no single, rigorous proof but all lines of evidence indicate that the transition state is, in essence, that suggested by Kornblum, *et al.*,[14] and shown in equation 3.

$$X^- + R{-}I + Ag^+ \longrightarrow \underset{\substack{\text{transition}\\ \text{state}}}{X^-\overset{+}{R}\,IAg} \longrightarrow \text{products} \quad (3)$$

There is difficulty, however, in accounting for the reaction products from silver perchlorate. The logical product to be expected would be the neutral ester, $ROClO_3$. The ultimate products are perchloric acid and dark colored materials which have not been characterized. It might be presumed that alkyl perchlorates are formed and then undergo solvolytic reactions, such as 4 and 5, to give alkylates which undergo further condensation reactions with the solvent



$$ROClO_3 + CH_3COCH_3 \longrightarrow CH_3\overset{\overset{+}{O}R}{\overset{\|}{C}}CH_3 + ClO_4^- \quad (4)$$
$$\downarrow$$
$$CH_2{=}\overset{OR}{\overset{|}{C}}CH_3 + HClO_4$$



$$ROClO_3 + CH_3CN \longrightarrow CH_3C\overset{+}{N}R + ClO_4^- \quad (5)$$
$$\downarrow$$
$$CH_2{=}C{=}NR + HClO_4$$

However, the report of Meyer and Spoorman,[22] who appear to be the only experimenters to have survived a study of alkyl perchlorates, makes it seem doubtful that these compounds would be sufficiently active solvolytically to undergo these reactions. They observed that, although the formation of methyl perchlorate from silver perchlorate and methyl iodide in benzene was inhibited by moisture, alkyl perchlorates, once formed, reacted only slowly with water. To attribute this slow reaction to the fact that the esters were insoluble in water would require that their solubility be far less than would be expected (*cf.* nitroalkanes). It is also difficult to support the assumption that traces of water in our supposedly anhydrous solvents were responsible for the failure to produce the esters. In the first place, the concentrations used were high enough to preclude the possibility that minute traces could divert the reaction stoichiometrically. Secondly, if water in sufficient amount were present the products would be expected to be alcohols and ethers and there would be little reason to expect any attack on the solvents to occur.

Our conclusion is that the reactions of silver perchlorate have the earmarks of carbonium ion reactions which are "catalyzed" by perchlorate ions. A two-step mechanism incorporating these features can be written with an ion-pair as the first reaction product

$$X^- + R{-}I + Ag^+ \longrightarrow X^-R^+ + AgI \quad (6)$$

$$X^-R^+ \begin{cases} \longrightarrow R{-}X \\ \longrightarrow HX + \text{olefin or solvent alkylates} \end{cases} \quad (7)$$

The low aptitude of the carbonium–perchlorate ion pair for collapse is consistent with the observations of Winstein and his co-workers[23] concerning the low aptitude of perchlorate ion pairs for the internal return reaction. If the mechanism is right, it must be conceded that in dry benzene, collapse occurs because of the low dielectric constant and low nucleophilicity of the solvent.

The mechanism receives robust support from reevaluation of the work of Burke and Donnan[2] and from the recent studies of Kornblum and Hardies.[24] The former workers made a particularly careful study of the reaction of ethyl iodide with silver nitrate in ethanol. They found that nitric acid and ethyl nitrate were produced in the ratio 70:30. The yield of nitric acid was studied carefully under a variety of conditions. Very significantly it was found that the yield was *independent of the concentration of nitrate in the solution*. This is shown by invariance over the course of a run and with the addition of nitrate salts. Since the reaction is accelerated by the addition of nitrate and product distribution is not affected, the rate-determining and product-determining steps must be distinct from one another. It is hard to see how this conclusion can be altered by consideration of the mild autocatalytic effects observed in ethanol.

It is immediately evident that the ion pair mechanism, equations 6 and 7, provides an explanation of the observed results.

Kornblum and Hardies[24] reported that optically active 2-octyl iodide reacted with silver nitrate, either in acetonitrile solution or in suspension in ether, to give 2-octyl nitrate of inverted configuration. The steric result is easily explained by the attack of nitrate on the substrate and is perfectly compatible with a mechanism involving a rigidly oriented ion pair as an intermediate. The result is clearly incompatible with mechanisms involving free carbonium ions. Kornblum and Hardies also showed that there must be significant variation in the mechanisms of displacements by silver salts by showing that optically active α-phenylethyl chloride reacts with both silver nitrate and silver nitrite in ether with retention of configuration although silver nitrate gave inversion in acetonitrile solution.

The mechanism which we propose has much in common with the merged E_2–S_N2 mechanism which has recently been proposed by Winstein[25] and supported by Eliel.[26] The intermediate in our mechanism is visualized as having more carbonium ion character than one would read into the

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(22) J. Meyer and W. Spoorman, *Z. anorg. allgem. Chem.*, **228**, 341 (1936).

(23) S. Winstein, E. Clippinger, A. H. Fainberg and G. C. Robinson, THIS JOURNAL, **76**, 2597 (1954); *Chemistry & Industry*, 664 (1954); S. Winstein and A. H. Fainberg, THIS JOURNAL, **80**, 459 (1958), and intervening papers in the series.

(24) N. Kornblum and D. E. Hardies, Abstracts of the 130th Meeting of the American Chemical Society, September, 1956, p. 2-O.

(25) S. Winstein, D. Darwish and N. J. Holness, THIS JOURNAL, **78**, 2915 (1956).

(26) E. Eliel and R. S. Ro, *Tetrahedron*, **2**, 353 (1958).

TABLE II

REACTION OF ETHYL IODIDE WITH SILVER NITRATE IN ACETONITRILE AT 25°

t in sec.	$[AgNO_3]$	[RI]	$k_3 \times 10^2$, l.^{2} mole^{-2} sec.$^{-1}$	$k_2 \times 10^3$, l. mole^{-1} sec.$^{-1}$
0	0.0510	0.2511		
117	.0468	.2469	5.72	3.54
350	.0402	.2403	6.13	2.80
576	.0353	.2354	6.25	2.64
1190	.0263	.2264	6.55	2.35
1785	.0205	.2206	7.08	2.19
2385	.0168	.2169	7.37	2.02
2974	.0134	.2133	8.30	1.98
3834	.0107	.2108	8.70	1.81
4752	.0091	.2092	8.67	1.62
5950	.0048	.2049	15.0	1.81

TABLE III

REACTION OF ISOPROPYL IODIDE WITH SILVER NITRATE IN ACETONITRILE AT 0°

t in sec.	$[AgNO_3]$	$[C_3H_7I]$	$k_3 \times 10^2$, l.^{2} mole^{-2} sec.$^{-1}$	$k_2 \times 10^3$, l. mole^{-1} sec.$^{-1}$
0	0.225	0.195		
180	.184	.154	2.6	6.4
600	.147	.117	4.4	3.4
900	.135	.105	2.5	4.2
1260	.123	.093	2.3	3.6
1680	.110	.080	2.4	3.5
2100	.103	.073	2.3	3.2
2700	.095	.065	2.2	2.9
3180	.091	.061	2.1	2.7
3900	.084	.054	2.1	2.5
5700	.074	.044	2.1	2.2

TABLE IV

REACTION OF NEOPENTYL IODIDE WITH SILVER NITRATE IN ACETONITRILE AT 25°

t in sec.	$[AgNO_3]$	$[C_5H_{11}I]$	$k_3 \times 10^4$, l.^{2} mole^{-2} sec.$^{-1}$	$k_2 \times 10^6$, l. mole^{-1} sec.$^{-1}$
0	0.2754	0.3077		
1360	.2632	.2955	6.6	18.4
1860	.2592	.2915	6.6	18.2
2800	.2521	.2844	6.8	17.8
4230	.2437	.2760	6.3	16.5
6050	.2324	.2647	6.5	16.4
9945	.2139	.2462	7.0	15.4
14100	.2010	.2333	6.0	14.9
18730	.1866	.2189	6.0	13.9
28420	.1625	.1948	6.2	12.8

descriptions of the intermediates suggested by Winstein. Such a difference should probably be expected since the silver salt reactions involve the operation of a powerful electrophile and weak nucleophiles. Since both elimination and substitution result from kinetically similar reactions of silver salts, one could even push the point and maintain that the S_N1, S_N2, E_1 and E_2 have all converged to a common ground.

Kinetic Analysis.—The mechanism of equations 6 and 7 should lead to a third-order rate law.

$$-\,d[Ag^+]/dt = k_3[RI][Ag^+][X^-] \qquad (8)$$

At infinite dilution the law would become equivalent to equation 9 in which $[AgX]_s$ is the total stoichiometric concentration of silver salt.

$$-\,d[Ag^+]/dt = k_3[RI][AgX]_s^2 \qquad (9)$$

Under similarly ideal conditions the carbonium ion mechanism would give second-order kinetics.

$$-\,d[Ag^+]/dt = k_2[RI][Ag^+] = k_2[RI][AgX]_s \qquad (10)$$

In actual fact, the rates of reaction of silver nitrate in acetonitrile do not fit a constant, integral order, but fall between second and third order. Surprisingly, the fit to third-order kinetics is best at the highest concentrations of silver nitrate. Illustrative examples are included in Tables II–IV. The data of Table II show that with an initial silver nitrate concentration of 0.0051 molar the drift in the third-order rate constants is about as pronounced as is the variation in the second-order constants. On the other hand, the data in Tables III and IV show that the fit to the third-order law is much better in runs in which the initial concentration of silver salt was higher. While different alkyl groups were involved in the experiments reported in detail, the pattern of behavior is not dependent on the structure of the substrate. For example, runs with methyl iodide and ethyl iodide were done with a range of initial concentrations and the fit to third-order kinetics was always improved by increasing the initial concentrations.

A better method for observing trends was used in a detailed study of the reaction rates with ethyl iodide. Runs were made with varying initial concentrations of the reactants and the data were plotted on large-scale graphs. Smoothed curves were drawn through the points and tangents to the curves were measured in the vicinity of each experimental point. The instantaneous rates were then used to calculate third- and second-order rate constants. The treatment shows that the third-order rate constants always increase throughout the run. On the other hand, second-order rate constants decrease, by large amounts in the more concentrated solutions and by small amounts in dilute solutions. The data are summarized in Table V. The consistent pattern is broken by the run in which the initial concentration of silver nitrate was lowest (0.01 *N*). The reaction proceeded markedly more rapidly than would be predicted by any empirical extrapolation of either the second- or third-order treatments of the data gathered in more concentrated solutions. The discontinuity may indicate a change in mechanism to one of lower kinetic order or it may be a spurious effect introduced by a systematic error in the measurement of low concentrations of silver ions. The data agree reasonably well with those reported by Donnan and Potts[3] in the concentration range in which the two studies overlapped. In order to

TABLE V

REACTION OF ETHYL IODIDE WITH SILVER NITRATE IN ACETONITRILE AT 25°

Run	$[AgNO_3]_0$	$[C_2H_5I]_0$	Range of $k_3 \times 10^2$, l.^{2} mole^{-2} sec.$^{-1}$	Range of $k_2 \times 10^3$, l. mole^{-1} sec.$^{-1}$
II	0.1019	0.2057	2.7–4.1	2.4–1.0
III	.0816	.2571	4.1–8.2	2.9–1.0
IV	.0510	.4018	5.4–16	2.5–0.8
V	.0510	.2511	6–9	2.8–0.9
VI	.0216	.2511	7.8–12	1.3–0.8
VII	.01037	.4018	27–105	2.3–1.2

determine the importance of heterogeneous catalysis, two duplicate runs were made with initial concentrations of the reactants ($[AgNO_3]_0$ = 0.0263, $[C_2H_5I]_0$ = 0.225) exactly equal to the concentrations remaining at the fourth experimental point in run V. The curves for the duplicate runs coincided within experimental error with the late portion of run V, indicating that no autocatalytic effect is measurable.

The main body of data is consistent with a mechanism involving both nitrate and silver ions in the rate-determining step, but do not fit well with mechanisms involving only one ion. Under the conditions of the experiments, the third-order rate constants should increase as the reactions progress because the ionic strength of the medium decreases continuously. On the other hand, a second-order reaction should show either a steady value of the rate constant or a small increase. It is clear that *the decrease in the second-order constant denies a rate-determining step involving only one ionic species.*

It is a curious fact that the fit to third-order kinetics is best at high concentrations of silver nitrate, as is illustrated by the data in Tables III and IV. That the effect is not due to competition between third- and second-order mechanisms is assured by the great difference between the reactivity of silver nitrate and silver perchlorate. The difference between the reactivities of the two salts virtually assures that if one of the two were reacting by a mixed mechanism the other would react by an essentially pure mechanism. It is possible that the ionic activity coefficients of silver nitrate in acetonitrile vary little with concentration in the concentration range above 0.1 *M*. Consideration of the theories of concentrated electrolyte solutions indicates that this may be true. Even though acetonitrile has a fairly large dielectric constant (38.5) one would expect that at concentrations above 0.1 *M* interionic interactions should be relatively enormous. Fuoss and Kraus[27] have used the conductivity data of Walden and Birr[28] to estimate the dissociation constant of silver nitrate in acetonitrile as 0.017. This value would indicate that the salt should be about 40% dissociated to free ions in 0.1 *M* solution. However, this value of the dissociation constant leads to a ridiculously small value (1.90 Å.) for the sum of the ionic radii. The high solubility of silver salts in acetonitrile[29] tells us that silver ions must be very highly solvated and that, consequently, they should have a very large true volume. Recalculation[30] of the dissociation constants using larger ionic radii does not alter the qualitative conclusions unless one assumes that the sum is 7.7 Å. or greater, in which case the radius sum exceeds the Bjerrum radius for acetonitrile and the ion pair concept disappears. That the latter condition may obtain is also indicated by the fact that the critical concentration,[31] above which the ion pair concept is meaningless because of the space-filling properties of the ions, is about 0.2 *N* for acetonitrile at 25°. Above these concentrations, the addition of more salt may either "salt in" or "salt out," depending on the nature of the short-range, interionic interactions. A similar condition exists in aqueous solutions in the concentration range above 1 *M* where it is well known that the activity coefficients of 1–1 electrolytes show a wide range of behavior,[32] including invariance over considerable ranges of concentrations. Our net conclusion is that the close approach of the reaction rates to the third-order law at relatively high concentrations is due to a fortuitous constancy of $\partial\gamma/\partial c$ at those concentrations.

The rate of loss of soluble silver was also followed in solutions of isopropyl iodide and silver perchlorate in acetonitrile. Titration established that one equivalent of strong acid was produced for every mole of silver ion reacted. Dark, nitrogenous products were also produced, indicating that the solvent was attacked by the isopropyl moiety. That condensation had progressed beyond the first stage was indicated by the fact that the crude reaction mixture had an absorption maximum at 257 mμ. There was also a strong infrared maximum at 1640 cm.$^{-1}$ which may be attributed to the presence of C=N linkages. While no evolution of gas was observed, we cannot be sure that no propylene was produced. The following, ion-pair mechanism accommodates the results insofar as we know them.

$$ClO_4^- + i\text{-}C_3H_7I + Ag^+ \longrightarrow ClO_4^-C_3H_7^+ + AgI \qquad (11)$$

$$\begin{array}{c} ClO_4^-C_3H_7^+ + CH_3CN \longrightarrow CH_2{=}C{=}NC_3H_7 + H^+ \\ \qquad\qquad\qquad\qquad CH_3CN \Big\downarrow \\ \qquad\qquad\qquad\qquad \text{condensation products} \end{array} \qquad (12)$$

Evidence for inclusion of perchlorate ions in the rate-determining step is obtained from the kinetic measurements. The strongest evidence is the qualitative observation (Fig. 2) that added lithium perchlorate accelerates the reaction. If all electrolyte effects are ignored, one would expect the reactions to follow the second-order rate law within individual runs if perchloric acid behaves as a strong acid in acetonitrile. The second-order constants should increase as the initial concentration of silver perchlorate is increased. The data summarized in Table VI show that the prediction is true if second-order constants, calculated from the early points in various runs, are compared. The rate constants always drift downward as runs progress, suggesting that silver perchlorate furnishes

Table VI

Reaction of Isopropyl Iodide with Silver Perchlorate in Acetonitrile at 25°

$[AgClO_4]_0$	$[i\text{-}C_3H_7I]_0$	$[LiClO_4]_0$	$k_2 \times 10^{-4}$, l. mole^{-1} sec.$^{-1}$
0.1022	0.1124	None	2.7
.230	.201	None	5.6
.2662	.2642	None	6.3
.2636	.2149	0.2752	11.9

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TABLE VII

REACTION OF SILVER NITRATE WITH METHYL IODIDE IN BENZONITRILE AT 25°

t in sec.	[$AgNO_3$]	[CH_3I]	k_3, l.^{2} mole^{-2} sec.$^{-1}$
0	0.0596	0.153	
300	.0430	.136	0.15
600	.0329	.126	.17
1200	.0226	.116	.18
1500	.0190	.112	.19
2100	.0145	.108	.21

TABLE VIII

VARIATION IN RATE WITH CONCENTRATION IN REACTION OF SILVER NITRATE WITH METHYL IODIDE IN BENZONITRILE AT 25°

[$AgNO_3$]$_0$	[CH_3I]$_0$	k_3,[a] l.^{2} mole^{-2} sec.$^{-1}$
0.0596	0.153	0.18
.0477	.204	.20
.0111	.0411	.53
.0221	.0822	.37
.0332	.123	.30
.0442	.164	.27
.0553	.206	.25

[a] First two runs averaged over run; last five calculated from single points (see text).

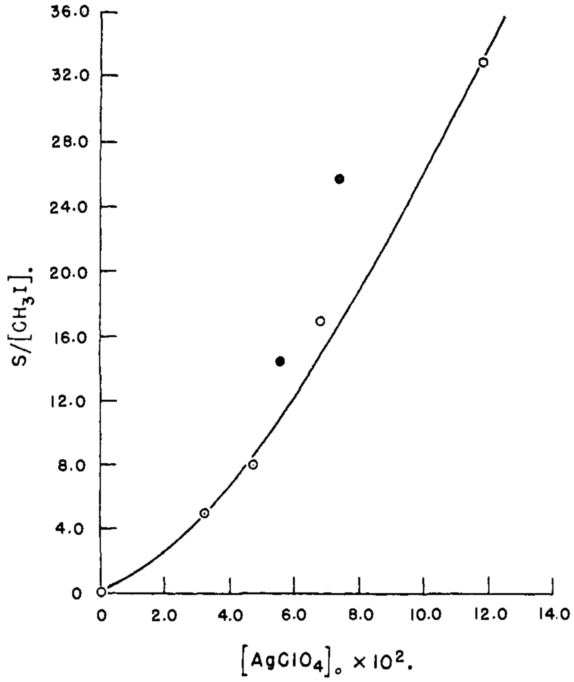

Fig. 2.—Initial rates of reaction of $AgClO_4$ with CH_3I in acetone at 25°; solid circles for added $LiClO_4$; see Table IX.

a higher perchlorate activity than does an equal concentration of perchloric acid.

Reactions in Other Solvents.—Brief studies were made of the reactions of methyl iodide with silver nitrate in benzonitrile and with silver perchlorate in acetone. The former reaction showed qualitative similarity to the same process in acetonitrile. At comparable concentrations of reactants, the reaction is about five times as fast in benzonitrile as it is in acetonitrile. Definitive comparisons cannot be made because the variation in rate with concentration of the silver salt is different in the two solvents. In benzonitrile the rates appear to be between first- and second-order with respect to the concentration of silver nitrate, although no conditions were found under which the rates approached a fit to third order as good as that observed at high concentrations in acetonitrile. Table VII shows the details of an individual run and Table VIII shows the results of a rapid survey of the behavior of the rates as a function of the initial concentrations of reactants. The last five entries in Table VIII are derived from runs in which only a single analytical point was taken. Varying amounts of benzonitrile and solutions of methyl iodide and silver nitrate were mixed and analyzed after a standard time interval of 30 minutes. Conversions in the experiments varied from 29 to 80% so the kinetic constants serve only to indicate a strong trend and are not otherwise comparable.

Since the reaction of silver perchlorate with methyl iodide was very slow in acetonitrile, this reaction was studied in dry acetone. The reaction was previously studied by Redies and Iredale[13] who fitted their data to a five-halves order rate law.

$$-d[Ag^+]/dt = k[RI][AgClO_4]^{3/2} \qquad (12)$$

We have repeated their measurements and found quantitative agreement with their results. We do not attach any particular significance to the three-halves order dependence on silver perchlorate concentration, other than to show that the order with respect to silver perchlorate is higher than first. It is once again difficult to account for the results without invoking some function for the perchlorate other than that of providing ionic atmosphere. The rates are not easily analyzed since perchloric acid is produced in the reaction. A preliminary analysis has been based upon initial rates and is summarized in Fig. 2 and Table IX. First, the analytical values for remaining soluble silver salt were plotted against time and smooth curves were drawn through the points. These smoothed curves were then used to read adjusted values of the silver concentrations at the times corresponding to the experimental points. The adjustments made in this manner were all small, corresponding to 0.15 ml. or less, of the standard silver nitrate solution used in back titration. The slopes were calculated as $\Delta[Ag^+]/\Delta t$ for each experimental increment. In order to further refine the values the slopes were divided by the mean methyl iodide concentration in the increment. The values of $S/[CH_3I]$ for the first few points (points below 21% reaction) were averaged to give the values shown in the last column of Table IX. In run 31 the value was based upon a single point at 17% reaction and only two points, at 13 and 21%, determined the slopes in run 32. The absence of data for really small conversions will tend to make the values for initial rates calculated for these runs low in comparison with all of the others, thus increasing the significance of the actual location of the points, marked with solid circles, in Fig. 2.

In Fig. 2 the values of $S/[CH_3I]$ are plotted against the initial concentrations of silver per-

TABLE IX

RATES OF REACTION OF METHYL IODIDE WITH SILVER PERCHLORATE IN DRY ACETONE AT 25°

Run	$[AgClO_4]_0$ × 10^2	$[CH_3I]_0$ × 10^2	$[LiClO_4]_0$ × 10^2	$S/[CH_3I]^a$ × 10^5 sec.$^{-1}$
20	3.25	3.38	None	5.0
22	6.34	6.64	None	16.8
29	4.74	7.06	None	8.0
30	11.08	8.13	None	33
31	7.39	4.69	13.88	25.8
32	5.54	3.52	20.85	14.5

[a] $S = \Delta[Ag^+]/\Delta t$; see Discussion for method of calculation.

chlorate. The points for runs with no added lithium perchlorate are shown as open circles and define a curve with a definite upward concavity. This demonstrates that the reaction must be greater than first order with respect to silver perchlorate. Furthermore, despite the nature of the error expected for the runs with added perchlorate, the points for those runs lie above the curve. Since an inert electrolyte effect would be expected to be negative, there is a strong implication that either lithium or perchlorate ion (or both) may become involved in the reaction. The most probable interpretation is that the weakly nucleophilic perchlorate ion plays a role similar to that assigned to nitrate in the reactions of silver nitrate.

The fact that strong interionic interactions occur in solutions of silver perchlorate in acetone was demonstrated by the increase of the solubility of the salt in the presence of lithium perchlorate. The data are summarized in Table X. The magnitude of the solubilizing effect by a common ion salt almost certainly bespeaks a specific interaction between silver and perchlorate ions.

We conclude that the rate of a reaction between a silver salt and an alkyl iodide is very sensitive to the state of solvation of the silver ion in the medium. Reaction is very fast in acetone, a relatively poor solvent for silver salts, indicating that those silver ions which are present are highly reactive. The rates in acetonitrile and benzonitrile are surprisingly close together despite the fact that silver salts are much more soluble in the former solvent. However, the solubility of silver salts in benzonitrile is remarkably high in *comparison with the solubility of salts containing other cations*. It is reasonable to believe that silver ions are tightly complexed by solvent molecules in both media and the difference between the solubilities of silver nitrate in the two nitriles is due largely to differences in the dielectric stabilization of ions in the two media. This last factor and variation in the solvation energies of the anions seem to have smaller effects on the reactivity of the silver salts than does the complexing of the silver ion.

If the ion-pair mechanism is involved in the reactions of silver salts, it is reasonable to expect that it should also apply in the reactions of mercuric salts with alkyl halides. The latter reactions have been studied carefully.[33,34] Roberts and Hammett found that the reaction of benzyl chloride with mercuric nitrate and perchlorate in dioxane–water mixtures showed catalysis by nitrate and perchlorate ions. They attribute the effect to the superiority of $Hg(NO_3)^+$ and $Hg(ClO_4)^+$ over other mercuric species as electrophiles. Benfey[34] accounted for the effects by attributing them to a salt effect on the mercuric ion–mercuric chloride equilibrium. Both explanations are tenable but not compelling. It is clear that a termolecular mechanism will fit the data since it is the kinetic equivalent of that of Roberts and Hammett. They did not consider the possibility that carbonium ion formation might be aided by nucleophilic assistance from nitrate and perchlorate ions which do not become permanently attached to the seat of substitution. Their results did differ from those of Donnan and Burke in one respect since it was found that the product distribution was influenced by the nitrate level in the solution. This would indicate that benzyl cations are sufficiently long lived to undergo reversible ion-pair formation. This is entirely consistent with the observation that benzyl cations, produced in acetone–water solutions, can be captured by nitrate ions which are not involved in the rate-determining step of the reaction.[35]

Experimental

Materials.—The silver nitrate and silver perchlorate were reagent grade and were dried in a vacuum desiccator over magnesium perchlorate. Methyl iodide, reagent grade, was used without further purification.

The acetonitrile was Eastman Kodak Co. white label grade and was distilled from calcium hydride before use, b.p. 80°. The acetone was purified by distillation from potassium permanganate followed by distillation from Drierite and, finally, by fractionation with a 50-plate bubble-cap column. It was stored in a closed system and drawn off as required for use through a column of activated alumina.

Ethyl iodide, J. T. Baker analyzed reagent, was distilled from sodium wire before use. The product retained a slight pinkish tinge.

The isopropyl iodide was purified by washing with sodium thiosulfate and water and by drying over calcium chloride. It was then distilled, b.p. 87°, and subsequently stored in the dark over a drop of mercury. The *t*-butyl iodide was distilled *in vacuo*, but retained a faint orange color after distillation.

The neopentyl iodide was prepared according to the method of Whitmore and his co-workers.[36] First neopentyl chloride was prepared by the chlorination of neopentane at 0°.[37] From this the Grignard reagent was prepared and then the corresponding mercuric chloride. Neopentyl mercuric chloride was shaken with potassium iodide and iodine. The neopentyl iodide was extracted with ether after the excess iodine was removed with thiosulfate. The iodide was then washed, dried and distilled, b.p. 47–50° (40–45 mm.), $n^{20}D$ 1.4885. A portion of the neopentyl iodide was distilled at atmospheric pressure, b.p. 135–137° (740 mm.).

Kinetic Procedures.—The solutions of silver nitrate and silver perchlorate in acetonitrile were prepared by estimation and then standardized with sodium thiocyanate solution using the Volhard method.

All of the various alkyl iodides, except methyl, were weighed out accurately in volumetric flasks and diluted to the mark at the proper temperature.

Methyl Iodide Rates.—The proper volume of the standardized silver nitrate solution was added to a 100-ml. glass-stoppered erlenmeyer flask, and the solution was brought

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(36) F. C. Whitmore, E. L. Wittle and B. R. Harriman, *ibid.*, **61**, 1585 (1939).

(37) F. C. Whitmore and G. H. Fleming, *ibid.*, **55**, 4161 (1933).

to 25.5°. At zero time a sealed ampoule of methyl iodide containing a known quantity of methyl iodide was broken under the surface of the solution. Samples were withdrawn at various time intervals with an automatic pipet carrying a filter tip and delivered to a definite excess of standard thiocyanate solution. The excess thiocyanate was determined by a Volhard titration with a standard silver nitrate solution. No transience of the ferric thiocyanate color was observed when methyl iodide was added to a solution from which the silver had been precipitated with excess thiocyanate.

Ethyl Iodide Rates.—The procedure in the more concentrated solutions was similar to that described above for runs with methyl iodide. In dilute solutions the Volhard titration was not sufficiently accurate and was replaced by direct potentiometric titration of the residual silver ion with aqueous sodium chloride using platinum and calomel electrodes.

Isopropyl Iodide Rates.—The procedure for both silver nitrate and perchlorate with isopropyl iodide is the same. It was found that the rate could not be followed by the indirect Volhard titration as in the methyl iodide runs. When excess sodium thiocyanate was added to quench the reaction and ferric alum indicator added, the indicator color faded upon standing. The excess thiocyanate apparently reacts with something, probably excess isopropyl iodide, other than silver since thiocyanate was in excess.

The proper volumes of the reactants were mixed at zero time in a glass-stoppered erlenmeyer flask. Samples were withdrawn with an automatic pipet and delivered into a separatory funnel containing 15 ml. each of cold water and carbon tetrachloride. The contents were shaken and the two phases separated. The water layer was washed with two additional 10-ml. portions of carbon tetrachloride. The layers were then separated again and the water phase was titrated with standard thiocyanate solution using ferric alum indicator.

Neopentyl Iodide Rates.—The proper volumes of the iodide and silver solutions were mixed at zero time in several 25-ml. stoppered erlenmeyer flasks. At various intervals the flasks were removed and 10 ml. of 1 *N* HNO_3 was added. The unreacted silver was titrated with standard thiocyanate solution. Again the data were analyzed by use of the proper integrated rate expressions.

Solubility Measurements.—A large test-tube carrying a standard taper Trubore stirrer was charged with excess powdered silver nitrate and the acetone solution of lithium perchlorate was added. The mixtures were stirred for 10 hours while thermostated at 25.5 ± 0.05°. The contents of the tube were then centrifuged, and an aliquot was removed from the surface of the solution and titrated for silver by the Volhard method with a standard sodium thiocyanate solution. Control experiments showed that equilibrium was attained in two hours. Table X summarizes the results.

TABLE X

SOLUBILITY OF SILVER PERCHLORATE IN ACETONE AT 25.5°

Concentrations, mole/l. × 10^2	
Lithium perchlorate added	Silver at equilibrium
None	1.03
10.3	2.50
15.6	3.06
46.7	5.85
77.9	8.15

Products.—Products were not studied in the nitrate reactions, but published examples[21] show that methyl, ethyl and isopropyl iodides must give high yields of alkyl nitrates in acetonitrile. Titration of a solution after complete precipitation of silver iodide in a reaction with isopropyl iodide showed that no acid was produced in the reaction.

A solution remaining after completion of a kinetic run with isopropyl iodide and silver perchlorate in acetonitrile was examined in some detail. Titration with standard 0.1 *N* sodium hydroxide showed that acid equivalent to the original charge of silver nitrate was produced. A sample was diluted with water and tested for chlorate with brucine[38] with negative results. Addition of 2,4-dinitrophenylhydrazine and acid gave no precipitate although it was shown by a control that the 2,4-dinitrophenylhydrazone was easily obtained from acetonitrile solutions containing acetone equivalent to the original silver perchlorate. An infrared spectrum of the solution, run in a double beam instrument against acetonitrile, showed only one maximum, at 6.1 μ in the 4-6 μ region. The ultraviolet spectrum showed a maximum at 257 mμ. Addition of cupric acetate to the solution, in an attempt to isolate a copper chelate of the absorbing species, gave no precipitate. The solution decolorized 2% aqueous permanganate as did a solution of perchloric acid in acetonitrile.

The reaction of silver perchlorate with methyl iodide in acetone produced dark brown solutions. These solutions neutralized an indeterminate amount of 0.1 *N* aqueous sodium hydroxide.

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[CONTRIBUTION FROM THE RESEARCH LABORATORIES OF THE UPJOHN CO.]

The Solvolysis of Aspirin Anhydride

BY EDWARD R. GARRETT

RECEIVED MAY 20, 1959

Aspirin anhydride hydrolyzes to aspirin with no evidence of prior or concomitant hydrolysis of the acetyl linkages and with no evidence of hydrogen ion accelerated hydrolysis. These facts do not support a cyclization mechanism. Aspirin anhydride is hydrolyzed by water, acetate and hydroxyl ions; undissociated acetic acid inhibits hydrolysis. Dielectric constant and temperature effects on the kinetics have been studied.

The enhancement of hydrolysis of the *ortho* ester in salicyl phosphates,[1-3] aspirin,[1,4,5] 4-(2′-acetoxyphenyl)-imidazole,[6] methyl pyrrolidylacetylsalicylate hydrochloride[7] and diethyl aminoethylacetylsalicylate hydrochloride[8] by an *o*-phenyl substitutent has been considered in the light of possible cyclic intermediates or intramolecular condensations involving interaction of the adjacent

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