$(O_2CCH_3)_6(H_2O)_3]^{2+}$, although in the latter the NMR spectrum showed some line shape and chemical shift effects as well.[14] In the case of compound **2**, the ^{1}H NMR spectrum has a perfectly normal appearance, indicating that unpaired spin density does not reach the pivalate protons.

The mechanism and factors contributing to the formation of the trinuclear complexes of niobium are still rather obscure. Analogous Mo and W compounds form under a variety of conditions and show unusual stability. Once formed they are chemically inert, and the replacement of axial ligands or substitution reactions on phenyl groups of the RCO_2 ligands are the only chemical changes short of disintegration to monomers they are known to undergo. The niobium compounds are less stable, but nevertheless, their "self-assembly" suggests that all such systems have a special stability relative to mononuclear or binuclear species.

So far the source of capping oxygen atoms has not been identified with certainty for any bi-oxo-capped trimer. The most viable possibility is that oxygen atoms are extracted from carboxylato groups. However, since no definite evidence is available yet we cannot rule out some other sources, e.g., hydrolysis due to the presence of traces of water in solvents. On the other hand, the latter does not account for the oxidation of Nb(III) to species with $3^2/_3$ oxidate state. In general rather complex reaction paths are probably taking place in systems which produce compounds with an $M_3X_2{}^{n+}$ core. Unexpected formation of $NbOCl_4(THF)^-$ in the Nb–benzoate reaction is a further indication that complex chemical transformations are occurring.

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Registry No. 1, 89746-82-7; **2**, 89746-84-9; $Nb_2Cl_6(SMe_2)_3$, 61069-51-0.

Supplementary Material Available: Tables of structure factors, anisotropic thermal vibration parameters, and additional bond distances and angles (33 pages). Ordering information is given on any current masthead page.

MNDO Study of S_N2 Reactions and Related Processes[1]

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Abstract: Recent experimental and theoretical work has shown that S_N2 reactions of anions commonly take place with little or no activation in the gas phase, indicating that the barriers in solution are due primarily to desolvation of the ion. This conflicts with current theories of S_N2 reaction rates where the solvent is assumed to play a minor role. Detailed MNDO calculations for S_N2 reactions of chloride ion with alkyl chlorides, benzyl chlorides, allyl chloride, and chloroacetaldehyde, and of various anions with methyl chloride, have now suggested an explanation and have also elucidated the roles of alkyl and +E groups. The S_N2' reaction of chloride ion with allyl chloride is predicted to take place without activation, its lower rate in solution being an expected consequence of solvation. According to simple MO theory, the S_N2 and S_N2' reactions should *both* take place without activation. The S_N2 barriers are now attributed to the small size of the carbon atom which inhibits binding to five ligands.

Nucleophilic aliphatic substitution has been studied more intensively than any other organic reaction, and the results form the basis of much of the currently accepted theory concerning the mechanisms of organic reactions in solution and the effects of solvents on their rates. Some years ago, however, doubt was thrown on these conclusions by the discovery that many S_N2 reactions of anions take place with little or no activation in the gas phase.[2-4] The activation barriers in solution must therefore be attributed to the energy required to remove solvent molecules from the anion so that the alkyl derivative can approach it. Yet, as Ingold pointed out many years ago,[5] the solvent seems to have only a minor effect on reactions of this kind when they are carried out in solution. The situation was further confused by studies[6,7] of the interactions between halide ions and alkyl halides in the gas phase which seemed to suggest that the trigonal-bipyramidal species commonly regarded as the transition states (TS) in S_N2 reactions are in fact stable intermediates. These conclusions, if true, would moreover throw doubt on the entire current theory of reactions of anions in solution because *any* such reaction of an anion with a neutral molecule must involve analogous desolvation of the ion and its rate must be correspondingly reduced. *Any* reaction of an anion that takes place as rapidly in solution as its S_N2 reaction with methyl chloride should also then take place without activation in the gas phase.

Since resolution of this paradox clearly represented a very pressing problem, we decided some years ago to undertake detailed calculations for a wide range of S_N2 reactions in the hope of finding a solution. In the period since this work started, ab initio calculations[8] and detailed experimental studies[10] have in fact clarified the situation, showing that the S_N2 reaction itself is not as anomalous in this respect as Dougherty et al.[6,7] had supposed. Both theory and experiment now indicate that the reaction profile for the S_N2 reaction of chloride ion with methyl chloride has the form indicated in Figure 1a. The reactants first combine to form a charge/dipole (CD) complex (the species observed by Dougherty et al.[6,7]) which undergoes conversion to the products via the trigonal-bipyramidal TS commonly postulated. The activation energy in the gas phase under the conditions used in the ICR studies[9] is small because the energy liberated in the exothermic

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(6) (a) Dougherty, R. C.; Dalton, J.; Roberts, J. D. *Org. Mass. Spectrom.*, **1974**, *8*, 77. (b) Dougherty, R. C.; Dalton, J.; Roberts, J. D. *Ibid.* **1974**, *8*, 81.

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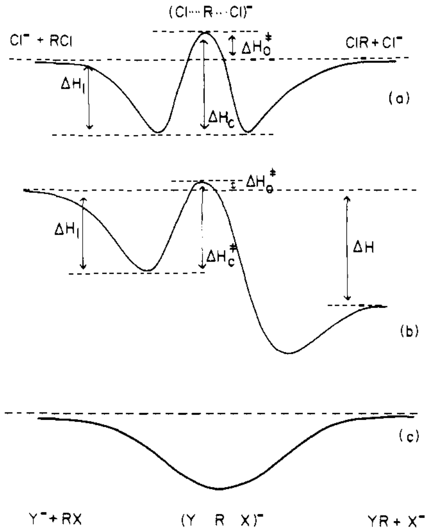

Figure 1. MERPS for (a) a degenerate S_N2 reaction, (b) an exothermic S_N2 reaction, and (c) a bimolecular reaction where the reactants combine without activation to form a stable adduct.

formation of the CD complex cannot be dissipated quickly and can therefore assist crossing of the potential barrier involved in the reaction. Since this assistance is not available in solution, the activation barrier there is much greater. These conclusions have been supported by ab initio calculations[9] for the S_N2 reactions of other anions with methyl chloride and methyl fluoride. Thermoneutral reactions followed the course indicated by Figure 1a while exothermic ones followed that indicated in Figure 1b.

However, while this work has softened the paradox indicated above, it still fails to explain why the solvent seems to play the very minor role that current theories predict. Furthermore, as we shall see presently, the situation indicated in Figures 1a,b applies only to certain kinds of reactions. In other cases the reaction profile in the gas phase contains only a single minimum, the reactants combining without activation to form a stable adduct; see Figure 1c. Here the arguments presented by Dougherty,[7] and the paradox resulting from them, hold with full force.

The calculations reported here were carried out with use of MNDO.[12] We were able in this way to survey a wide range of S_N2 reactions and related processes whereas the ab initio calculations[8,9] were inevitably restricted to a few simple cases. Lack of data makes it difficult to assess the relative accuracy of the procedures used in the latter and MNDO. The available evidence seems to suggest that they are in general comparable.[13]

Procedure

The MNDO method has been fully documented.[12] The calculations were carried out with use of the standard[14] parameters.

Geometries of stable species were calculated by minimizing the energy with respect to *all* geometrical variables, without making any assumptions, using the Davidon–Fletcher–Powell (DFP) algorithm[15] as implemented in the MOPAC[16] package of computer programs.

Transition states were located approximately by the reaction coordinate method,[17] using the length of a breaking (forming) bond as the reaction coordinate, and then refined by minimizing the norm of the energy, following McIver and Komornicki.[18] All stationary points were characterized[18] by calculating and diagonalizing the corresponding Hessian (force constant) matrix. The force constants were also used to calculate molecular vibration frequencies and hence molecular entropies and entropies of activation.[19] Options for all these procedures are included in MOPAC.

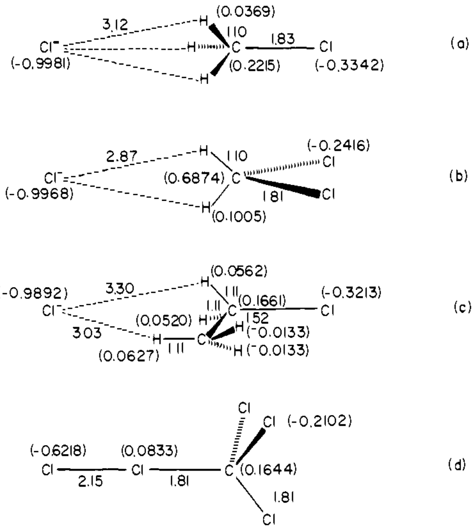

Figure 2. (a–c) Structures of CD complexes formed by the chloride ion with (a) methyl chloride, (b) methylene chloride, and (c) ethyl chloride. (d) Structure of the covalent complex from the chloride ion and carbon tetrachloride.

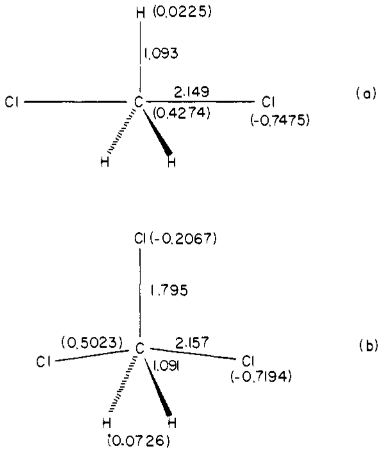

Figure 3. Geometries of transition states for S_N2 reactions of chloride ion with (a) CH_3Cl_2 and (b) CH_2Cl_3.

Results and Discussion

A. Reactions of Chloride Ion with Chloroalkanes. We first studied the reactions of the chloride ion with all four chloromethanes and with methyl, ethyl, isopropyl, and *tert*-butyl chlorides, starting with the separated reactants ($Cl^- + RCl$) and taking the length of the forming (CCl) bond as the reaction coordinate. No constraints were applied other than the initial direction of approach.

All but one of the reactions followed the pattern indicated by the schematic MERP (minimum energy reaction path) shown in Figure 1a, in agreement with earlier conclusions from ab initio calculations[8,9] and experiment.[10] The reactants first associate to form a charge/dipole (CD) complex (**1**) with virtually no change in the geometry of the alkyl chloride. The structures of some examples are shown in Figure 2. The bonding in them is clearly electrostatic in nature, due to charge/dipole interactions between the chloride ions and polar bonds in the alkyl chlorides. The

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(12) Dewar, M. J. S.; Thiel, W. *J. Am. Chem. Soc.* **1977**, *99*, 4899, 4907.

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(16) Available from QCPE in versions for VAX, CYBER, and IBM computers. MOPAC includes options for various kinds of open-shell calculations, CI, following reaction paths, locating transition states, and the calculation of force constants, vibration frequencies, and derived thermodynamic quantities (entropies, specific heats), for both MINDO/3 and MNDO.

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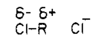
Table I. Adducts from Chloride Ion and Chloroalkanes

chloroalkane	ΔH_1[a,b]	ΔS_1[b,c]	ΔH_2[a,d]	ΔS_2[c,d]	ΔH[e]	ΔS[e]
CH_3Cl	6.3	17.1	1.0	25.0	8.6	15.3
CH_3CH_2Cl	5.8	16.7	1.3	24.9	11.6	19.2
$(CH_3)_2CHCl$	6.5	16.7	3.6	24.7	12.2	19.9
$(CH_3)_3CCl$	6.7	17.3	4.9	25.4	12.4	19.3
$(CH_3)_3CCH_2Cl$	9.0	13.0	2.8	25.0	14.4	25.2
CH_2Cl_2	9.5	17.3	12.3	25.2	12.4	22.0
$CHCl_3$	11.9	22.1	22.8	24.5	19.1	24.5
CCl_4			32.0	22.3	14.1	27.8

[a] In kcal/mol. [b] Change in enthalpy (ΔH_1) or entropy (ΔS_1) on formation of the CD complex. [c] In entropy units. [d] Change in enthalpy (ΔH_2) or entropy (ΔS_2) on formation of the covalent complex. [e] Experimental values[6,7] for ΔH or ΔS.

complex then undergoes a degenerate rearrangement to its mirror image with breaking of one CCl bond and formation of another, the symmetrical intermediate being the TS. Figure 3 shows the structures of two typical transition states.


$\overset{\delta-}{Cl}\!-\!\overset{\delta+}{R}\quad Cl^-$

1

$(Y\cdots R\cdots X)^-$

3

$(H_2C-CH-CH_2)^-$

4

The one exception was carbon tetrachloride, which, being nonpolar, cannot form CD complexes. Here MNDO predicts bonding between the chloride ion and a chlorine atom of CCl_4, giving rise to an adduct (**2**) whose structure is shown in Figure 2d. The length (2.148 Å) of the Cl–Cl bond shows that the approaching chloride ion is covalently bound, being little greater than the experimental (1.988 Å) or MNDO (1.986 Å) values for Cl_2 and much less than double the van der Waals radius of chlorine (3.6 Å).[11] The C–Cl–Cl bonding presumably involves a three-center four-electron bond of the kind now thought[22] to be generally involved in hypervalent compounds of elements in the third and later periods. The rest of the MERP for the CCl_4 reaction was, however, normal, the reaction taking place via a normal trigonal-bipyramidal TS.

While the other chlorides also formed covalent complexes of this type, i.e., $(R\text{–}Cl\text{–}Cl)^-$, in all but one case they were less stable than the CD ones. Table I shows the heats (ΔH_1) and entropies (ΔS_1) of reaction calculated for formation of the two types of complex together with (where available) the values reported by Dougherty et al.[6,7] for the formation of the adducts observed by them in the gas phase. Our calculated ΔH_1 agree quite well with the latter, apart from being systematically a little too small. This error might have been expected because MNDO is known[20] to overestimate interatomic repulsions at internuclear separations near the van der Waals distance. It consequently underestimates electrostatic binding in complexes of this kind.

The results for CCl_4 indicate that MNDO overestimates the stabilities of the covalent complexes. Since the heat of reaction calculated for $CHCl_3$ is *less* than that observed, the complex formed here must be of the CD type, like those from all the other chlorides.

Table II shows the heats ($\Delta H_0^\ddagger$) and entropies ($\Delta S_0^\ddagger$) of activation calculated for the overall S_N2 reactions, starting with the reactants ($Cl^- + RCl$) widely separated, and also corresponding values ($\Delta H_c^\ddagger$, $\Delta S_c^\ddagger$) for reactions starting from the CD complexes. The last two columns of Table II show activation parameters reported for the corresponding S_N2 reactions in solution.

Table II. Activation Parameters for S_N2 Reactions of the Chloride Ion with Chloroalkanes

chloroalkane	$\Delta H_0^\ddagger$[a,b]	$\Delta S_0^\ddagger$[b,c]	$\Delta H_c^\ddagger$[a,d]	$\Delta S_c^\ddagger$[c,d]	$\Delta H^\ddagger$[e]	$\Delta S^\ddagger$[e]
CH_3Cl	3.2	26.0	10.6	9.8	15.8	10.7
CH_3CH_2Cl	11.8	25.7	17.7	9.5	17.5	10.1
$(CH_3)_2CHCl$	17.5	26.2	24.0	9.5	19.7	9.7
$(CH_3)_3CCl$	28.2		34.9			
$(CH_3)_3C$-CH_2Cl	19.9	23.2	23.9	10.2	22.1	8.6
CH_2Cl_2	7.4	26.0	16.9	8.7		
$CHCl_3$	15.3	26.2	27.2	4.0		
CCl_4	25.7	25.6				

[a] Enthalpies of activation in kcal/mol. [b] Calculated activation parameters starting from isolated reactants. [c] Entropies of activation in entropy units. [d] Calculated activation parameters starting from the CD complex. [e] Observed activation parameters for S_N2 reactions in solution.

Table III. Calculated and Observed Heats of Reaction and Activation for S_N2 Reactions of Methyl Chloride

	ΔH[a,b]				$\Delta H_0^\ddagger$[a,e]	
anion	calcd	obsd	ΔH_1[a,c]	ΔH_2[a,d]	calcd	obsd[f]
HO	84	49	9.0	6.5	5.8	0.3
HS	24	22	7.8	3.9	3.7	2.8
CH_3O	44	52	6.9	2.5	8.9	0.2
CH_3S	20	32	7.2	3.8	0.7	1.6
H_2N	87	64	8.8	5.2	8.0	0.3
CN[g]	68	28	7.6	6.2	6.1	
CN[h]	27	16	6.4	6.0	7.1	
HCC	96		8.6	1.4	8.6	<4

[a] In kcal/mol. [b] Overall heat of reaction. [c] Heat of formation of the first adduct ($Y\cdot CH_3Cl$) from ($Y + CH_3Cl$). [d] Heat of formation of the second adduct ($YCH_3\cdot Cl$) from ($YCH_3 + Cl$). [e] Enthalpy of activation for overall reaction, starting with the reactants widely separated. [f] Estimated from the observed collision efficienty. [g] Reaction leading to acetonitrile (CH_3CN). [h] Reaction leading to methyl isocyanide (CH_3NC).

Only one of the reactions in Table II has been studied in the gas phase, i.e., that of Cl^- with CH_3Cl. Since the measurements were carried out at low pressures, where collisional deactivation is expected to be slow, the rates observed should correspond to the parameters $\Delta H_0^\ddagger$ and $\Delta S_0^\ddagger$ in Table I. While no activation parameters were determined, the collisional efficiency observed (0.003) corresponds, in the transition-state model, to an activation energy of ~3 kcal/mol, in agreement with MNDO and in reasonable agreement with the ab initio calculations by Keil and Ahlrichs[8] (SCF, 2.2; CEPA, 9.7 kcal/mol) and by Wolfe et al.[9] (5.5 kcal/mol).

B. Reactions of Other Anions with Methyl Chloride. Given that degenerate S_N2 reactions follow the pattern indicated in Figure 1a, the reaction profile for an exothermic S_N2 reaction would be expected to be of the type indicated in Figure 1b. If the reaction is sufficiently exothermic, or if the central barrier is low, the energy of the TS will then be less than that of the reactants. Such a reaction should take place in the gas phase without activation, and this has indeed been found to be the case for the reactions of various anions with methyl chloride;[2-4] i.e.

$$Y^- + CH_3Cl \rightarrow YCH_3 + Cl^- \qquad (1)$$

We studied a number of these reactions, using MNDO. All of them followed the expected course, indicated by the schematic MERP in Figure 1b. Table III lists the calculated overall heats (ΔH) of reaction, the heats (ΔH_1) and entropies (ΔS_1) of formation of the intermediate CD complexes, and activation parameters both for the overall reactions ($\Delta H_0^\ddagger$, $\Delta S_0^\ddagger$), and for reactions starting with the CD complex ($\Delta H_c^\ddagger$, $\Delta S_c^\ddagger$); see Figure 2. Experimental values for ΔH, and estimates of overall activation energies ($\Delta H_0^\ddagger$), are also included. While some of these reactions were also studied by Wolfe et al., no details were given in their preliminary communication[9] and no other account has yet appeared in print.

While MNDO predicts zero values for $\Delta H_0^\ddagger$ for several reactions where the observed rates indicate that the activation energies must be very small, it gives heats of reaction that are often

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(20) For this reason MNDO gives energies for crowded molecules (e.g., neopentane) that are too positive, fails to reproduce hydrogen bonds and other weak intermolecular interactions, and predicts cycloaddition reactions (where one of the forming bonds is very weak in the transition states) to take place in a nonconcerted fashion.

(21) Dewar, M. J. S.; Rzepa, H. S. *J. Am. Chem. Soc.* **1978**, *100*, 784.

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much too negative, and in one case (CH_3O^-) it predicts an activation barrier when none is observed. The former error is not surprising because MNDO is known[21] to give heats of formation for anions that are too positive by 20–30 kcal/mole if the negative charge is localized on a single small atom. Thus while the heats of formation of Cl^- and CH_3O^- are reproduced satisfactorily, those for F^-, HO^-, CN^-, and $HC^-{=}C^-$ are too positive. The heats of reaction given by MNDO for the S_N2 reactions of the latter with methyl chloride should therefore be correspondingly too negative, as indeed they are (Table III).

C. Why Is the Conventional Interpretation of Solvent Effects in S_N2 Reactions So Successful? The rates of S_N2 reactions between anionic nucleophiles and neutral substrates are less by many orders of magnitude in solution than in the gas phase, due to the intermediate CD complex being formed with excess energy which cannot be dissipated fast enough in the gas phase. However, while this argument explains why the gas-phase reactions are much faster, it does not explain why the rates in solution usually vary so little with changes in the solvent.[5] The difference in free energy between the separated reactants in solution and the S_N2 transition state (TS) must be almost independent of the solvent, a very surprising conclusion given that both are ions whose solvation energies must be large.

Attempts to solve this problem by direct calculation would be pointless at present because no adequate treatment of solvent effects is available. Besides, even if such a calculation could be carried out and gave a good estimate of the rate of some specific S_N2 reaction in solution, the results would not explain why the rates of S_N2 reactions in general are so little affected by changes in the solvent. A calculation adds nothing to experiment unless it explains *why* things happen in the way they do. A clue is, however, provided by comparison of our calculated values for $\Delta H_c^\ddagger$ and $\Delta S_c^\ddagger$ with the activation parameters observed in solution; see Table II. The agreement between them is quite reasonable. Indeed, it would probably be still better for the real values of $\Delta H_c^\ddagger$ and $\Delta S_c^\ddagger$ because, as we shall see presently, the retarding effect of alkyl substituents on the S_N2 reactions of methyl derivatives is due mainly, if not entirely, to steric effects, which MNDO tends to overestimate.[14] Thus while the value of $\Delta G_0^\ddagger$ calculated for ethyl chloride agrees well with the free energy of activation observed in solution, the value of $\Delta G_0^\ddagger$ for methyl chloride is less, and that for isopropyl chloride greater, than the solution values. Note also that the agreement is good for neopentyl chloride, suggesting that the error may depend mainly on the number of groups attached to the central carbon atom rather than their size. No comparison is possible for *tert*-butyl chloride because it now seems to be generally agreed that it undergoes *no* S_N2 reactions in solution. The rate constants formerly quoted referred to other processes.

Consider the S_N2 replacement of X (in RX) by an anionic nucleophile, Y^-;

$$Y^- + RX \rightarrow [Y{\cdot\cdot}R{\cdot\cdot}X]^- \rightarrow YR + X^- \qquad (2)$$

The free energies of solvation of the CD complex, and of the TS, should therefore be similar. The parallel, noted above, between the calculated and observed activation parameters must then imply that formation of the CD complex in solution involves virtually no change in free energy. The difference between the free energies of solvation of the nucleophile and the CD complex must then be close to the free energy of formation of the latter in the gas phase, i.e.

$$Y^-(\text{solv}) + RX \rightarrow Y^-{\cdot\cdot}RX + (\text{solv}) \qquad \Delta G \sim 0 \qquad (3)$$

where (solv) represents the solvent molecule that must be displaced from the anion in order that the substrate can approach it; see Figure 5. Our problem is to explain this surprising conclusion.

Note first that the number of free particles does not change during the association of Y^- with RX to form the CD complex in solution. The total translational and rotational entropy will therefore change little.

Second, the gas-phase data for the chloride–chloroalkane reactions[2-4] show that the heats of association of anions with typical S_N2 substrates are large, comparable with those for similar attachment of typical solvent molecules. The heat of reaction for association in solution (eq 7), where chloroalkane displaces a molecule of solvent, should therefore also be small, unless the energy of attachment of solvent to Y^- is unusually large.

Third, association of RX or (solv) with Y^- leads to a decrease in freedom of the species involved and hence to a decrease in entropy. Any increase in the tightness of binding will therefore lead to a decrease of both energy and entropy. Since $\Delta G = \Delta H - T\Delta S$, the changes in energy and entropy will tend to compensate one another, the net effect on the free energy (ΔG) being consequently small. Thus any difference between the heats of association of Y with RX and with a molecule of solvent will be largely compensated by a corresponding change in entropy.

It is therefore quite reasonable that the reaction of eq 7 should lead, in solution, to only a small change in free energy.

The arguments used here can be applied quite generally to ionic reactions in solution and indeed were used some time ago by Dewar and Sampson[23] to resolve an analogous paradox which Hammett[24] had pointed out. Current theories of reactivity in organic chemistry were, and still are, necessarily based on the assumption that differences in rate between analogous reactions are determined solely by changes in the activation energy, not in the entropy of activation. These theories have proved very successful in practice in spite of the fact that measured entropies of activation often vary greatly. The variations are, however, due mainly to changes in solvation which should also lead to compensating changes in enthalpy. The net effect on the free energies of reaction, i.e., on rates of reaction, may then be small. This argument also implies that heats or energies of activation of reactions in solution are of minor mechanistic significance. No conclusions can be drawn from a lack of correlation between their observed values and those predicted by theories that do not take solvation explicitly into account. The calculated activation energies should, however, parallel the measured *free* energies of activation, i.e., the rates of the corresponding reactions. This is why current theories of reactivity work well in practice, in spite of Hammett's theoretically valid objections.

The arguments used here break down if there is a very strong association between an anionic nucleophile and the solvent. Energy will then be required to replace a solvating solvent molecule by a molecule of the substrate. Interactions of this kind are strongest when the anion is small and when solvation involves hydrogen bonding. In such cases the free energy of association of Y^- and RX in solution (eq 7) will become large and positive, leading to a large decrease in the rate of reaction. A change to an aprotic solvent will then lead to a large increase in rate. This effect is now well recognized, particularly in the case of fluoride, hydroxide, and alkoxide ions, where the charge is localized on small atoms (F or O). The rates of their reactions with neutral substrates increase by orders of magnitude on passing from a protic solvent to an aprotic one, a fact that forms the basis of phase-transfer catalysis.

D. Effect of Alkyl Substituents on the Rates of S_N2 Reactions. Alkyl groups attached to the reaction center retard S_N2 reactions. It is now generally agreed that the retardation is due largely to steric repulsions in the TS, between alkyl and the entering and leaving groups. However, alkyl groups also exert a $-I$ inductive effect. Does this lead to a further retardation of S_N2 reactions by alkyl substituents or do the steric and inductive effects act in opposition? This problem, which was the subject of controversy[25,26] many years ago, still remains unresolved.

In an S_N2 transition state (**3**), a 2p AO of the central carbon atom overlaps with AOs of the entering and leaving groups (Figure 4a), leading to a system of three center MOs topologically equivalent to, i.e., isoconjugate with, the π MOs in the allyl anion (**4**) (Figure 4b). Such a system contains a strongly bonding MO, a nonbonding MO, and a strongly antibonding MO, the first two

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[23] Dewar, M. J. S.; Sampson, R. J. *J. Chem. Soc.* **1956**, 2789.

[24] Hammett, L. P. "Physical Organic Chemistry"; McGraw-Hill: New York, 1940.

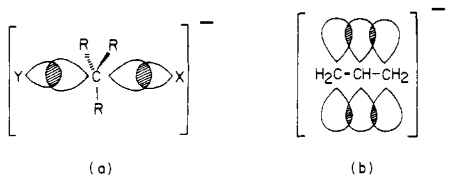


Figure 4. Hammett plots for S_N2 reactions of chloride ion with para-substituted benzyl chlorides: (a) ΔH_0 vs. σ and (b) ΔH_c vs. σ.

of which are doubly occupied in **3** or **4**.

In a HMO description of **4**, where the electronegativities of the atoms are assumed to have fixed values, the formal charge is shared equally between the terminal carbon atoms, the central carbon atom remaining neutral. In an SCF MO description, a negative charge on an atom leads to a decrease in its electronegativity, but it leads to a greater decrease in electronegativity at neighboring atoms.[27] Thus while the negative charges at the terminal atoms in **4** lower their electronegativities, they lower the electronegativity of the central atom still more. The terminal atoms in **4** consequently become more electronegative than the central atom and so attract negative charge away from it. As a result, each terminal carbon atom in **4** ends up with *more* than half a unit of negative charge while the central atom becomes *positive*. This effect, for which there is a simple physical explanation,[27] is also responsible for the well-known tendency of SCF charges to alternate along a chain of atoms. Since the Hartree–Fock method is known to give good estimates of charge distributions in normal closed-shell molecules, there seems little doubt that the central carbon atom in **4** must have a positive formal charge. The same should also be true for **3**. The central atom in **3** should indeed be even more positive than that in **4**, both because the terminal atoms in an S_N2 transition state are always inherently more electronegative than carbon and because the AOs of the terminal atoms are hybrid AOs whereas that of the central carbon atom is a pure p AO.

Our MNDO calculations support these conclusions. Thus the formal charge on the carbon atom in methyl chloride is much more positive in the TS for the S_N2 reaction with Cl^- (Figure 3a) than it is in the corresponding CD complex (Figure 2a).

If the central atom in the TS does indeed have a net positive charge, $-I$ substituents attached to it should stabilize the TS while +I ones should destabilize it. Since no such effect is possible in the parent alkyl chloride, $-I$ substituents should reduce, and $+I$ ones increase, the activation energy of an S_N2 reaction, as Evans[25] orginally suggested. The retarding effect of $-I$ (alkyl) groups is then *entirely* due to steric effects. In the absence of steric hindrance, alkyl substituents would *increase* the rates of S_N2 reactions. The available evidence certainly seems to support Evans. For example, S_N2 replacement of chlorine is much slower in FCH_2CH_2Cl than in CH_3CH_2Cl, as would be expected if the $+E$ effect of fluorine leads to retardation. Steric effects cannot be responsible for this difference because *n*-propyl chloride ($CH_3CH_2CH_2Cl$) reacts at almost the same rate as ethyl chloride, showing that methyl, although larger than fluorine, does not retard the reaction.

E. Effect of Electromeric (Conjugative) Substituents. Electromeric substituents[27,28] of ±E type (e.g., vinyl, phenyl) or $+E$ type (e.g., RCO, ROOC) accelerate S_N2 reactions, the latter very strongly, whereas $-E$ substituents (e.g., RO, F) retard them. These effects can be explained[28] in terms of mesomeric interactions between the substituent and the reaction center in the TS, the central carbon atom in the latter being analogous to the negatively charged center in a carbanion; cf. Figure 5a,b. In order to test this intuition, we carried out calculations for the S_N2 reactions of Cl^- with several p-substituted benzyl chlorides (**5**). Reactions of benzene derivatives are particularly convenient for purposes such as this since no complications should arise from steric effects or variations in the entropy of activation.[25]

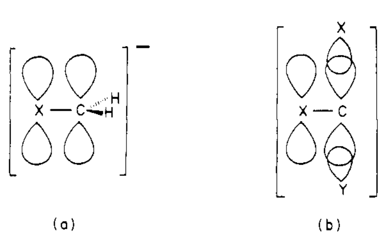


Figure 5. The effect of solvation on the MERP for an S_N2 reaction.

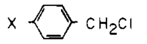
Table IV. Calculations for S_N2 Reactions of Benzyl Chlorides with Chloride Ion[a]

X in $X\text{–}C_6H_4\text{–}CH_2Cl$	$\Delta H^{\ddagger}$	ΔH_0	ΔH_c
H	6.0	8.0	14.0
F	8.7	5.7	14.4
HO	14.6	2.3	16.9
CH_3O	6.2	9.5	15.7
H_2N	7.7	7.8	15.4
O_2N	12.7	1.0	11.7

[a] For notation, see Tables I and II.

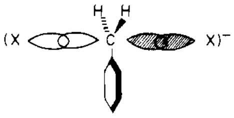
$(Cl_3C\text{-}Cl\text{-}Cl)^-$

2



5

a, X = H
b, X = F
c, X = OH
d, X = OCH_3
e, X = NH_2
f, X = NO_2



6

$ClCH_2CHO$

7

The reactions followed the same pattern as those of the chloroalkanes, and a similar notation is used for them (see Figure 2a). The results are shown in Table IV. No comparisons with experiment are possible because no gas-phase data are available. The transition states had structures of the type indicated in **6**, the benzene ring lying in the plane bisecting the Cl–C–Cl three-center bond. This orientation allows a conjugative interaction between the three-center bond and the π MOs of the ring.

If the reaction center is anion-like, the reaction should be accelerated by substituents in the phenyl group that increase its $+E$ activity and retarded by ones that reduce it. A further advantage of benzene derivatives in situations such as this is that the effects of substituents on the rates normally conform to the Hammett relation[24] and the S_N2 reactions of benzyl halides, in solution, give reasonable Hammett plots.[29] The values of ΔH_0 in Table IV, however, show only a very poor correlation with σ (Figure 6a), implying a qualitative difference between the relative rates in solution and in the gas phase. This of course would be expected in view of the arguments given above, according to which the rates in solution should correlate with ΔH_c, not with ΔH_0. A passable correlation (Figure 6b) was indeed obtained by using ΔH_c in place of ΔH_0, i.e., by assuming each reaction to start from the CD complex instead of from the free reactants. No experimental data are available for comparison because their rates could be studied only by using isotopically labeled chlorine. The values of ΔH_c are, however, in the range observed for S_N2 reactions of benzyl chlorides.

These results support our interpretation of the mode of action of conjugative substituents and also that of solvent effects given in section C.

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(25) Evans, A. G. "The Reactions of Organic Halides in Solution"; Manchester University Press: Manchester, 1946.

(26) Dostrovsky, I.; Hughes, E. D.; Ingold, C. K. *J. Chem. Soc.* **1946**, 173.

(27) Dewar, M. J. S. "The Molecular Orbital Theory of Organic Chemistry"; McGraw-Hill: New York, 1969; p 184.

(28) Dewar, M. J. S. "The Electronic Theory of Organic Chemistry"; Clarendon Press: Oxford, 1949.

(29) Streitwieser, A., Jr.; *Chem. Rev.* **1956**, *56*, 571; "Solvolytic Displacement Reactions"; McGraw-Hill: New York, 1962.

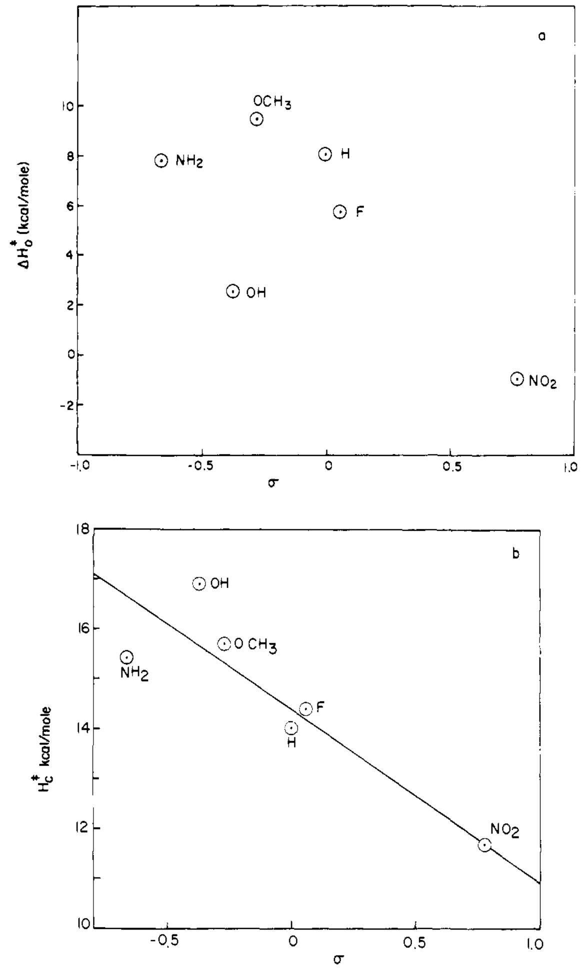
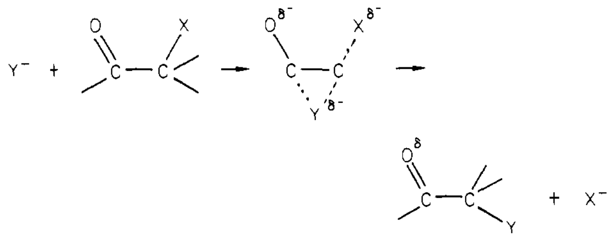


Figure 6. Comparison of conjugative interactions in a carbanion and in an S_N2 transition state.

We next studied the S_N2 reaction of chloride ion with chloroacetaldehyde (**7**), as an example of an alkyl chloride activated by a $+E$ substituent attached directly to the reaction center, because there has been some discussion concerning the mode of action of the substituent in such cases. While Bartlett and Trachtenberg[30] have shown that an attacking nucleophile does not first add to the CO bond of the acyl group, partial addition might help to stabilize the S_N2 transition state; i.e.,



(4)

The reaction followed the usual pattern (Figure 1a) with one exception. In the CD complex, the chlorine ion lay opposite the midpoint of the CC bond (cf. (4)) instead of in line with the CCl bond. This difference would, however, be expected if such complexes are indeed of the charge-dipole type. In **7** there are *two* highly polar bonds, CO and CCl, so the dipolar field is strongest halfway between them. For the same reason the heat of formation of the complex from the reactants is unusually large (−11.0 kcal/mol). The TS, on the other hand, had a normal geometry (Figure 7a). There is no question of even a partial attachment to the carbonyl carbon atom. Indeed, an extensive search of the potential surface showed no path for addition to CO. Any attempt to optimize the geometry of such an adduct led to dissociation into Cl^- and **7**, without activation.

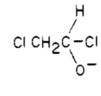
The acceleration of an S_N2 reaction by an adjacent carbonyl group must therefore be due *entirely* to a mesomeric interaction in the transition state, analogous to that in an α-acylcarbanion; see Figure 5. The existence of such an interaction is moreover indicated by comparison of the bond lengths and charge distributions in **7** (Figure 7b) with those in the TSs for the S_N2 reactions of **7** (Figure 7a) and of methyl chloride (Figure 3a) with Cl^-.

(1) The suggested conjugative interaction in the TS from **6** should transfer negative charge from chlorine to oxygen. The (negative) formal charge on oxygen is indeed greater in the TS (−0.329) than in **7** (−0.286) while the corresponding charge on chlorine is less in the TS from **7** (−0.713) than in the TS from methyl chloride (−0.747).

(2) Such conjugation should also tend to lengthen the CO bond and shorten the CC bond. The CO bond length is indeed greater (1.224 vs. 1.220 Å) and the CC bond length less (1.513 vs. 1.526 Å) in the TS from **7** than in **7** itself (Figure 7).

Similar considerations presumably also apply in other cases where $+E$ substituents accelerate S_N2 reactions.

F. Why Are S_N2 Reactions Slow? Allyl anion is planar and the barrier to internal rotation in it is quite large. The barrier corresponds to the difference in energy between the planar ion (**9**) and an isomer (**10**) where one methylene group has rotated through 90°. This difference represents the difference in bond energy between the three-center four-electron π bond in **3** and the two-center two-electron σ bond in **10**. As we have already noted (see Figure 4), the three-center four-electron σ bond in an S_N2 TS is isoconjugate with the three-center four-electron π bond in **9**. The two-center $H_3C{-}X$ σ bond in the reactant (CH_3X) is likewise isoconjugate with the two-center π bond in **10**. This analogy implies that combination of X^- with CH_3X to form an adduct with pentacoordinated carbon should be exothermic, just as the conversion of **10** to **9** is exothermic. Why then is the adduct a TS and not a minimum on the corresponding potential surface? Three-center four-electron σ bonds are believed to be responsible for the bonding in the xenon fluorides and other hypervalent main-group compounds.[22] There is no indication that bonds of this type are any weaker than the analogous three-center σ bond in **9**. It is therefore very difficult to see why addition of X^- to RX should not be exothermic, leading to a stable adduct, e.g., $CH_3Cl_2^-$.



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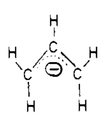

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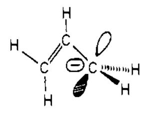

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The reason for this difference has recently been indicated by MNDO calculations[31] for the reactions of anions with silyl halides, R_3SiX, where X is halogen. Reactions of this kind take place very easily, many orders of magnitude faster than analogous S_N2 reactions on carbon, and this difference has been attributed to stabilization of the trigonal-bipyramidal intermediate (**11**) by participation by the 3d AOs of silicon. The MNDO calculations, however, predicted the addition of anions to R_3SiX to take place exothermically and without activation, by exothermic formation of a three-center four-electron bond. Silicon 3d AOs are not involved because d AOs were not included in the calculations. The

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[30] Bartlett, P. D.; Trachtenberg, E. N. *J. Am. Chem. Soc.* **1958**, *80*, 5808.

[31] Dewar, M. J. S.; Healy, E. F. *J. Organomet. Chem.* **1982**, *1*, 1705.

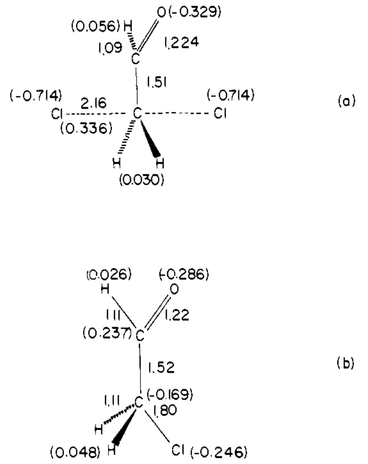


Figure 7. Bond lengths (formal charges) in (a) the transition state for the S_N2 reaction of the chloride ion with chloroacetaldehyde and (b) chloroacetaldehyde.

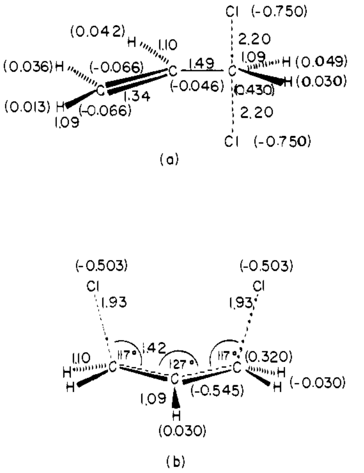
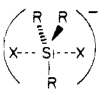


Figure 8. Bond lengths (formal charges) in reactions of the chloride ion with allyl chloride; (a) the S_N2 transition state; (b) the syn S_N2' intermediate; and (c) the anti S_N2' intermediate. In b and c the Cl–C–C–C dihedral angles are ±90°.

reactions of silyl halides therefore follow the pattern that would have been expected for S_N2 reactions on carbon, the three-center four-electron ClSiCl σ bond in the "S_N2 TS" (**11**) for substitution on silicon being stronger than the two-center two-electron SiCl σ bond in the reactant. Since the difference cannot be attributed to any difference between the valence shells of carbon and silicon, it can be due only to the different sizes of the carbon and silicon atoms. Because carbon is small, the repulsions between adjacent groups become excessive if five of them try to form bonds to the same carbon atom simultaneously. This problem does not arise in the case of silicon because its atoms are bigger. Similar considerations presumably apply to the other second-period elements, in particular nitrogen and oxygen. Since the steric requirements of lone pairs of electrons are considerable, it is difficult to pack more than four ligands and/or lone pairs around these atoms. This is why nitrogen fails to form pentacovalent compounds (cf. NF_5 with PF_5) and why oxygen fails to form tetracovalent or hexacovalent ones (cf. OF_4 or OF_6 with SF_4 or SF_6). Phosphorus and sulfur can form hypervalent compounds primarily because their atoms are bigger.



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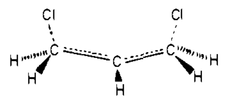

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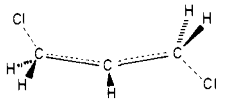


16

$ClCH_2CH_2^-$

17

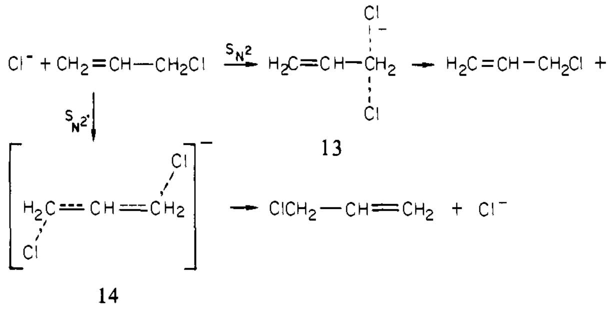
$(H_2C\text{—}CH\text{—}CH\text{—}CH\text{—}CH_2)^-$

18

$H_2C{=}CH{-}CH{=}CH_2$

19

G. The S_N2' Reaction. The S_N2 reaction involves nucleophilic attack at the γ position in an allyl derivative, leading to substitution with migration of the double bond. We studied a simple example, the reaction of chloride ion with allyl chloride (**12**).



(5)

The S_N2 reaction of Cl^- with **12** followed a normal course via a CD complex. The calculated values for the various parameters were

$$\Delta H_c = -6.0 \text{ kcal/mol} \qquad \Delta H_0 = 8.8 \text{ kcal/mol}$$
$$\Delta H_c^{\ddagger} = 14.8 \text{ kcal/mol} \tag{6}$$

The geometry and distribution of formal charge in the corresponding transition state are shown in Figure 8a. The enthalpy of activation of the reaction, starting from the CD complex, would be expected to be less than that for ethyl chloride ($\Delta H_c^{\ddagger}$ = 17.7 kcal/mol; Table II) but a little greater than that for benzyl chloride (**3a**) ($\Delta H_c^{\ddagger}$ = 14.0 kcal/mol; Table IV), as indeed is the case. Note that since MNDO overestimates repulsions in S_N2 transition states, comparisons of this kind should be made between species with the same number of groups attached to the reaction center. As noted earlier in the case of neopentyl chloride, the error seems to depend only on the number of substituents, not on their type.

Next we studied the S_N2' reaction.

Simple considerations of orbital overlap suggest that in the transition state (**14**; eq 9) the CCl bonds must be more or less coplanar with the axis of the unhybridized 2p AO of the central carbon atom. Two structures are then possible, the chlorine atoms being either syn (**15**) or anti (**16**) to one another. Both structures were found to correspond to stationary points on the MNDO potential surface. However, in contrast to the S_N2 reaction, both **15** and **16** were *minima* on the potential surface, not transition states. Formation of either of them, from Cl^- and **12**, takes place without activation. The geometries, heats of formation, and distributions of formal charge, calculated for **15** and **16**, are shown in Figure 8, parts b and c, respectively. The anti isomer (**16**) is predicted to be the more stable, the heats of reaction for their formation from (Cl^- + **12**) being

$$\mathbf{15}\text{: } \Delta H = -2.2 \text{ kcal/mol} \qquad \mathbf{16}\text{: } \Delta H = -5.8 \text{ kcal/mol} \tag{7}$$

Our calculations and arguments thus imply that S_N2' reactions of anions with allyl halides should take place without activation in the gas phase, thus at least competing with the alternative S_N2 processes, and that the products should correspond mainly to anti attack by the anion. No gas-phase studies of such reactions have as yet been reported.

The prediction that Cl^- adds without activation to the double bond of **8** surprised us greatly. To make sure that this was not an odd eccentricity on the part of MNDO, we studied the reaction of Cl^- with ethylene. Here, however, no addition took place. Indeed, the chloroethyl anion (**17**) dissociated into chloride ion and ethylene without activation.

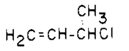
The CCl bonds in **15** and **16** are longer (1.93, 1.95 Å) than the CCl bond in **12** (1.81 Å). The lengths (1.42 Å) of the CC bonds are the same and intermediate between those of C—C and C═C bonds. The three p AOs of the allyl moiety (in **15** or **16**) evidently coalesce with the two chlorine AOs to form five-center MOs, isoconjugate with the π MOs in pentadienyl anion (**18**) with which **15** and **16** are consequently isoconjugate. The conjugated system in each ion is of course linear because the chlorine atoms are too far apart for there to be any exchange interaction between them. Even in the syn isomer the Cl–Cl distance is 3.55 Å, equal to the van der Waals separation and almost double the distance in Cl_2.

The negative charges on the central carbon atoms in **15** or **16** are very large and negative, while those on the terminal carbon atoms are smaller and positive, as they are in **18**. Since the five-center six-electron π bond in **18** is stronger than the pair of two-center two-electron π bonds 1,3-butadiene (**19**), one would expect the analogous five-center six-electron bonds in **15** or **16** to be stronger than the two corresponding two-center two-electron bonds in **12**. The fact that chloride ion combines with **12** to form **15** or **16**, exothermically and without activation, would not therefore be surprising, were it not for the fact that the analogous intermediate in an S_N2 reaction, in particular in the S_N2 reaction of Cl^- with **12**, is a saddle point on the potential surface, i.e., a transition state, not a minimum.

This difference can be understood if the instability of the S_N2 transition state is indeed due solely to steric effects. In the S_N2' reaction, the adduct from the nucleophile and the allyl derivative does *not* have pentacovalent carbon, because the attack is on an unsaturated carbon atom which initially has only three neighbors. Attack by an anion at the γ position in **12** can therefore take place exothermically and without activation, like attack on silicon in R_3SiCl, because the extra ligand can in each case be accommodated without undue steric crowding.

Experimental studies have shown that S_N2' reactions of allyl compounds with anionic nucleophiles in solution are much slower than their S_N2 analogues. Thus in the reactions of Br^- with 1- (**20**) or 3- (**21**) methylallyl bromide in acetone,[32] each of the S_N2 rates is greater than either S_N2' one. The measured values suggest that the ratio for allyl bromide itself would be about 1000:1. While no data are available for the S_N2' reaction of **12** (eq 10), it seems certain that it will prove to be comparably slower than its S_N2 counterpart. The S_N2' reaction must therefore be retarded much more strongly by solvent than is the competing S_N2 one. This difference is not in fact surprising. In an S_N2 reaction in solution, the reactants are expected to form the corresponding CD complex with little change in free energy, because the energy of solvation of the anion by the polar substrate is comparable with that of solvation by the solvent molecule which it displaces. This can no longer be the case in an S_N2' reaction because the anion is approaching the wrong end of the allyl compound, far away from the polar CX group. Formation of the CD complex will consequently be strongly endothermic, the heat of reaction being roughly equal to *minus* the heat of solvation of the anion by one solvent molecule. The solvent should therefore have a far larger retarding effect on an S_N2' reaction than on its S_N2 counterpart. The activation barrier to the S_N2' reaction in solution must indeed arise entirely from the energy needed to remove solvent from the anion so that the allyl derivative can approach, little or no change in bonding having taken place in the TS, because once the reactants are in contact, they can combine without activation. The effects of substituents on the rates of S_N2' reactions should then be different from their effects on S_N2 ones. No data are available to test this prediction.

These remarks apply only to anionic nucleophiles. Neutral nucleophiles should be much less affected by solvation, and the cases where S_N2' mechanisms have been found to predominate have usually involved such species, in particular primary and secondary amines.[33] The S_N2' products formed from allyl halides and amines naturally correspond to syn attack by the nucleophile because the syn adduct, corresponding to **15**, will be selectively stabilized by the electrostatic attraction between the positively charged amine and the negatively charged leaving group, further assisted by hydrogen bonding; see **22**. No such effect is possible in the anti isomer. The S_N2' reaction was formerly believed to take place preferentially by syn attack on the basis of experiments of this kind (see, e.g., ref 33), but later studies, using other nucleophiles, have shown that anti attack can predominate in other cases.[34]

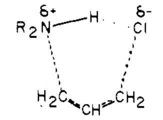


$H_2C{=}CH{-}\overset{CH_3}{CH}Cl$

20

$CH_3CH{=}CH{-}CH_2Cl$

21



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The S_N2' reaction has presented problems in so far as conventional qualitative MO theory is concerned because it is impossible to predict in any convincing way whether the syn or anti route should be preferred. Our calculations also show an interesting dichotomy. Thus the CCl bond lengths (1.93 Å) in **15** are slightly less than those in **16** (1.95 Å), suggesting that **15** should have the larger net binding energy; yet that of **16** is predicted to be the greater. The reversal is clearly due to the electrostatic repulsion between the negatively charged chlorine atoms, which, according to our calculated geometries and formal charges, is greater in **15** than in **16** by ca. 6 kcal/mol. Otherwise **15** would indeed be the lower in energy. Since the repulsions between the chlorine atoms will be greatly reduced in solution, particularly in a solvent with a reasonably high dielectric constant, the syn isomer may then become the more stable, even if our estimate of the difference in the gas phase is correct. Syn attack should also be favored by solvents where the nucleophile is present almost exclusively in the form of ion pairs, the gegenion interacting with the entering and leaving groups in the transition state; see **14**.

Conclusions

(A) The calculations reported here support earlier conclusions concerning the mechanisms of S_N2 reactions in the gas phase, based on mass spectrometric studies and ab initio calculations for some simple examples.

(B) The low activation energies observed for S_N2 reactions in the gas phase are due to a "hot molecule" process, energy being liberated in forming the intermediate charge-dipole (CD) complex. Our calculations indicate that formation of the complex in solution involves little or no change in free energy, the thermodynamic parameters calculated for reaction in the gas phase, starting from the CD complex, agreeing quite well with those observed in solution. Qualitative considerations indicate why this is the case.

(C) An S_N2 TS is isoconjugate with the allyl anion. According to current theory, the central atom in this is positively charged and the same should be true of an S_N2 TS. Our MNDO calculations indicate that this is indeed the case. $-I$ substituents (e.g., alkyl) should therefore accelerate S_N2 reactions while $+E$ ones should retard them. The retardation due to alkyl substituents is due to steric effects.

(D) The acceleration of S_N2 reactions by $\pm E$ or $+E$ substituents is due to mesomeric stabilization of the anion-like TS. This is indicated by the effects of substituents on the rate of the S_N2 reaction of chloride ion with benzyl chloride and by calculations

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[32] de la Mare, P. B. D.; England, B. D.; Fowden, L.; Hughes, E. D.; Ingold, C. K. *J. Chim. Phys. Phys.-Chim. Biol.* **1949**, *45*, 236.

[33] Stork, G.; White, G. N. *J. Am. Chem. Soc.* **1956**, *78*, 4609.

[34] For a review and references, see: Magid, R. M. *Tetrahedron* **1980**, *36*, 1901.

J. Am. Chem. Soc. **1984**, *106*, 3539-3548

for the corresponding reaction of chloroacetaldehyde. The carbonyl group does not interact directly with the attacking nucleophile.

(E) The S_N2 reaction of the chloride ion with allyl chloride is predicted to take place without activation in the gas phase, by addition of chloride ion to the CC double bond to form a species superficially resembling the 1,3-dichloro-2-propyl anion. It contains a delocalized six-electron system, isoconjugate with the π system in pentadienyl anion and derived from the allyl cation by interaction of its terminal 2p AOs with the two chloride ions. The anti isomer is the more stable. S_N2' reactions of anionic nucleophiles in solution are slower than their S_N2 counterparts because of the greater energy needed to form the intermediate complex. Syn S_N2' attack by primary or secondary amines is attributed to hydrogen bonding between the entering and leaving groups. Preliminary studies indicate that the S_N2' reaction may be favored in a poor solvent for anions if ion pairing is repressed by use of a large cation.

(F) Since the bonding in hypervalent compounds is now commonly attributed to three-center four-electron bonds which are entirely analogous to that in an S_N2 TS, it seems surprising that the latter should be a saddle point, rather than a minimum, on the potential surface. This problem is made even more acute by the calculations reported here, which indicate this to be the case for S_N2' reactions. The difference seems to be due to the small size of the carbon atom. This leads to excessive steric repulsions when five other groups are attached. The failure of nitrogen or oxygen to form hypervalent compounds can be explained in the same way, the steric requirements of a lone pair of electrons being by no means negligible.

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Registry No. 5a, 100-44-7; **5b**, 352-11-4; **5c**, 35421-08-0; **5d**, 824-94-2; **5e**, 65581-19-3; **5f**, 100-14-1; **7**, 107-20-0; **12**, 107-05-1; CH_3Cl, 74-87-3; CH_3CH_2Cl, 75-00-3; $(CH_3)_2CHCl$, 75-29-6; $(CH_3)_3CCl$, 507-20-0; $(CH_3)_3CCH_2Cl$, 753-89-9; CH_2Cl_2, 75-09-2; $CHCl_3$, 67-66-3; CCl_4, 56-23-5.

Quassinoids: Total Synthesis of *dl*-Quassin

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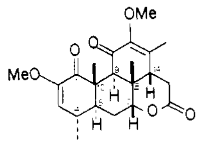
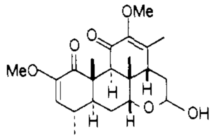
Abstract: The total synthesis of quassin (**1**), the major constituent of quassia wood, is described in racemic form. The synthesis features the Lewis acid catalyzed intermolecular Diels–Alder reaction between dienophile **8** and ethyl (*E*)-4-methyl-3,5-hexadienoate (**9**). Diels–Alder adduct **10** is transformed in straightforward fashion into tetracyclic diketone **15**, which is elaborated via a two-step sequence into neoquassin in β-*O*-methyl ether **49** (R = Me). Selective hydrolysis of **49** (R = Me) and subsequent oxidation provides *dl*-quassin.

The existence of bitter principles in quassia wood (*Quassia amara*) was first reported[2] in the literature in 1835; however, early attempts to isolate and purify the chemical constituents were unsuccessful. It was not until 1937, a century later, that Clark[3] succeeded in isolating and partially purifying quassin (**1**). During the early 1950s, Robertson and co-workers succeeded in characterizing the two major constituents of quassia wood, quassin (**1**) and neoquassin (**2**).[4] A decade later, after extensive studies, Valenta and co-workers[5] elucidated by classical methods the structures of quassin and neoquassin, as major constituents of *Simaroubaceae*. Since the structure of quassin was put forth over 20 years ago, numerous highly oxygenated quassinoids[6,7] have been isolated from *Simaroubaceae* [cf. quassimarin (**3**)[8] and glaucarubolone (**4**)[9]]. Extensive studies have been carried out on quassinoid bitter principles, since these naturally occurring substances possess potent cytotoxic properties.[10]



1



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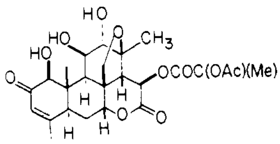

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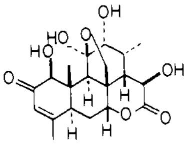

4

The highly oxygenated tetracyclic carbon skeleton of quassin coupled with its complex stereochemical arrangement of carbon atoms has stimulated a great deal of synthetic activity.[11] Early

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[6] The term quassinoid refers to chemically related Simaroubaceae constituents, which form the bitter principles of the quassin group.

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