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Review

S_Ni fragmentations of alkoxychlorocarbenes – a perspective

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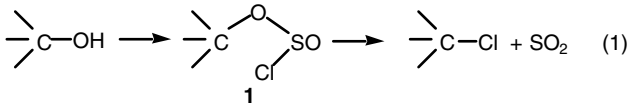
ABSTRACT: After a review of the early literature concerning S_Ni fragmentations of alkyl chlorosulfites and chloroformates, we present experimental and computational results for the S_Ni fragmentations of alkoxychlorocarbenes. Examples include cyclohexyloxychlorocarbene, 7-norbornyloxychlorocarbene, 3-nortricyclyloxychlorocarbene, *exo*-5-norbornenyl-2-oxychlorocarbene, and *endo*-5-norbornenyl-2-oxychlorocarbene. Computations generate a 'family' of closely related charge-separated S_Ni structures which approximate asynchronous, polar, concerted transition states and tight, short-lived ion pair intermediates. The precise description and behavior of these species in a given reaction depends on the identities of the alkyl group, the potential counterion, and the solvent. Copyright © 2007 John Wiley & Sons, Ltd.

KEYWORDS: alkoxychlorocarbenes; concerted transition states; ion pairs; S_Ni reactions

INTRODUCTION

The designation S_Ni (substitution, nucleophilic, internal) was early applied to the conversion of an alcohol by thionyl chloride to an alkyl chloride with stereochemical retention.[1] This transformation was depicted as proceeding via a 4-center rearrangement of an intermediate alkyl chlorosulfite (**1**); eqn (1).[1]

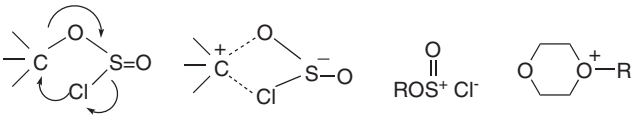


(1)

1

It was also noted that a similar analysis applied to the thermal decomposition of alkyl chloroformates in the absence of base, which also gave alkyl chlorides with retention of configuration.[1b]

Early physical organic chemistry textbooks offered concerted mechanisms for the decomposition of **1**, as in Hine's representation (**2**),[2] although it was recognized that ionic character was often attached to S_Ni reactions.



2 **3** **4** **5**

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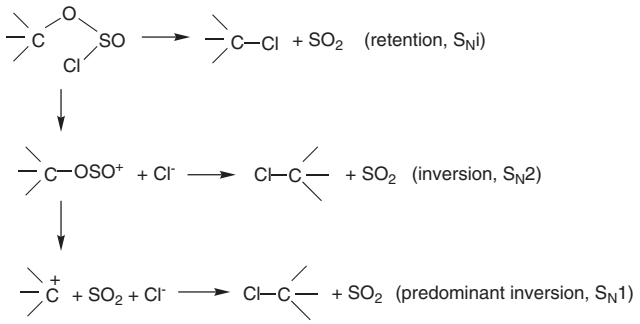
Thus, Hughes and Ingold had already noted that the S_Ni decomposition of alkyl chlorosulfites involved competition with both S_N2 and S_N1 mechanisms, as shown in Scheme 1.[1]

In this scheme, the addition of pyridine liberated chloride for an inverting S_N2 attack on $ROSOPy^+$ or ROSOCl, whereas ionization to a carbocation and an ensuing S_N1 reaction competed in the absence of base and in a good ionizing solvent, especially if the R group supported ionization (e.g., α-phenylethyl).[1]

Cram proposed that S_Ni and S_N1 reactions both involved initial ionization to ion pairs.[3] In the S_Ni variation, a complex anion (e.g., SO_2Cl^-) afforded a daughter anion (Cl^-) which led to product more rapidly than competing modes of nucleophilic attack.[3] Gould's[4] textbook emphasized this point, modifying the 4-center transition state for chlorosulfite fragmentation (**2**) to reflect ion pair character, as in intermediate **3**.

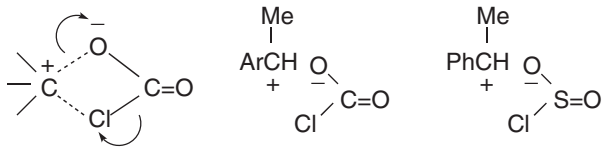
Lewis and Boozer[5] made a careful stereochemical and kinetics study of the decomposition of secondary alkyl chlorosulfites in a variety of solvents. The reactions were first order in either ethereal (e.g., dioxane) or non-ethereal solvents (e.g., toluene), with stereochemical retention in the former and inversion in the latter. They suggested[5b] an initial S—Cl cleavage to ion pair **4**, as postulated by Hughes and Ingold (Scheme 1).[1] In dioxane, rear-side solvation of **4** would lead to loss of SO_2 and formation of the oxonium ion (**5**), which would 'invert' the stereochemistry at the



Scheme 1

chiral center. Subsequent inverting attack on **5** by Cl^- would then afford RCl with overall retention, that is, two inversions lead to retention. Solvents like toluene, however, would not attack ion pair **4**, and rear-side substitution by Cl^- directly on RSO_2^+ would give inverted RCl.[5b]

Hine[2] and Gould[4] also consider S_Ni reactions on alkyl chloroformates,[1] with Gould offering 4-center ion pair intermediate **6**. Studies of α-arylethyl chloroformates by Wiberg and Shyrne[6] accord with this formulation. The conversions of these substrates to α-arylethyl chlorides occur with retention in either dioxane or toluene with ρ values of -3.86 or -3.56, respectively.[6]



6 **7** **8**

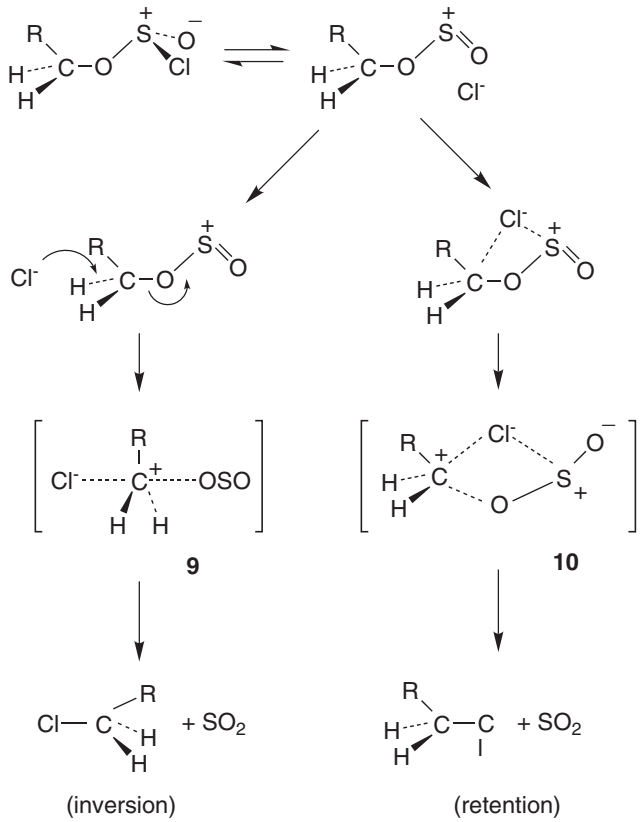
Formation of an α-arylmethyl cation chloroformate anion ion pair (**7**) is considered the rate-limiting step, with subsequent breakdown of the anion to Cl^- and CO_2.[6] Indeed, the reaction of α-phenylethanol with $SOCl_2$ also gives the chloride with retention in either solvent,[6] as was recognized by Hughes and Ingold,[1] for which one can draw the analogous ion pair (**8**). In a related experiment, Lewis *et al*.[7] found that the gas phase decomposition of 2-butyl chloroformate gave 2-chlorobutane with complete retention of configuration. Because ionic character should be suppressed in the gas phase, the stereochemical outcome was attributed to a 4-center cyclic transition state.[7]

Subsequent years witnessed waning interest in 'classical' S_Ni reactions. For example, the S_Ni mechanism is not explicitly considered in the well-known textbooks by Lowry and Richardson,[8] Carey and Sundberg,[9] Carroll,[10] or Ansyln and Dougherty.[11] Only March presents a brief mechanistic discussion of the S_Ni reaction.[12] It is also ironic that many undergraduate organic chemistry textbooks discuss the reaction of alcohols with thionyl chloride, and the associated stereochemistry, without mentioning the S_Ni designation.

More recently, important contributions were made by Schreiner, Schleyer, and Hill.[13,14] Noting that the concerted 4-center front-side mechanism (**2**) is at least formally forbidden by the Woodward–Hoffmann rules, they presented ion pair mechanisms for alkyl chlorosulfite S_Ni reactions. In their view, primary ROSOCl ionize to alkylsulfinyl cations ($ROSO^+$) and Cl^- in a rate-determining step, followed by Cl^- attack at either the front or back side of the cation in the subsequent product determining step. Tertiary ROSOCl, in contrast, ionize directly to carbocations and chlorosulfinyl anions ($R^+\ ^-OSOCl$), with subsequent reaction of R^+ and Cl^- (derived from ^-OSOCl). Secondary ROSOCl may ionize in either fashion, depending on the structure of R and the solvent polarity.[13]

Schreiner *et al*. propose differentiating 'S_N2-like' and 'S_N1-like' S_Ni mechanisms, as illustrated in Schemes 2 and 3. In the 'S_N2i' mechanism of Scheme 2, a primary alkyl chlorosulfite ionizes to $ROSO^+$ and Cl^-, followed by Cl^- attack on the cation from either the back side (TS **9**) or the front side (TS **10**), affording RCl with inversion or retention, respectively.

In the 'S_N1i' mechanism of Scheme 3, a tertiary alkyl chlorosulfite (R = *t*-butyl or 1-adamantyl) fragments to a tertiary carbocation and $OSOCl^-$. The anion yields Cl^-, which can then attack the carbocation at either face (cf., **11**), giving RCl with significant racemization. Depending on the structure of R and the solvent polarity, which affect the lifetimes of the ions, more or less retention may be superimposed on the racemization.



9 **10**

Scheme 2

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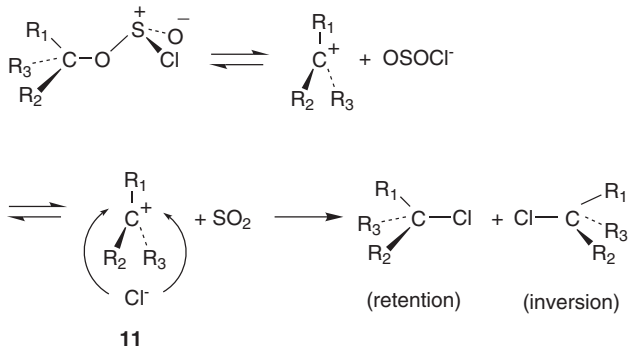


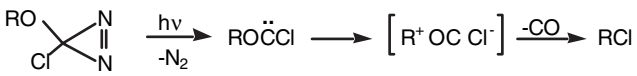
Scheme 3

Evidence for the S_N2i process of Scheme 2 includes the formation of unrearranged neopentyl chloride from neopentyl chlorosulfite and the (slow) formation of apocamphanyl chloride from the corresponding chlorosultfite. Both of these conversions are presumed to involve initial S—Cl ionizations and subsequent front side transition states analogous to **10**.[13]

Schreiner *et al*. also computed transition states for the S_Ni reactions of methyl and ethyl chlorosulfite [MP2(fc)/6-31 + G*//HF/6-31G*].[14] Both front and back side transition states were computed for the attack of Cl^- on $ROSO^+$. For R = Me in simulated hexane, front side was favored over back side attack by 4 kcal/mol, whereas, in simulated methanol, back side Cl^- attack was preferred by a similar margin. With R = Et, however, front side chloride attack was favored in both polar and non-polar solvents.[14] It is worth reproducing the computed transition states for the ethyl chlorosulfite decompositions for later comparison to the fragmentation transitions states of alkoxychlorocarbenes.

S_Ni REACTIONS OF ALKOXYCHLOROCARBENES

We have examined the fragmentations of alkoxychlorocarbenes (ROCCl) as a means of generating (R^+ Cl^-) ion pairs in various solvents:[15,16]



Computational studies at the B3LYP/6-31G* level afforded transition states which were consistent with the 'tight' ion pairs suggested by experiment and, in the limit, approached structures associated with the classical S_Ni mechanism.[1,17] For example, the computed front side TS for the fragmentation of EtOCCl is shown in Fig. 2,[17] where the similarity to the front side TS for the fragmentation of EtOSOCl (Fig. 1[14]) is apparent. Note especially the separations of the CH_2 carbon and Cl (3.10 Å) and O (2.23 Å) for the carbene fragmentation of Fig. 2, in comparison to the analogous distances (2.93 Å and 2.41 Å) for the EtOSOCl fragmentation of Fig. 1. The C—O bond length (r3) in Fig. 2 is 1.16 Å, en route to the CO bond length of 1.128 Å.[17] In parallel, the (internal) S—O bond length of EtOSOCl (1.58 Å) contracts to 1.45 Å in the front side TS of Fig. 1.[14] (We were unable to locate a back side fragmentation TS for EtOCCl.)

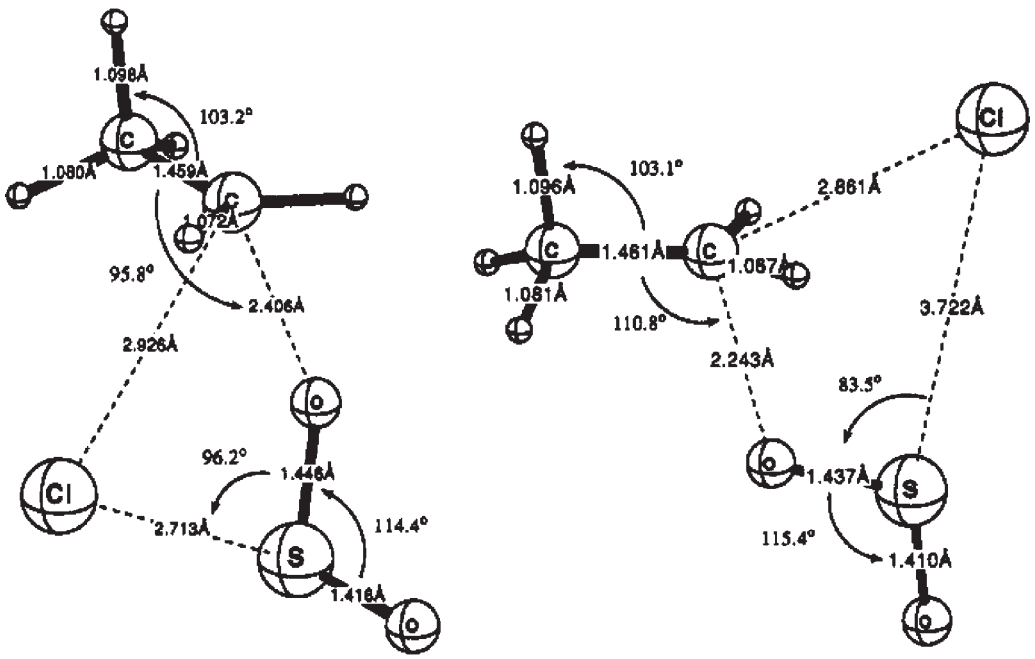


Figure 1. Transition states for the front side (left) and back side (right) fragmentations of ethyl chlorosulfite. (Reprinted with permission from ref. 14; copyright 1994 American Chemical Society)

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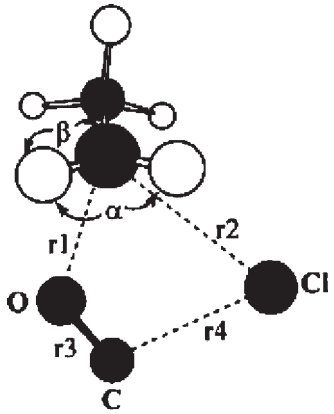
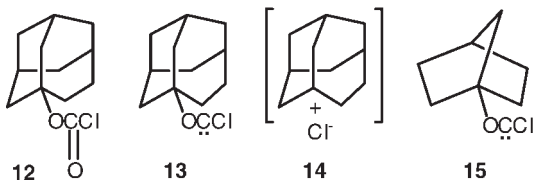


Figure 2. Computed TS for the front side fragmentation of EtOCCl: r1 = 2.227 Å, r2 = 3.102 Å, r3 = 1.162 Å, r4 = 2.589 Å, $\alpha = 117.7°$. (Reprinted with permission from ref. 17; copyright 1999 American Chemical Society)

The fragmentations of ROCCl to RCl also closely resemble the S_Ni decompositions of alkyl chloroformates to alkyl chlorides (cf., structures **6**–**8**):[1,6,7] CO is expelled from the carbenes, whereas CO_2 is expelled from the chloroformates. Indeed, when the R group affords a relatively stable cabocation and the solvent is polar, identical R^+Cl^- ion pairs arise from either the alkoxychlorocarbene or the alkyl chloroformate. For example, fragmentations in $MeOH/CH_2Cl_2$ of 3-homoadamantyl chloroformate (**12**) or 3-homoadamantyloxychlorocarbene (**13**) give the same 3-homoadamantyl cation chloride



12 13 14 15

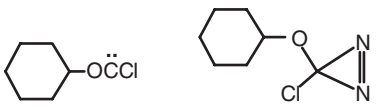
anion pair (**14**).[18] Identical ROMe/RCl product ratios were obtained from either precursor,[18] and the time required for equilibration of the ion pair with its solvent cage was determined to be ~20–30 ps by laser flash photolysis experiments.[19,20]

Of special note are the very low activation energies required for the carbene fragmentations. B3LYP/6-31G* values for the fragmentations of ROCCl in vacuum are only 9.2 kcal/mol with R = *i*-propyl and 6.7 kcal/mol with R = benzyl. Even with R = ethyl (Fig. 2), front side fragmentation is calculated to require 25.5 kcal/mol in vacuum and 17.9 kcal/mol in simulated methanol. Experimental results are in accord with the calculations. For instance, the measured activation energy for fragmentation of 1-norbornyloxychlorocarbene (**15**) to 1-norbornyl chloride in dichloroethane is only 9.0 kcal/mol.[21] An even lower E_a of 3.5 kcal/mol was determined for the conversion of 7-norbornyloxychlorocarbene to 7-norbornyl chloride.[22]

Given the low activation energies for the fragmentations of ROCCl to RCl, it is not surprising that these reactions readily occur in hydrocarbon solvents.[23] It is under such conditions, particularly with secondary ROCCl, that experimental and computational studies point to fragmentation mechanisms that closely approach the classical S_Ni paradigm.[1] To illustrate this, we will now discuss several specific reaction systems.

THE CYCLOHEXYL SYSTEM

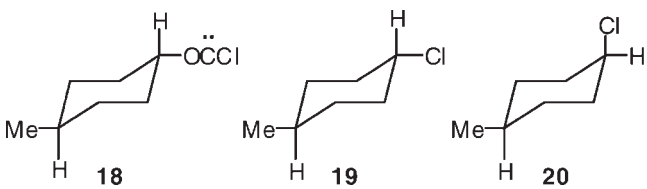
Cyclohexyloxychlorocarbene (**16**), generated from diazirine **17** by photolysis in *pentane*, gave 53% of cyclohexyl chloride and 42% of cyclohexene.[23] The substitution branch of this reaction seemed a propitious place to prospect for the S_Ni mechanism, and it was examined with B3LYP/6-31G(d) methodology.[24] We located *two* transition states for the fragmentation of equatorial **16** to cyclohexyl chloride; cf., Fig. 3.



16 17

One TS led with inversion to axial cyclohexyl chloride via a back side attack, whereas the second TS led with retention to equatorial cyclohexyl chloride via a front side process. Importantly, intrinsic reaction coordinate (IRC) calculations revealed *no* minima between the TS and product for either pathway (see below); both appeared to be direct S_Ni-like processes. Moreover, they were nearly isoenthalpic: the calculated values of $\Delta H^{\ddagger}$ were 17.0 kcal/mol for the inversion pathway and 17.9 kcal/mol for retention.[24,25]

It is worthwhile noting the similarities in the essential C—O and C—Cl separations in the front side and back side transition states computed for the fragmentations of carbene **16** (Fig. 3) and ethyl chlorosulfite (Fig. 1). Furthermore, the near identical enthalpies of activation calculated for the two fragmentation modes of **16** imply that both should occur with comparable frequency. We therefore predict that a stereochemically-labeled equatorial cyclohexyloxychlorocarbene should fragment in vacuum or in a hydrocarbon solvent with a significant loss of stereospecificity. Indeed, the fragmentation of *trans*-4-methylcyclohexyloxychlorocarbene (**18**) in pentane gave



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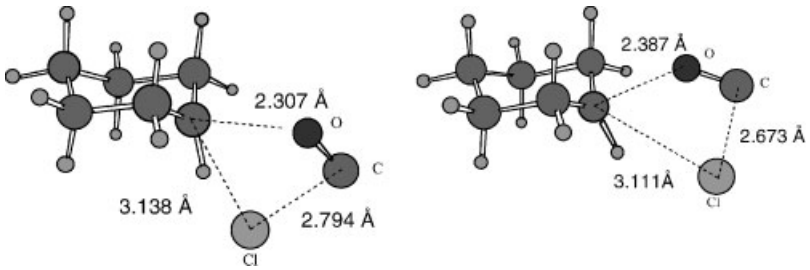
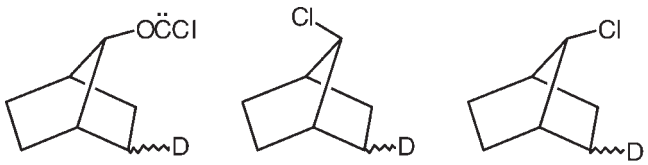


Figure 3. B3LYP/6-31G(d) transition states for the fragmentation of cyclohexyloxychlorocarbene (**16**) to cyclohexyl chloride with inversion (left) or retention (right). (Reprinted with permission from ref. 24; copyright 2005 American Chemical Society)

trans-1-chloro-4-methylcyclohexane (**19**) and *cis*-1-chloro-4-methylcyclohexane (**20**) in a ratio of 2.3:1.[24]

Similar results were obtained in the fragmentation of D-labeled 7-norbornyloxychlorocarbene (**21**).[22] Again, computational studies located inversion and



21 **22** **23**

retention S_Ni-type transition states leading to 7-norbornyl chloride isotopomers **22** and **23** (Fig. 4). IRC calculations verified that each TS proceeded to product in the forward direction and returned to carbene **21** in the reverse direction; there was no indication of an intermediate.

Computed $\Delta H^{\ddagger}$ values for each pathway were comparable, with $\Delta H^{\ddagger}$ (inversion) = 22.2 and $\Delta H^{\ddagger}$ (retention) = 23.3 kcal/mol in vacuum. (We do not believe the accuracy of these calculations exceeds ± 1 kcal/mol). Experimentally, the fragmentation of carbene **21** in $CDCl_3$ gave chlorides **23** and **22** in a ratio of 3.5:1, corresponding to 78% retention and 22% inversion.[22] The loss of stereospecificity can be attributed to competitive fragmentations via the retention or inversion transition states of Fig. 4.[22] Less likely, in view of the high energy of the 7-norbornyl cation, is the intervention of ion pairs as agents of stereochemical randomization.

To further explore these phenomena, we turned to the nortricyclyl-norbornenyl system, where the relation between product distribution and ion pair intervention has been extensively studied.[26]

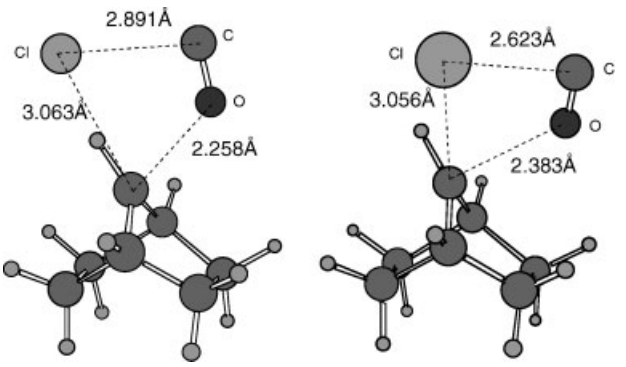
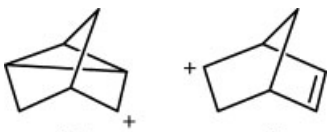


Figure 4. B3LYP/6-31G(d) transition states for the fragmentations (in vacuum) of carbene **21** to chlorides **22** with inversion (left) and **23** with retention (right). The deuterium marker is omitted from the computed structures. (Reprinted from ref. 22 with permission of the National Research Council of Canada)

THE NORTRICYCLYL-NORBORNENYL SYSTEM

The nortricyclyl cation (**24**) and the 5-norbornen-2-yl cation (**25**) are generally regarded as canonical forms of a single resonance hybrid with a structure close to **24**.[27]



24 **25**

Accordingly, solvolyses of either nortricyclyl or 5-norbornen-2-yl sulfonates, as well as deaminations of the corresponding amines, afford similar product mixtures dominated by the nortricyclyl product, usually with a nortricyclyl/norbornenyl distribution of ~90:10.[26]

Although a single nortricyclyl/norbornenyl cationic intermediate adequately accounts for the products, Olah[28] notes an important qualification: the cation normally arises as part of an ion pair, and the precise nature of the cation 'clearly depends on the degree of ionization, the acid strength, the nucleophilicity of the solvent system, and possible ion pair effects.' In this regard, we might expect the product distributions from norbornenyl and nortricyclyl reactants to exhibit increasing 'memory' of precursor structure as the key 'intermediate' of the reaction mechanism morphs from a fully solvated cation, to a cation anion pair, to a S_Ni transition state. These considerations are well-illustrated by the fragmentations

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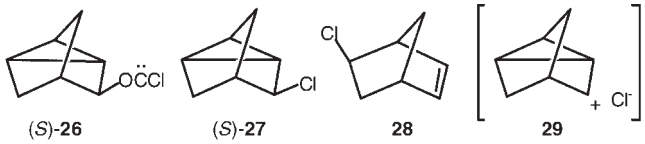
of 3-nortricyclyl and 5-norbornen-2-yl oxychlorocarbenes.

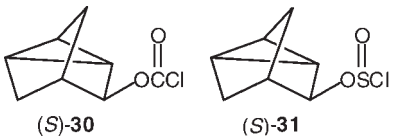
Fragmentation of 3-nortricyclyloxychlorocarbene **26** (from the diazirine) in pentane gives *only* 3-nortricyclyl chloride (**27**); no (exo) 5-norbornen-2-yl chloride (**28**) is formed.[26] Repetition of this reaction in cyclohexane-d_{12} also gives **27**, accompanied by traces of **28**.[24] When carbene **26** is enriched in the (*S*) enantiomer (ee = 46.5%), stereochemical analysis of chloride **27** indicates that the conversion proceeds with 91–96% *racemization*; product **27** contains only a slight excess of the (*S*)- enantionmer.[24] What causes the extensive racemization?



Computational studies afford both retention and inversion transition states for the fragmentation of carbene **26**; cf., Fig. 5. The calculated activation parameters[24,26] are: retention, $\Delta G^{\ddagger} = 12.0$ and $\Delta H^{\ddagger} = 14.2$ kcal/mol; inversion, $\Delta G^{\ddagger} = 11.1$ and $\Delta H^{\ddagger} = 14.8$ kcal/mol. Again, both pathways are energetically comparable and should be competitive. Given the absence of norbornenyl chloride **28**, indicating that ion pairs do not intervene,[26] the conversion of (*S*)-**26** to near racemic **27** seems best attributed to competitive S_Ni fragmentations proceeding via the two nearly isoenergetic transition states of Fig. 5.[24,26]

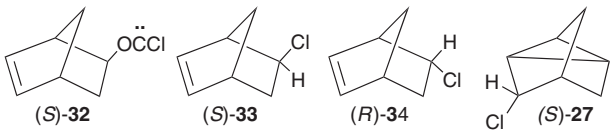
Interestingly, in more polar $CDCl_3$ or CD_3CN solvents, 10–11% of norbornenyl chloride **28** appears,[26] and retention in the (*S*)-**26** → (*S*)-**27** conversion *increases* to 13% or 24%, respectively.[24] In the more polar solvents, the S_Ni transition states may evolve to ion pair **29**, where chloride return with retention can account for the minor increase in retention.[24]

Direct stereochemical comparisons of the fragmentations of oxychlorocarbene **26** with those of the analogous chloroformate (**30**) and chlorosulfite (**31**) were carried out in $CDCl_3$, CD_3CN, and THF (for **31**).[29] Similar results were obtained for all three substrates: in $CDCl_3$, net



retention for the formation of (*S*)-**27** was 13% from (*S*)-**26** and 22% from (*S*)-**30**; in CD_3CN, the corresponding values were 24% and 28%. From (*S*)-**31** in THF, net retention was 28%. We conclude that in these moderately polar solvents, similar blends of S_Ni and ion pair mechanisms are involved in the fragmentations of the three nortricyclyl precursors to nortricyclyl chloride. The extensive racemization is largely due to the competing retention and inversion S_Ni transition states, which for carbene **26** in hydrocarbon solvents, is effectively the exclusive mechanism.

A more complicated situation arises for the fragmentation of (*S*)-*exo*-5-norbornenyl-2-oxychlorocarbene (**32**) in C_6D_{12}, where the products include (*S*)-*exo*-5-norbornenyl-2-chloride (**33**), (*R*)-*endo*-5-norbornenyl-2-chloride (**34**), and (*S*)-3-nortricyclyl chloride (**27**) in a distribution of ~53:31:16, respectively.[30]



Conversion of (*S*)-**32** to major product (*S*)-**33** occurs with *complete retention* upon thermolysis of the diazirine precursor of carbene **32** at 25°C.[30] This is clearly a S_Ni process, for which a transition state with $\Delta G^{\ddagger} = 12.1$ kcal/mol (in vacuum) can be calculated, cf., Fig. 6.[30,31]

As the solvent becomes more polar, retention decreases for the (*S*)-**32** → (*S*)-**33** conversion; it is only 60–70% in $CDCl_3$ or CD_3CN. We suggest that the increased racemization stems from competitive fragmentation of **32** to ion pair **35**, which affords either (*S*)-**33** or (*R*)-**33** upon collapse; cf., Scheme 4.[30]

Conversion of (*S*)-**32** to *endo*-chloride (*R*)-**34** occurs in part via the inversion S_Ni TS depicted in Fig. 6 ($\Delta G^{\ddagger}$ is calculated at 11.6 kcal/mol[26]), but (*R*)-**34** forms with only

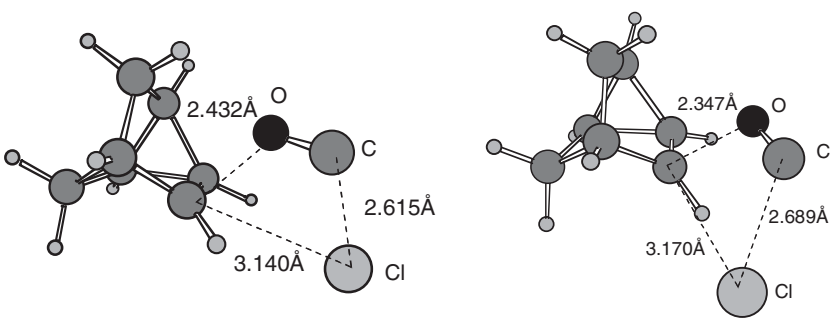


Figure 5. B3LYP/6-31G(d) computed transition states for the conversion of 3-nortricyclyloxychlorocarbene (**26**) to 3-nortricyclyl chloride (**27**) with retention (left) or inversion (right). (Reprinted with permission from ref. 26; copyright 2004 American Chemical Society)

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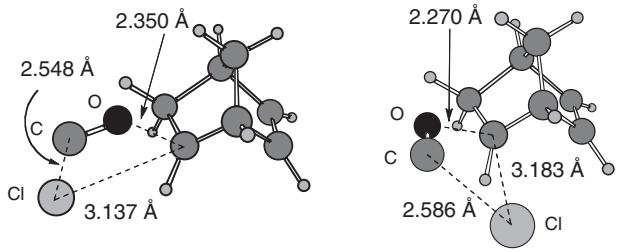
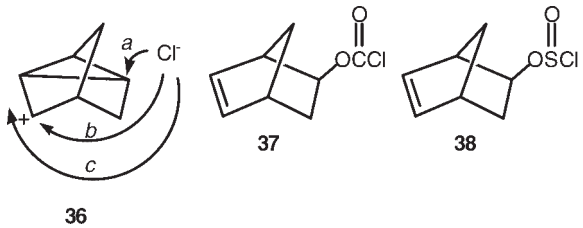


Figure 6. Transition states for the S_Ni fragmentations of carbene (*S*)-**32** with retention (left) to (*S*)-**33** or inversion (right) to (*R*)-**34**

~18% ee. We attribute the extensive racemization to the incursion of ion pairs. A simple possibility involves migration of Cl^- from the exo to the endo face of the norbornenyl cation in ion pair **35** prior to collapse. Alternative ion pair pathways are discussed in Reference 30. With increasing solvent polarity, the formation of chloride **34** decreases; it is only 4–5% of the product mixture in $CDCl_3$ or CD_3CN (with ~20% ee). In these solvents, the product mixture comprises mainly norbornenyl chloride **33** and nortricyclyl chloride.[27]

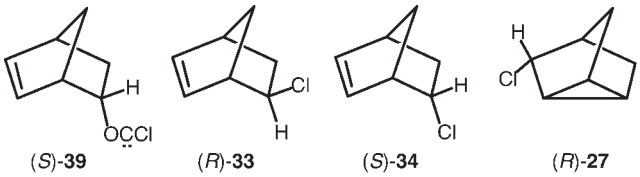
Chloride **27** forms from carbene **32** in ~17% yield in C_6D_{12}; the yield rises to ~36% in $CDCl_3$ or CD_3CN. The stereochemistry of the conversion links (*S*)-**32** and (*S*)-**27** with 13–25% ee over the range of solvents. Focusing on its nortricyclyl cation canonical form, we suggest that ion pair **35** can account for the products and stereochemistry as illustrated by structure **36**. Here, collapse *a* leads to chloride (*S*)-**33**, collapse *b* affords (*S*)-**27**, and collapse *c* yields (*R*)-**27**. Least motion preferences account for the observed dominance of (*S*)-**33** in the product mixture and of (*S*)-**27** over (*R*)-**27**.[30]



36 **37** **38**

Stereochemical comparisons of the fragmentations of oxychlorocarbene (*S*)-**32**, chloroformate (*S*)-**37**, and chlorosulfite (*S*)-**38** in $CDCl_3$, CD_3CN, and THF (for **38**) indicated the intermediacy of ion pairs (e.g., **35**), leading to the formation of (mainly) (*S*)-**33** and (*S*)-**27** with ee's ranging from ~20 to 90%, depending on the substrate and solvent.[29]

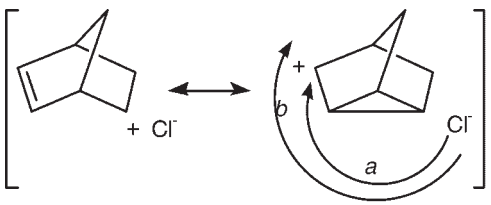
Finally, we examined the fragmentation of *endo*-5-norbornenyl-2-oxychlorocarbene (**39**).[32] In C_6D_{12}, the products from (*S*)-**39** include 65–70% of *exo*-chloride (*R*)-**33**, ~20% of *endo*-chloride (*S*)-**34**, and ~12% of 3-nortricyclyl chloride (*R*)-**27**. The dominant process, (*S*)-**39** → (*R*)-**33**, is a S_Ni reaction which proceeds via the inversion TS shown in Fig. 7 ($\Delta H^{\ddagger} = 17.1$ kcal/mol in vacuum), conserving the chirality (ee > 95%).[32]



(*S*)-**39** (*R*)-**33** (*S*)-**34** (*R*)-**27**

Competitively, conversion of (*S*)-**39** to (*S*)-**34** occurs with ~50% ee, in part via the computed retention S_Ni TS shown in Fig. 7 ($\Delta H^{\ddagger} = 17.6$ kcal/mol in vacuum). The incursion of ~50% racemization here reflects leakage to an ion pair analogous to **35**, but with an endo chloride counterion, where collapse furnishes both (*S*)-**34** and (*R*)-**34**.[32]

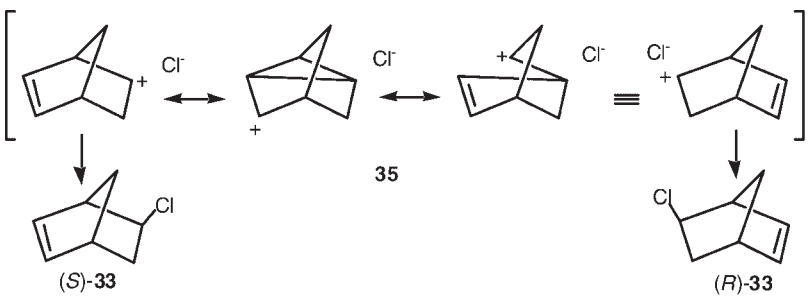
In the more polar $CDCl_3$ or CD_3CN, *endo*-chloride **34** becomes a minor product (2–7%), while the yield of nortricyclyl chloride (*R*)-**27** (20% ee) increases to 30–40%. We can rationalize the (*S*)-**39** → (*R*)-**27** conversion in terms of ion pair **40**, where least motion



40

collapse *a* affords the major (*R*)-3-nortricyclyl chloride enantiomer, while a slightly longer collapse pathway (*b*) leads to the minor enantiomer, (*S*)-**27**.[32]

Also in $CDCl_3$ or CD_3CN, the stereospecificity of the dominant (*S*)-**39** → (*R*)-**33** conversion decays to ~50% ee,[29] rather than the >95% preservation of chirality observed in C_6D_{12}.[32] Again, ion pair intervention can



(*S*)-**33** **35** (*R*)-**33**

Scheme 4

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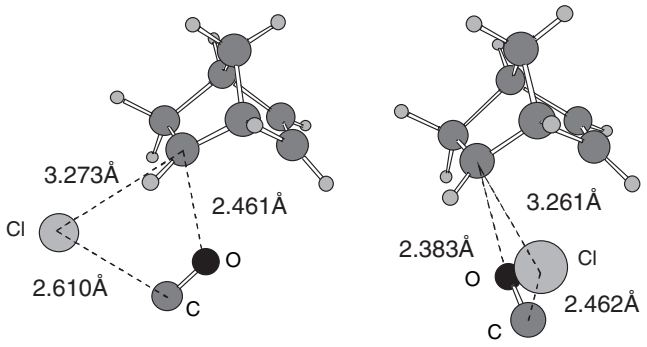

Figure 7. B3LYP/6-31G(d) transition states for the fragmentations of *endo*-carbene **39** to *exo*-chloride **33** with inversion (left) or *endo*-chloride **34** with retention (right). (Reprinted with permission from ref. 32; copyright 2005 American Chemical Society)

account for the loss of stereospecificity.[32] Similarly, fragmentations of the corresponding *endo*-5-norbornenyl-2-chloroformate and chlorosulfite in these moderately polar solvents proceed to chlorides **33** and **27** with comparable ee.[29]

THE S_Ni TRANSITION STATE

Above, we provide examples of the S_Ni fragmentations of several *sec*-alkoxychlorocarbenes in hydrocarbon solvents. These include the conversions of cyclohexyloxychlorocarbene (**16**) to cyclohexyl chloride,[24] 3-nortricyclyloxychlorocarbene (**26**) to 3-nortricyclyl chloride (**27**)[24]*exo*-5-norbornenyl-2-oxychlorocarbene (**32**) to the corresponding chloride (**33**),[30] and *endo*-5-norbornenyl-2-oxychlorocarbene (**39**) to *exo*-2-chloro-5-norbornene (**33**).[32] Both experimental and computational results support S_Ni mechanisms for these transformations.

A closer consideration of the S_Ni mechanism, however, brings us back to the earlier discussions of Hughes and Ingold,[1] Hine,[2] Cram,[3] Gould,[4] Lewis,[5,7] Wiberg,[6] and Schreiner, Schleyer, and Hill.[13,14] Is the S_Ni reaction concerted, or is it best represented as proceeding via discrete ion pair intermediates? In moderately polar solvents, rearrangements and the loss of stereospecificity argue strongly for ion pairs. But do concerted S_Ni reactions occur in hydrocarbon solvents? To examine this question more closely, we focused on the fragmentation of cyclohexyloxychlorocarbene, **16**. Inversion and retention transition states for the fragmentation of (equatorial) **16** appear above in Fig. 3.

Insight into the structural changes associated with the decay of the two transition structures was provided by intrinsic reaction coordinate (IRC) following methodology. IRC calculations track the lowest energy path downward from the transition structure on a potential energy surface, optimizing the geometry at each stage. They are routinely used to validate the connectivity of the TS with the reactants in one direction and the products in the other direction. Plots of the IRCs for the forward progress of the cyclohexyl inversion and retention transition structures appear in Fig. 8.

IRC following leads, in both cases, back to the starting carbene and (separately) forward to inverted or retained cyclohexyl chloride. Note that there are no intermediate stages, the computed energies along the IRC trajectories decline smoothly toward the endpoints: CO + (axial or equatorial) cyclohexyl chloride. There are no 'steps' in these decays and no evidence for intermediates.

Nevertheless, it is apparent from Fig. 3 that both transition states are asynchronous; the C-(ring)-Cl distances (3.11–3.14 Å) are longer than the C(carbene)-Cl separations (2.67–2.79 Å). Wiberg bond index (BI) parameters[33] associated with the ground and transition states are also consistent with unequal bonding changes. For example, the C(ring)-O BI changes from 0.75 to 0.13 and 0.10 for the inversion and retention TSs, respectively. At the same time, weak bonding is revealed between C(ring)-Cl at the TS, where the BI is 0.11 (inversion) and 0.21 (retention). The C(carbene)-Cl BI values change from 1.0 to 0.20 (inversion TS) and 0.21 (retention TS).

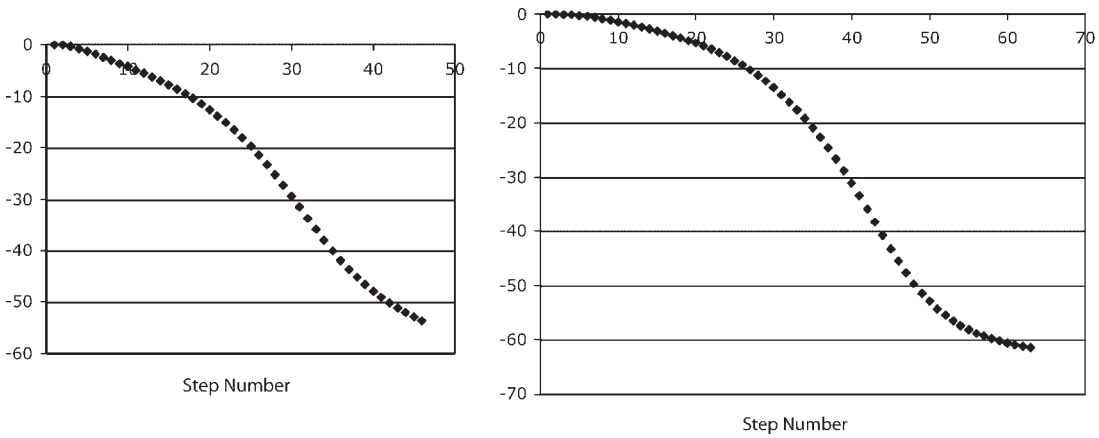

Figure 8. Intrinsic reaction coordinates for the decay of the inversion (left) and retention (right) transition states for the fragmentation of cyclohexyloxychlorocarbene to cyclohexyl chloride; cf., Fig. 3

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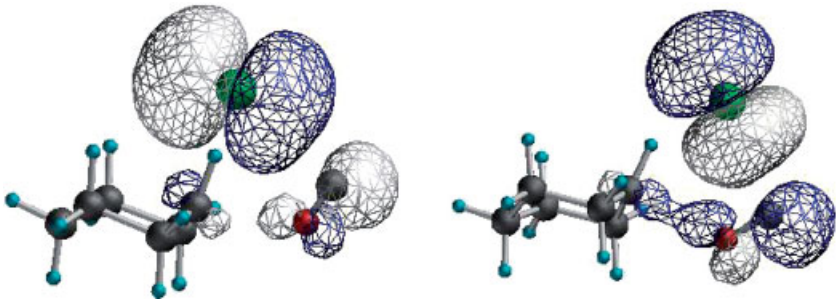

Figure 9. B3LYP/6-31G(d) computed transition states showing the HOMOs involved in the fragmentation of carbene **16** with inversion (left) or retention (right)

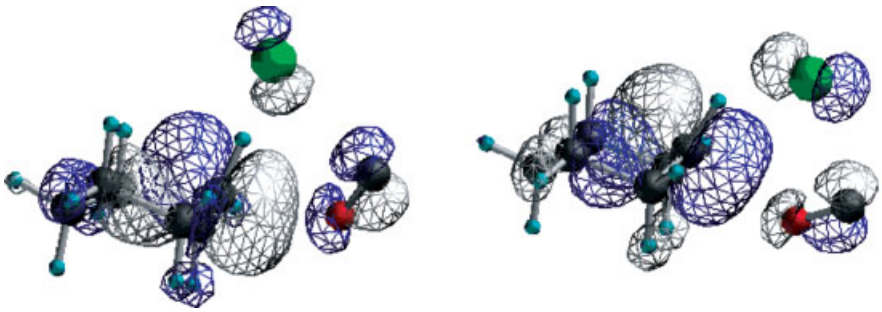

Figure 10. B3LYP/6-31G(d) computed transition states showing the LUMOs involved in the fragmentation of carbene **16** with inversion (left) or retention (right)

Electrostatic interactions also contribute to the overall bonding forces. For example, charges calculated by natural population analysis methods give rise to significant polarization, with positive charge centered on the reaction terminus C(ring) and negative charge on chlorine: +0.22 C, −0.70 Cl (retention TS) and +0.21 C, −0.74 Cl (inversion TS). Very little charge resides on the carbon monoxide atoms [−0.05 (retention TS) and −0.02 (inversion TS)], so that the remaining ring atoms bear significant positive charge: +0.52 (inversion TS) and +0.53 (retention TS).

The computed HOMOs (Fig. 9) of the two transition structures are consistent with both the bond index results and charge calculations, and emphasize the concentration of electron density on chlorine as well as the absence of significant orbital overlap between chlorine and the terminal carbon centers. The 'looseness' of these transition structures provides an escape from the formal Woodward–Hoffmann 'forbiddeness' of a concerted S_Ni process.[12,14,34]

The computed LUMOs in Fig. 10 underscore the delocalized nature of the cationic character implied by the large p orbital on the C(ring) reaction terminus and additional electron deficiencies on the neighboring ring atoms.

We suggest that, in vacuum or hydrocarbon solvents, these structures span an amorphous 'no-man's land' ranging from asynchronous, charge-separated, concerted transition states to very tight ion pairs.[35] Moderately polar solvents transform the charge-separated transition states into real ion pair intermediates. The inherent ambiguity of the situation is very well captured in a prescient comment by Winstein, writing in 1958, before the elucidation of orbital symmetry constraints: '... some covalent character may be visualized for the cation–anion attraction in an intimate ion pair.... Because of the character of intimate ion pairs, there is no sharp distinction between such an ion pair and a covalently bound intermediate in a so-called cyclic rearrangement. These are not qualitatively distinct, but form extremes in a graded series. Thus, there is no sharp distinction between formation of an intimate ion pair followed by internal return and a cyclic rearrangement, and marginal cases may be expected.'[36]

CONCLUSION

Transition structures for S_Ni fragmentations of alkoxychlorocarbenes inhabit a gray zone that reflects partial asynchronous bonding coupled with charge separation. A family of closely related structures is required to represent the electronic changes associated with differing alkyl groups, counter ions, and solvent.[17] Experimentally, one observes product formation that reveals the influence of structure and environment on the decay pathways available for a given transition structure; that is,

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concertedness in low polarity solvents and the formation of ion pair intermediates in polar solvents. This chameleon behavior accounts for the plethora of early representations of S_Ni transition states, and for the continuing ambiguity today.

Given that reactions involving ion pair intermediates can be considered variations of S_N1 reactions, one could argue for a more restrictive definition of S_Ni reactions, involving only concerted processes, that might serve to clarify the classification of these reactions. Subtle structural probes described above identify several reactions that fit this criterion, that is, transition states generated in non-polar solvents that appear to bypass cationic intermediates and to produce unique structural and stereochemical outcomes. What is beyond doubt, however, is that S_Ni reactions constitute a real, if limited, class of aliphatic substitution processes for which the fragmentations of alkoxychlorocarbenes provide excellent examples.

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