RECENT ASPECTS OF NUCLEOPHILIC SUBSTITUTION AT A SATURED CARBON*

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Nucleophilic substitution at a saturated carbon atom is one of the longest known and most thoroughly investigated reactions in organic chemistry and has been sub-divided into two categories, S_N1 and S_N2, where the numbers refer to the molecularity of the reactions in question, that is, to the number of molecules necessarily undergoing covalency change in the rate-determining step[1].

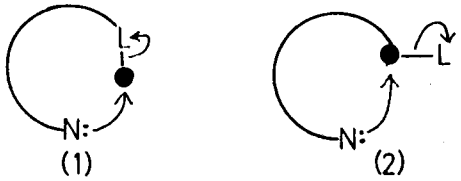
However, these reactions continue to attract interest and here the results of some recent investigations are described. These are concerned principally with the nature of the group R in the molecule R-X for the general substitution reaction shown in equation 1. Other work

$$R\text{-}X + Y \rightarrow R\text{-}Y + X \qquad (1)$$

on these substitution reaction that has centred mainly on ion-pairs and solvation effects[2] is not considered.

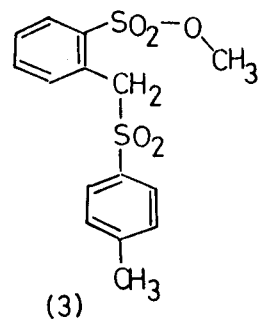
The S_N2 reaction is associated with one of the inviolate rules of organic chemistry *viz.* each act of substitution is associated with inversion of configuration at the carbon bearing the leaving group in the original molecule. This phenomenon is known as the Walden inversion after its discoverer[1].

Recent work of significance concerning the S_N2 reaction has its origin in a paper by Eschenmoser in 1970[3]. This publication was concerned with the importance of the ring size of the transition state in two cases in which the nucleophile (N), the central carbon (that is the carbon bearing the leaving group in the starting material) and the leaving group (L) are all in the same molecule. These two cases are termed endocyclic (1) and exocyclic (2) respectively. In the case of an organic halide (e.g. L = Br) the normal monovalency



of the halogen means that only (2) can be of significance.

The molecule chosen to investigate the significance of endocyclic nucleophilic substitutions was (3) and its isotopic modification (4) containing two CD_3 groups. On treatment of (3)



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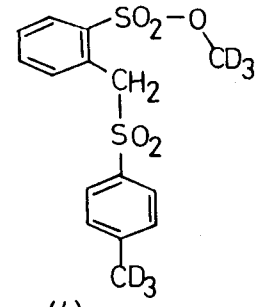

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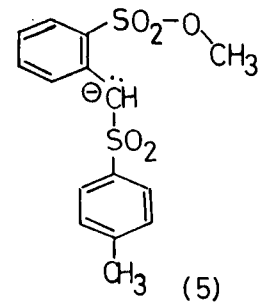

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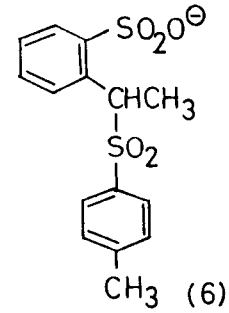

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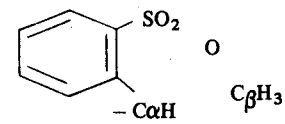

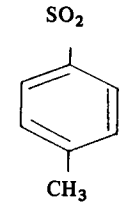

(7)

with base the carbanion (5) was formed and this gave rise to the product (6). An intramolecular endocyclic mechanism was excluded because when equimolar amounts of (3) and the hexadeuterio compound (4) were together reacted with base there was complete randomisation of the CH_3 and CD_3 groups in the product (shown in all protio form in (6)). This means that the nucleophilic substitution reaction is

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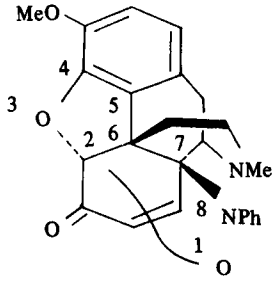
intermolecular and that the sequence of electron shifts depicted in (7) does not occur because C_α, C_β and O are unable to become collinear in the transition state for endocyclic nucleophilic substitution. This collinearity is a pre-requisite for the inversion of configuration observed in nucleophilic substitution at saturated carbon. Accordingly, Eschenmoser wrote, "The general experience according to which intramolecular reaction paths over ciclyc transition states with ring sizes of 5 or 6 are preferred to their intermolecular counterparts, is not to be extrapolated to S_N2 reactions at saturated carbon."[3]

Subsequent investigations have shed light on the question of what is the minimum ring size that can be tolerated in the transition state of an endocyclic nucleophilic substitution at saturated carbon.

Thus, the oxyanion, (8), of a codeine derivative was found to undergo a ready intramolecular endocyclic substitution reaction to give (9) in high yield.[4] In (8) there are several fused ring systems and the constraints imposed by this fusion are such that O_1, C_2 and O_3 are essentially collinear in the



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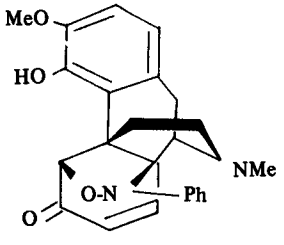
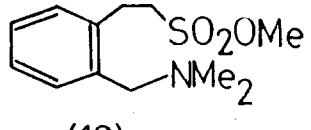


(9)

transition state for the endocyclic substitution reaction that leads to (9); this can be appreciated from a molecular model of (8). An eight-membered cyclic transition state, as indicated by the numbered atoms in (8) is thus seen to mediate this endocyclic reaction.

King and co-workers[5] showed that in benzene at very low initial concentrations of (10) (5 x 10^{-3}M), a transformation into (11) occurred to the extent of 16% by an intramolecular endocyclic S_N reaction; the balance of the reaction was intermolecular. In this case the intramolecular reaction was associated with a nine-membered cyclic transition state[5]. The proportion of the intramolecular reaction decreased with increasing initial concentration of (10).



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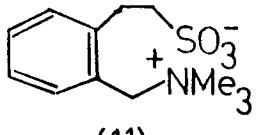

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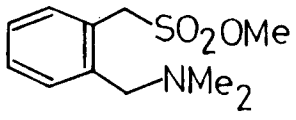
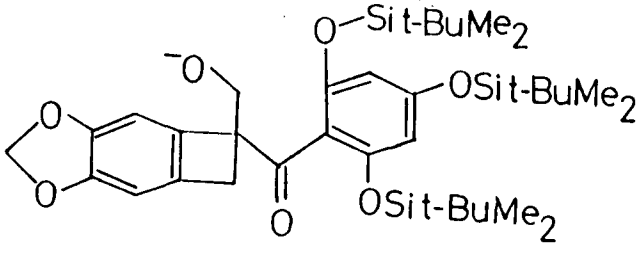


(12)

In the case of the lower homologue (12) where a potential endocyclic nucleophilic substitution reaction involves an eight-membered cyclic transition state, the reaction was found to occur exclusively by means of an intermolecular mechanism[5].

More recently Cava's group[6] has found that an eight-membered cyclic transition state mediated the transformation of (13) into (14). In this endocyclic reaction however it is a silicon atom rather than carbon which is undergoing nucleophilic attack.



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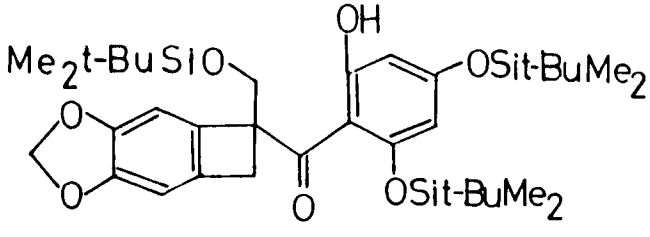
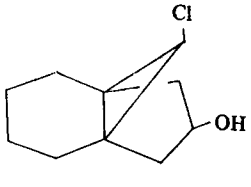


(14)

To date it appears that an eight-membered cyclic transition state is the smallest that can be tolerated in an endocyclic nucleophilic reaction at saturated carbon, and then under favourable circumstances.

The requisite collinearity between the nucleophile, the "central" carbon and the leaving group can be readily achieved in the transition state for exocyclic nucleophilic substitution reactions. One noteworthy example has been reported recently and involves conversion of the anion of (15) into (16); the anion was generated from (15) using t-BuOK in DMSO.



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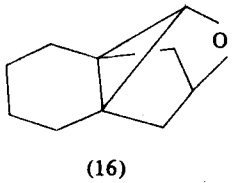


(16)

This transformation [7] ended the quest for the first unambiguous example of nucleophilic substitution at a cyclopropane carbon.

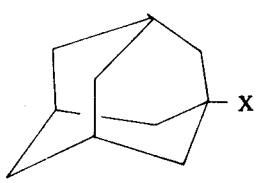
In S_N1 reactions at satured carbon the intermediate carbocation is planar in the ideal case. The rate of formation of the carbocation, which is the rate-limiting step in S_N1 reactions, is significantly reduced when the carbon that bears the positive charge is prevented from becoming coplanar. This is best exemplified in S_N1 reactions of bridgehead substituted compounds.

The relative rate constants shown in the Table indicate that the rate of cleavage of the C-X bond in (18) is *ca.* 10^{-12} that of the t-butyl counterpat which is taken as a model compound[8, 9]. For many years this compound was found to undergo the slowest S_N1 reaction known[10] (see reference 8 for rate constants; by comparison the rate constant for the 1-adamantyl system (17), within whose carbocyclic framework there is very little strain, is depressed by only *ca* 10^3). However, the rate constant for heterolysis of the 4-tricyclyl derivative (19) was *ca.* 10^5 slower still and the data in the Table indicate that this compound is now the record holder for the slowest experimentally observed S_N1 reaction. The rate constants for (19) were determined at very high temperatures (*ca.*230 °C) using stainless steel tubes, a very ionising solvent, 60% aqueous ethanol (w/w), and a very good leaving group ($—OSO_2CF_3$).[8] The rate data were transposed to 25°C (and the dangers inherent in such procedures were outlined).[8] At this temperature (19, X = OTs) was calculated to undergo aqueous ethanolysis in the above solvent mixture with a first order rate constant of 4.77 x 10^{-18} S^{-1}. This corresponds to a half life, $t_{1/2}$ = 4.6 x 10^9 years which is approximately that for radioactive decay of ^{238}U.[8]

TABLE

Relative rate constants fo rcleavage of a common C-X bond in bridgehead derivatives at 25°C (adapted from reference 8).

Compound	Relative rate constant
t-BuX	1
(17)	1.2×10^{-3}
(18)	2.0×10^{-12}
(19)	7.9×10^{-17}
(20)	"inert"
(21)	$\sim 10^4$
(23)	$\sim 3 \times 10^2$
(25)	$\sim 10^9$



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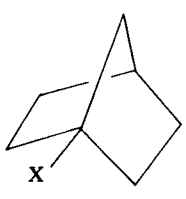

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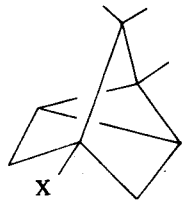

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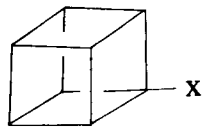
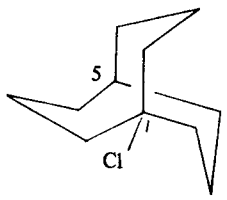


(20)

However, the rate constant calculated for the S_N1 reaction of (20) (X = OSO_2CF_3) in acetic acid at 250°C is calculated[11] to be less than 10^{-12} S^{-1} which corresponds to an essentially inert substrate. On the basis of calculation this compound reacts so slowly that it is probably outside the range of experimental observation.

The ionization rate constants (as their logarithms) correlate well with the calculated increases in strain energy involved in the ionization; greater strain energy is due almost entirely to distortion of the CCC bond angles at and adjacent to the cationic centre.[8]

Despite these very slow reactions, a very rapid rate of ionisation was reported for the solvolysis (80% aqueous ethanol) of 1-chlorobicyclo [3,3,3] undecane (1-chloromanxane) (21).[12] Indeed (21) is estimated to be *ca.* 10^4 as reactive as t-butyl chloride (Table). The reason for the enhanced reactivity of (21) may be discerned from inspection of the bond angles of the closely related salt (22). In this ammonium salt[13] the ring bond angles at C(5), exemplified by C(4)C(5)C(6) = 114.8(3)°, those at C(3), C(7) and C(10), exemplified by C(2)C(3)C(4) = 120.1(2)°, and those at the methylene carbons adjacent to the bridgehead exemplified by C(5)C(6)C(7) = 118.3(2)° are indicative of significant angle strain. Broadly similar values were calculated for the hydrocarbon manxane and the source of the rate enhancement experienced by (21) on ionisation was estimated from force field calculation to reside in the relief of this angle strain during ionisation.[14] Some flattening at the bridgehead position, at which a planar trigonal carbon is readily accommodated, also brings about a reduction in the non-bonded interactions involving C(3), C(7) and C(10). The flattening at the bridgehead carbons, which is possible only in larger ring systems, results in a slight



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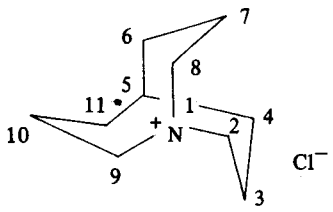
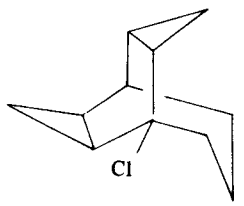


(22)

decrease of the C(1)...C(5) non-bonded distance in (21) from 3.322 Å to 2.990 Å after ionisation.[14]

Slightly earlier de Meijere and co-workers had shown that the related compound (23) underwent ionisation *ca.* 300 times more rapidly than t-butyl chloride (Table).[15] This group also reported that the rate of ionisation of (24) was still faster, a result that was attributed to the



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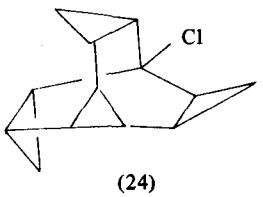

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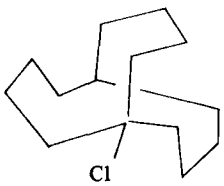

(25)

formation of a less strained bridgehead carbocation from (24) than from (23).

Finally, calculations indicate that the bridgehead substituted compound (25) (1-chloro-bicyclo[4.4.4] tetradecane) shows appreciable angle strain which would be relieved on rate-determining ionisation. The reactivity of (25) is *estimated* to be *ca.* 10^5 faster than that of (21) and hence *ca.* 10^9 faster than that of t-butyl chloride.[12]

CONCLUSION

Intramolecular endocyclic nucleophilic substitution at a satured carbon atom is permitted in one case at least when the size of the ring in the transition state is eight-membered. More generally this mechanism appears to become significant when the corresponding transition state in nine membered.

The S_N1 reactions of bridgehead substituted compounds are not universally slow. A range of more than twenty powers of ten is covered by the rate constants for ionisation. At the limits of this range is a rate constant that is probably too slow to measure and one that is probably too fast.

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