ORGANIC LETTERS

2005
Vol. 7, No. 7
1371−1374

Stereochemistry of Oxachlorocarbene S_Ni Reactions

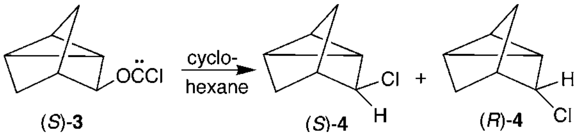
Robert A. Moss,*[†] Xiaolin Fu,[†] Jingzhi Tian,[†] Ronald Sauers,*[†] and Peter Wipf*[‡]

Department of Chemistry and Chemical Biology, Rutgers, The State University of New Jersey, New Brunswick, New Jersey 08903, and Department of Chemistry, University of Pittsburgh, Pittsburgh, Pennsylvania 15260

moss@rutchem.rutgers.edu

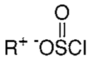
Received January 28, 2005

ABSTRACT



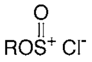
3-Nortricyclyloxychlorocarbene and *trans*-4-methylcyclohexyloxychlorocarbene both fragment in hydrocarbon solvents with extensive loss of stereochemical integrity to the corresponding chlorides via competitive and nearly isoenergetic S_Ni-like transition states.

The contemporary mechanism for the S_Ni reaction[1] ("substitution, nucleophilic, internal") is formulated in terms of ion pairs.[2−4] In the iconic case of chlorosulfite decomposition, the initial ion pairs are **1** from secondary or tertiary substrates and **2** from primary substrates.[2b,4a] In either case, the "internal" chloride nucleophile ultimately reacts with a cation (R^+ or $ROSO^+$) to form the product RCl.



$R^{+}\ {}^{-}OS(=O)Cl$

1



$ROS^{+}(=O)\ Cl^{-}$

2

The stereochemical outcomes of S_Ni reactions vary and depend on both the nature of R and the solvent: secondary or tertiary R groups and polar solvents favor retention via front-side return of chloride, whereas primary R groups and hydrocarbon solvents favor inverting, backside attack of chloride.[2,4] Shreiner et al. designated these mechanistic alternatives as "S_Ni" and "S_N2i", respectively.[4a]

The related fragmentations of alkoxychlorocarbenes (eq 1) can also be formulated in terms of ion pairs.[5] When the cation is sufficiently stable and the solvent is polar,

$$RO\ddot{C}Cl \rightarrow [R^{+}\,{}^{-}OCCl] \rightarrow RCl + CO \qquad (1)$$

solvent-equilibrated $[R^+Cl^-]$ ion pairs intervene,[6] but as R^+ becomes less stable and the solvent less polar, the stability and lifetime of the ion pairs decrease. In a vacuum, rare gas matrices, or pentane, calculations point to effectively "concerted" decompositions of ROCCl (or fragmentation that proceeds through very short-lived ion pairs).[7] One imagines that such ROCCl → RCl transformations would feature nearly complete frontside fragmentation and concomitant stereochemical retention. For example, the fragmentation of α-deuteriobenzyloxychlorocarbene to α-deuteriobenzyl chloride in acetonitrile, a reaction likely to involve a short-lived ion pair,[7a] occurs with at least 60% net retention.[8]

In remarkable contrast, however, computational studies of the fragmentation of cyclic, secondary ROCCl reveal *two*

[†] Rutgers University.

[‡] University of Pittsburgh.

(1) Cowdrey, W. A.; Hughes, E. D.; Ingold, C. K.; Masterman, S.; Scott, A. D. *J. Chem. Soc.* **1937**, 1252.

(2) (a) Lewis, E. S.; Boozer, C. E. *J. Am. Chem. Soc.* **1952**, *74*, 308. (b) Lewis, E. S.; Boozer, C. E. *J. Am. Chem. Soc.* **1953**, *75*, 3182.

(3) Wiberg, K. B.; Shryne, T. M. *J. Am. Chem. Soc.* **1955**, *77*, 2774.

(4) (a) Schreiner, P. R.; Schleyer, P. v. R.; Hill, R. K. *J. Org. Chem.* **1993**, *58*, 2822. (b) Schreiner, P. R.; Schleyer, P. v. R.; Hill, R. K. *J. Org. Chem.* **1994**, *59*, 1849.

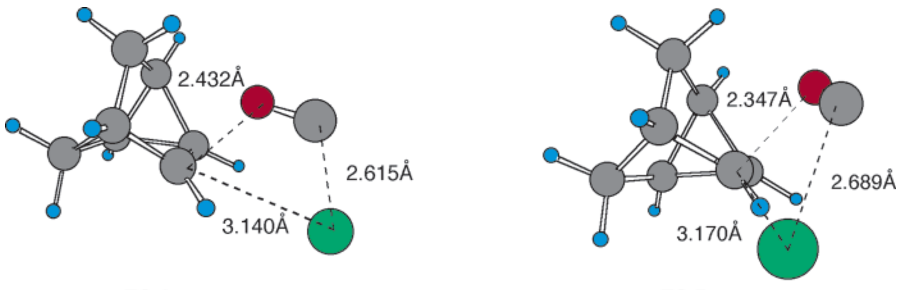
(5) Moss, R. A. *Acc. Chem. Res.* **1999**, *32*, 969.

(6) Moss, R. A.; Zheng, F.; Fedé, J.-M.; Johnson, L. A. Sauers, R. R. *J. Am. Chem. Soc.* **2004**, *126*, 12421.

(7) (a) Moss, R. A.; Ma, Y.; Zheng, F.; Sauers, R. R.; Bally, T.; Maltsev, A.; Toscano, J. P.; Showalter, B. M. *J. Phys. Chem. A* **2002**, *106*, 12280. (b) Moss, R. A.; Sauers, R. R.; Zheng, F.; Fu, X.; Bally, T.; Maltsev, A. *J. Am. Chem. Soc.* **2004**, *126*, 8466.

(8) Moss, R. A.; Kim, H.-R. *Tetrahedron Lett.* **1990**, *31*, 4715.

10.1021/ol050185k CCC: $30.25



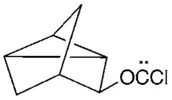
TS A

TS B

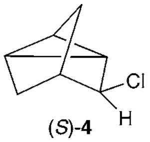
Figure 1. B3LYP/6-31G(d) transition states for the fragmentation of carbene **3** to chloride **4** with retention (TS **A**) or inversion (TS **B**); cf. ref 9.

transition states of comparable energies that, by intrinsic reaction coordinate (IRC) methodology, lead directly to either retained or inverted RCl by frontside or backside fragmentation. Ion pairs are not involved as energy minima along the reaction coordinates.

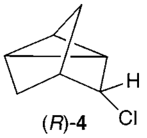
For example, in our study of the fragmentation of 3-nortricyclyloxychlorocarbene (**3**), we observed that 3-nortricyclyl chloride (**4**) was the exclusive product in pentane and that rearranged products were produced in solvents of increasing polarity.[9]



(*S*)-**3**



(*S*)-**4**

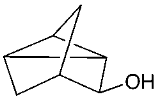


(*R*)-**4**

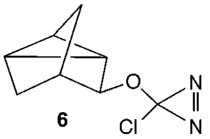
This led us to propose a spectrum of ion pair behavior for these reactions, with those in pentane proceeding via a limiting S_Ni process. Our suggestion was supported by computational results that gave rise to two fragmentation transition states of comparable energy, one leading to retention of configuration ($\Delta H^* = 14.2$ kcal/mol), as determined by analysis by IRC methodology, and the other to inversion of configuration ($\Delta H^* = 14.8$ kcal/mol); see transition states **A** and **B**, respectively, in Figure 1.[9]

The counterintuitive implication is that chiral carbene **3** should yield chloride **4** with extensive racemization in pentane *not* because of stereochemical randomization within an intermediate ion pair but because of competitive frontside or backside S_Ni fragmentations. Here we describe experimental tests of this idea in the nortricyclyl and cyclohexyl systems.

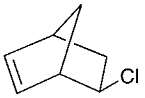
exo-Norbornene oxide[10] was converted to (*S*)-(−)-nortricylanol, (*S*)-(−)-**5**, by reaction with the Li salt of (*S*,*S*)-bis-(1-phenylethyl)amine in ether.[11] Our sample had $[\alpha]^{25}_D$ −19.0 (*c* 5.0, $CHCl_3$), corresponding to an ee of 46.5%.[12] The nortricyclanol was converted to the corresponding isouronium salt with cyanamide and methanesulfonic acid,[9,13] and the latter was oxidized to diazirine **6** with aqueous NaOCl.[9,14]



(*S*)-(-)-**5**



6



7

Diazirine **6** was decomposed photolytically (λ > 320 nm) or thermally at 25 °C in cyclohexane-d_{12}, $CDCl_3$, or CD_3CN. In cyclohexane (as in pentane[9]), carbene **3** formed from **6** and fragmented to 3-nortricyclyl chloride **4**, accompanied by traces of *exo*-5-chloro-2-norbornene (**7**).[15] With greater solvent polarity, the yield of **7** rose slightly: 5−7% in $CDCl_3$ and 4−7% in CD_3CN.

Defining the stereochemistry of the **3** → **4** conversion requires knowledge of the absolute configurations and rotation of chloride **4**, which are unknown. We computed this information. The initial assignment of a natural product by a linear-response HF-based calculation was made in 1998,[16] and there has since been a dramatic increase in the application of modern computational methods for $[\alpha]_D$ calculations of organic molecules.[17] There are now many successful cases in which an absolute configuration has been assigned by ab initio theory.[18]

---

[9] Moss, R. A.; Ma, Y.; Sauers, R. R.; Madni, M. *J. Org. Chem.* **2004**, *69*, 3628.

[10] Walborsky, H. M.; Loncrini, D. F. *J. Am. Chem. Soc.* **1954**, *76*, 5396.

[11] Hodgson, D. M.; Lee, G. P.; Marriott, R. E.; Thompson, A. J.; Wisedale, R.; Witherington, J. *J. Chem. Soc., Perkin Trans. 1* **1998**, 2151.

[12] Based upon $[\alpha]^{20}_D$ −22.3 (*c* 1.0, $CHCl_3$) for 54.7% ee (*S*)-**5**, which extrapolates to $[\alpha]^{20}_D$ −40.8 in $CHCl_3$ for the optically pure material: Hirose, Y.; Anzai, M.; Saitoh, M.; Naemura, K.; Chikamatsu, H. *Chem. Lett.* **1989**, 1939. A value of $[\alpha]^{20}_D$ −40 ($CHCl_3$) was reported by: Kirmse, W.; Knöpfel, N. *J. Am. Chem. Soc.* **1976**, *98*, 4672.

[13] Moss, R. A.; Kaczmarczyk, G.; Johnson, L. A. *Synth. Commun.* **2000**, *30*, 3233.

[14] Graham, W. H. *J. Am. Chem. Soc.* **1965**, *87*, 4396.

[15] Up to 14% of the dimer of carbene **3** was also formed.

[16] Kondru, R. K.; Wipf, P.; Beratan, D. N. *J. Am. Chem. Soc.* **1998**, *120*, 2204.

[17] (a)Kondru, R. K.; Wipf, P.; Beratan, D. N. *Science* **1998**, *282*, 2247. (b) Kondru, R. K.; Chen, C. H.-T.; Curran, D. P.; Beratan, D. N.; Wipf, P. *Tetrahedron: Asymmetry* **1999**, *10*, 4143. (c) Ribe, S.; Kondru, R. K.; Beratan, B. N.; Wipf, P. *J. Am. Chem. Soc.* **2000**, *122*, 4608. (d) Specht, K. M.; Nam, J.; Ho, D. M.; Berova, N.; Kondru, R. K.; Beratan, D. N.; Wipf, P.; Pascal, R. A.; Kahne, D. *J. Am. Chem. Soc.* **2001**, *123*, 8961.

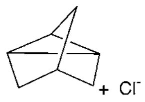
[18] For a recent review, see: Polavurapu, P. L. *Chirality* **2002**, *14*, 768. For a recent application, see: Giorgio, E.; Maddau, L.; Spanu, E.; Evidente, A.; Rosini, C. *J. Org. Chem.* **2005**, *70*, 7.

Figure 2. B3LYP/6-31G(d) transition states for the fragmentation of cyclohexyloxychlorocarbene to cyclohexyl chloride with inversion or retention. See Supporting Information for a more complete rendering with IRC intermediate structures.

The structure of chloride **4** was minimized at the DFT-RB3LYP level with a 6-31G(d) basis set, and the optical rotation value at the sodium D line was calculated with RB3LYP/6-311++G(2d,p) from the Gaussian 03 suite.[19] The calculations predict $[\alpha]_D$ −114 for (*S*)-(**4**) in solvents such as CH_2Cl_2 or $CHCl_3$. A sample of **4**, chromatographically isolated from the fragmentation of (*S*)-carbene **3** in C_6D_{12}, had $[\alpha]^{25}_D$ $-0.117 \pm 0.001°$.[20] The levorotatory character indicated that the sample was (*S*)-**4**, so that the fragmentation of (*S*)-**3** (derived from (*S*)-**5**) occurred with overall *retention*.

GC analysis of the chloride on a 30 m × 0.25 mm Chiraldex GTA column at 50 °C gave (*S*)-**4**/(*R*)-**4** in ratios of 1.09:1 (*hν* fragmentation of **6**) or 1.05:1 (thermal fragmentation), corresponding to an ee of 4 or 2%, respectively. (An example of the GC separation is included in Supporting Information.) Given that the initial (*S*)-(−)-**5** from which diazirine **6** was prepared had an ee of 46.5%, we conclude that the fragamentation of carbene **3** to chloride **4** occurred with 4−9% *net* retention; i.e., with *extensive racemization*. This result accords with the competitive frontside and backside S_Ni-like fragmentations of carbene **3** predicted by theory; cf. Figure 1.

In the more polar $CDCl_3$ or CD_3CN solvents, retention in the **3** → **4** fragmentation increased to ∼13 or ∼24%, respectively, with comparable results from either photolytic or thermolytic generation of **3**. Here, TS **A** or **B** might evolve into ion pair **8**.[9,21] Return with net retention could then account for the marginal increase in overall retention observed in $CDCl_3$ or CD_3CN compared with cyclohexane.



8

We next considered the cyclohexyl system. As for carbene **3**,[9] B3LYP/6-31G(d) calculations[19,22,23] located two transition states for the fragmentation of equatorial cyclohexyloxychlorocarbene to cyclohexyl chloride: one led to axial cyclohexyl chloride with inversion, while the second led to the equatorial chloride with retention; cf. Figure 2.

The corresponding ΔH^* values (in vacuo) were 17.9 and 17.2 kcal/mol for the inversion and retention pathways, respectively. IRC calculations revealed no ion pair minima between TS and product for either pathway; both fragmentations were direct S_Ni-like processes. (In Supporting Information, we provide intermediate structures along the IRC to illustrate this point.) Again, the implication of the calculations is that the fragmentation of equatorial cyclohexyloxychlorocarbene should occur (in vacuo or in hydrocarbon solvent) with substantial loss of stereospecificity.

We reported that menthyloxychlorocarbene, with an equatorial OCCl unit, fragments in polar solvents (e.g., 1,2-dichloroethane, DCE) preferentially with retention to menthyl chloride (59%) rather than with inversion to neomenthyl chloride (16%).[24] Similarly, *trans*-4-methylcyclohexyloxychlorocarbene (**9**) fragments in DCE to *trans*-4-methylcyclohexyl chloride (**10**) with retention (59%), in preference to *cis*-4-methylcyclohexyl chloride (**11**) with inversion (17%).[25] Now, we have also examined the fragmentations of **9** in pentane, benzene, and MeCN.

trans-4-Methylcyclohexanol was converted to the isouronium methanesulfonate salt,[13] and the latter was oxidized[14] to diazirine **12**; experimental details appear in Supporting Information. Photolyses of **12** in several solvents gave chlorides **10** and **11**, as well as 4-methylcyclohexene, by fragmentation of carbene **9**. The products were identified by capillary GC spiking experiments with authentic samples. A tabular survey of the three fragmentation products appears

---

[19] *Gaussian 03,* revision B.03; Gaussian, Inc.: Pittsburgh, PA, 2003. See Supporting Information for the full reference.

[20] The 83.5 mg sample of **4** was dissolved in 5 mL of $CDCl_3$ and read in a 1 dm cell.

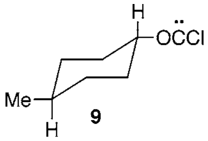
[21] Attempts to computationally optimize TSs **A** and **B** in simulated dichloroethane by the polarized continuum method were unsuccessful.

[22] All structures were fully optimized by analytical gradient methods using the Gaussian 98 and Gaussian 03 suites[19] and density functional (DFT) calculations at the 6-31G(d) level, the exchange potentials of Becke,[23a] and the correlation functional of Lee, Yang, and Parr.[23b] Activation energies were corrected for zero-point energy differences (ZPVE) (unscaled) and thermal effects at 298.150 K. Vibrational analyses established the nature of all stationary points as either energy minima (no imaginary frequencies) or first-order saddle points (one imaginary frequency).

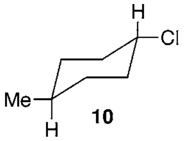
[23] (a)Becke, A. D. *J. Chem. Phys.* **1993**, *98*, 5648. (b) Lee, C.; Yang, W.; Paar, R. G. *Phys. Rev. B.* **1988**, *37*, 785.

[24] Moss, R. A.; Johnson, L. A.; Kasprzynski, M.; Sauers, R. R. *J. Org. Chem.* **2003**, *68*, 5114.

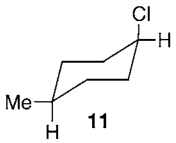
[25] See ref 18 in: Moss, R. A.; Ma, Y.; Sauers, R. R.; Madni, M. *J. Org. Chem.* **2004**, *69*, 3628. The repetition (Table 1) gave 57% retention.



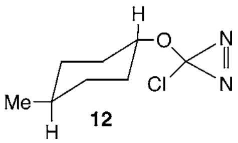
9



10



11



12

in Table 1; a complete tabulation of all products is included in Supporting Information.[26]

Table 1. Chloride Products from Carbene **9**

solvent	**10** (%)^a	**11** (%)^a	alkene (%)^{a,b}	net retention^c
pentane	44.8 ± 0.5	19.3 ± 0.4	20.8 ± 0.9	25.5
benzene	58.2 ± 0.5	18.6 ± 0.2	15.9 ± 0.6	39.6
DCE^d	57.0 ± 0.8	17.1 ± 1.4	17.7 ± 0.8	39.9
MeCN	51.5 ± 0.8	11.6 ± 0.2	15.3 ± 1.6	39.9

[a] Percent yield of product. See Supporting Information for a complete survey of the products. Errors are average deviations of 3−4 experiments. [b] 4-Methylcyclohexene. [c] %**10** − %**11**. [d] 1,2-Dichloroethane.

We observe extensive loss of stereospecificity in all four solvents;[27] as anticipated, this is maximized in pentane. The stereochemical outcome of the ROCCl → RCl conversion for carbene **9** in pentane, like that of carbene **3** in cyclohexane (see above), accords with the computationally predicted simultaneous operation of retention and inversion S_Ni-like transition states (Figures 1 and 2). The observed stereochemical randomization is a consequence of the S_Ni character of these reactions and their transition states rather than of processes occurring within ion pair intermediates that might intervene if more stable carbocations were generated.

The observed behavior may be reasonably general for secondary cyclic alkoxychlorocarbenes that lack additional carbocation-stabilizing features, at least in nonpolar solvents.[28,29] Extensions to open-chain secondary systems are in progress, but the computational studies are complicated by a plethora of available conformations.[30]

Acknowledgment. We are grateful to the National Science Foundation for financial support and to the National Center for Computer Applications for an allocation of time on the IBM P Series 690 (CHE 030060 to RRS).

Supporting Information Available: Experimental details for the preparation of diazirine **12**; expanded version of Table 1; expanded version of Figure 2; and chiraldex GC separation of (*S*)-**4** and (*R*)-**4**. This material is available free of charge via the Internet at http://pubs.acs.org.

OL050185K

---

(26) Small quantities of *trans*-4-methylcyclohexyl formate and *trans*-4-methylcyclohexyl dichloromethyl ether were also formed via carbene capture by H_2O or HCl, respectively. In MeCN, 8−11% of *trans*-4-methyl-*N*-cyclohexylacetamide was formed by carbene attack on the solvent, followed by hydrolysis by traces of water.

(27) Distributions of **10**/**11** within Table 1 are insensitive to a doubling of diazirine concentration and are therefore unlikely to reflect S_N2 reactions of Cl^- and carbene **10**.

(28) See: Likhotvorik, I. R.; Jones, M., Jr.; Yurchenko, A. G.; Krasutsky, P. *Tetrahedron Lett.* **1989**, *30*, 5089.

(29) We have made similar observations in the fragmentation of 7-norbornyloxychlorocarbene to 7-norbornyl chloride.

(30) For an earlier experimental study, see: Moss, R. A.; Balcerzak, P. *J. Am. Chem. Soc.* **1992**, *114*, 9386.