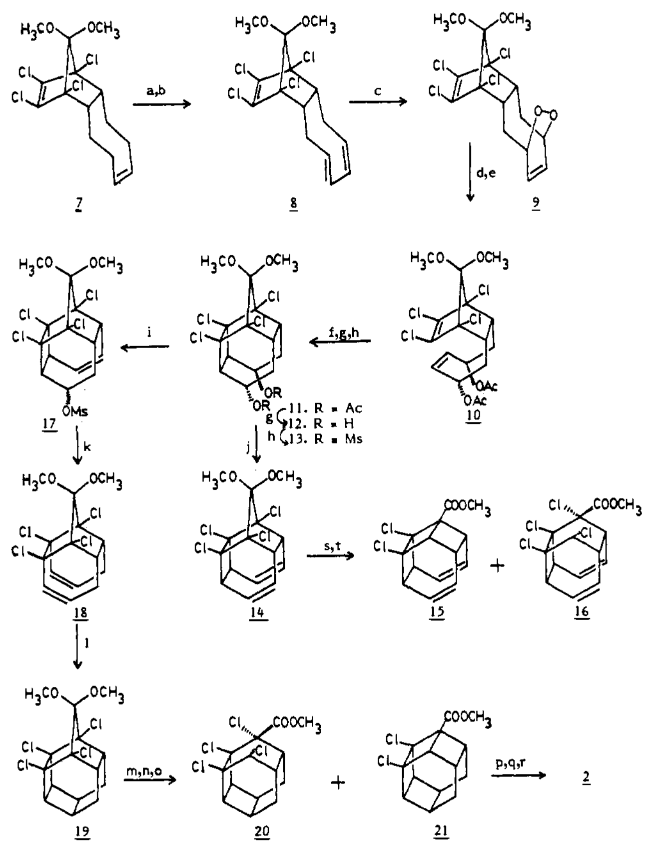
Scheme II[a]



[a] Reagents and yields: (a) *N*-bromosuccinamide-CCl_4, AIBN, reflux, 4 h, 100%; (b) DBU-Me_2SO, room temperature, 8 h, 70%; (c) O_2–CH_2Cl_2, methylene blue, 500-W tungsten lamp, 15 °C, 7 days, 70%; (d) $LiAlH_4$–Et_2O, room temperature, 3 h; (e) Ac_2O-Py, room temperature, 4 h, 75% from **9**; (f) $h\nu$, acetophenone-benzene, 20 °C, 8 h, 73%; (g) aqueous KOH-MeOH, room temperature, 2 h, 100%; (h) CH_3SO_2Cl-Py, room temperature, 5 h, 85%; (i) NaI-HMPA, 100 °C, 60 h, 55%; (j) NaI-HMPA, 130 °C, 72 h, 73%; (k) B_2H_6-THF, room temperature, 2 h, aqueous NaOH, reflux, 1.5 h, 74%; (l) $h\nu$, acetone, 20 °C, 14 h, 60%; (m) 90% H_2SO_4–CH_2Cl_2, 0 °C → room temperature, 10 h, 85%; (n) NaOH-toluene, reflux, 10 min; (o) CH_2N_2–MeOH, 0 °C, 15 min, 60% **21** and 25% **20**; (p) aqueous KOH-MeOH, reflux, 2 h; (q) HgO-CH_2Cl_2, reflux, 1 h, Br_2, reflux, 2 h, 82% from **21**; (r) Li-THF-*t*-BuOH, reflux, 3 h, 32%; (s) 90% H_2SO_4–CH_2Cl_2 0 °C → room temperature, 12 h, 85%; (t) NaOH-toluene, reflux, 10 min, CH_2N_2–MeOH, 0 °C, 15 min, 46% **15** and 46% **16**.

substitution–elimination reaction and the olefinic monomesylate **17** could be readily obtained. Diborane-induced fragmentation[13] of **17** took the projected course and the tetracyclic diene **18**[8] was delivered in just two steps from **13**. Irradiation of **18** with acetone as sensitizer led to the (2 + 2) ring closure and the now much sought hexacyclic compound **19**[8] was realized quite uneventfully. Unmasking of the carbonyl group in **19** set up the Favorskii ring contraction and a 2:5 ratio of the secohexaprismane ester **21**[8] and the Haller–Bauer ester **20** was obtained. Finally, a three-step sequence consisting of alkaline hydrolysis, Hunsdiecker reaction, and reductive dehalogenation (Scheme II) furnished the hexacyclic hydrocarbon secohexaprismane **2**, a highly volatile waxy solid, sublimed at 80 °C, mp > 250 °C. The EI and CI mass spectrum of **2** did not show a molecular ion but a base peak at m/e 79.0559 corresponding to $M^+/2$ ($C_6H_7^+$; calcd for C_6H_7, 79.0548) was observed. The 300-MHz ^1H NMR spectrum had four resonances at δ 3.12–3.06 (m), 2.90–2.79 (m), 1.78 (d with st, J = 14 Hz), and 1.30 (d, J = 14 Hz) in a ratio of 1:4:1:1 and the ^{13}C NMR spectrum exhibited four resonances at δ 35.0, 33.8, 29.2, and 20.5 in accordance with its symmetry. With the attainment of secohexaprismane (**2**), we are now pursuing the general synthetic strategy outlined here toward hexa and higher prismanes with tactical adjustments.

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Registry No. 2, 106880-88-0; **2** (dichloride), 106880-90-4; **7**, 67335-74-4; **8**, 106880-92-6; **9**, 106880-93-7; **10**, 106880-94-8; **11**, 106880-95-9; **12**, 106880-96-0; **13**, 106880-97-1; **14**, 106880-98-2; **14** (ketone), 106880-91-5; **15**, 106880-99-3; **16**, 106881-00-9; **17**, 106881-01-0; **18**, 106881-02-1; **19**, 106881-03-2; **19** (ketone), 106880-89-1; **20**, 106881-04-3; **21**, 106905-23-1.

Supplementary Material Available: 300 MHz ^1H NMR spectrum of secohexaprismane (1 page). Ordering information is given on any current masthead page.

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[13] Marshall, J. A.; Bundy, G. L. *J. Am. Chem. Soc.* **1966**, *88*, 4291.

Stereochemical Consequences of Thermal Fluorine-for-Chlorine Atomic Substitution with 2(*S*)-(+)-Chloropropionyl Chloride

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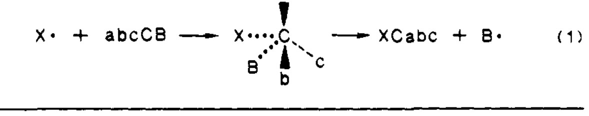
Considerable interest exists in understanding the fundamental aspects of homolytic bimolecular substitution (S_H2) reactions at sp^3 hybridized carbon atoms[1] perhaps because of the practical implications to understanding radical substitution reactions in organic synthesis. Over the years, particular attention has been given to the halogen atom substitution reactions.[2-4] Ingold and Roberts pointed out in an early monograph that available data could not provide unequivocal evidence for the existence of thermoneutral substitution reactions at thermal energies. However, it was suggested that highly exothermic substitutions might be more probable. A recent study by Rowland and Subramonia demonstrated this point where thermal F-for-X substitutions were observed with CH_3X (X = Cl, Br, I).[5] The rate constants for reaction were found to be somewhat slow, ranging between 8×10^{-13} and 3.7×10^{-14} cm^3 $molecule^{-1}$ s^{-1}, compared to H-abstraction, but increased as the reaction exothermicity increased.

A second point made by Ingold and Roberts[1] is that substitution of an atom or radical at an asymmetric carbon atom could provide fundamental insight into a long-pursued question of how the attacking species approaches the molecule. For a synchronous mechanism, the approach of the displacing agent is coordinated with the loss of the leaving group on a time scale that falls within the period for a single vibration. Under these circumstances, the stereochemical configuration of the substrate should be preserved if attack occurs on the front or side of the molecule.



$$X\cdot + abcCB \longrightarrow X\cdots\overset{a}{\underset{B\;\;b\;\;c}{C}} \longrightarrow XCabc + B\cdot \qquad (1)$$

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(1) Ingold, K. U.; Roberts, B. P. *Free Radical Substitution Reactions*; Wiley: New York, **1971**.

(2) Ogg, R. A., Jr.; Polanyi, M. *Trans. Faraday Soc.* **1935**, *31*, 482–495.

(3) Avonda, F. P.; Gervasi, J. A.; Bigelow, L. A. *J. Am. Chem. Soc.* **1956**, *78*, 2798–2800.

(4) Tedder, J. M. *Adv. Fluorine Chem.* **1961**, *2*, 104–137.

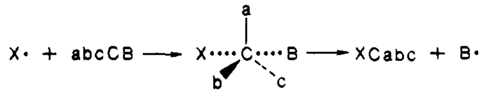
(5) Subramonia, I.; Rowland, F. S. *J. Phys. Chem.* **1981**, *85*, 2488–2492.

Table I. Yields of ^{18}F-for-Cl Substitution at the Asymmetric Carbon of 2(*S*)-(+)-Chloropropionyl Chloride as a Function of Neon Moderator[a]

mol fractn neon	absolute yield of substitun prod	mol fractn neon	absolute yield of substitun prod
0.05	1.1 ± 0.1[b]	0.96	0.35
0.40	0.53	0.98	0.33
0.90	0.38	0.99	0.29

[a] Yields based on total induced ^{18}F activity in gaseous targets. [b] Value taken from ref 8.

On the other hand, complete inversion of configuration would be expected subsequent to back-side attack.



$$X\cdot + abcCB \longrightarrow [X\cdots C(a)(b)(c)\cdots B] \longrightarrow XCabc + B\cdot \quad (2)$$

It is not possible to say whether repulsive exchange energies between altered and preserved bonds, and between lone and paired electrons in altered bonds are any different for the above two transition states. However, by analogy to the S_N2 mechanism, complete inversion of configuration might be expected for thermal homolytic substitution (S_H2) reactions. In contrast to this, previous work published by this group on *nonthermal* ^{18}F, ^{34m}Cl, ^{38}Cl, and more recently ^{75}Br atom substitutions on 2(*S*)- and 2(*R*)-halopropionyl halides, 2-chloro-4-methylvaleryl chloride, and 2-chloro-1-propional have shown higher retention of stereochemical configuration.[6-9]

In the present report, the stereochemical consequences from thermalized ^{18}F atom substitution on the chiral center of 2(*S*)-(+)-chloropropionyl chloride were investigated in the gas phase. The purpose of this work was not only to provide evidence in support of a dual approach channel for substitution, but to qualitatively establish the energy requirements of each channel. This was accomplished through a comparison of results obtained in both nonthermal and thermalized ^{18}F atom substitutions.

Experimental Section. The experimental techniques employed in this study have been previously described by us.[6-8] The 2-(*S*)-chloropropionic acid was prepared according to the method of Fu et al.[10] The method of Fickett et al.[11] was employed to convert the acid to 2(*S*)-(+)-chloropropionyl chloride. Irradiations were carried out at the Brookhaven National Laboratory 60-in. cyclotron. For ^{18}F-substitution reactions with 2-chloropropionyl chloride containing neon additive, a 13-MeV deuteron beam was employed producing ^{18}F by the ^{20}Ne(d,α)^{18}F reaction. Irradiation targets were constructed of quartz, with 0.01 in. thick entrance windows and were 30 mL in volume. All targets were kept at least at the boiling point of the acyl chloride (105 °C) during irradiation. The partial pressure exerted by this substrate was adjusted by varying the amount of liquid placed in the evacuated cells during preparation. Targets were then filled with neon gas to the appropriate pressures such that a total pressure of 1400 torr was obtained when heated. Neon not only served as the ^{18}F precursor, but also as an efficient kinetic energy moderator for the recoil atoms. If left unmoderated, these atoms will carry excess kinetic energy obtained from the nuclear event into the reaction coordinate. Post irradiation derivatization and separation of diastereomers was accomplished by the methods previously described.[6,8] Enantiomer distributions and absolute yields were obtained by correlating the ^{18}F radioactivity measured in the diastereomers to the total induced ^{18}F radioactivity.

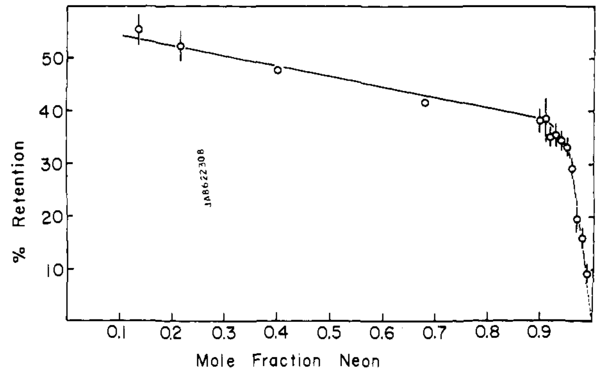


Figure 1. Percent retention of stereochemical configuration from ^{18}F-for-Cl substitution on 2(*S*)-(+)-chloropropionyl chloride as a function of neon moderator.

Results and Discussion. The absolute yields of substitution product arising from ^{18}F-for-Cl exchange at the asymmetric carbon center of 2(*S*)-(+)chloropropionyl chloride with varied mole fractions of neon moderator are listed in Table I. These results show a significant drop in the substitution yield as excess kinetic energy of the ^{18}F atom is removed with increasing neon concentrations. However, the reaction is not entirely eliminated, and does not appear to diminish much further when extrapolated to 100% neon. This observation coincides with Rowland's observation that thermal halogen substitutions will indeed occur for highly exothermic reactions, but only to a minor extent.[5]

Plotted in Figure 1 is the distribution of ^{18}F-labeled 2(*S*)-(+)-fluoropropionyl chloride and 2(*R*)-(−)-fluoropropionyl chloride substitution products, presented as percent retention of configuration, for varied concentrations of neon moderator. The error bars on the data represent one standard deviation. The results clearly show that nonthermal (energetic) F-for-Cl substitutions yield a slight preference for stereochemical retention. Previous studies[8,9] have clearly demonstrated that the stereochemical outcome of energetic substitutions is dependent on the mass of the displacing and displaced atoms but appears not to be dependent on the free energy requirements of reaction. On the other hand, thermal F-for-Cl substitutions yield extensive, if not exclusive, stereochemical inversion. (Extrapolation of the moderator curve to 100% neon yields 100% inversion within the experimental error.)

The results reported in this study provide strong evidence in support of the two-channel substitution mechanism. Of course, this assumes that the reaction proceeds via a synchronous mechanism. Stepwise substitution yielding an intermediate of finite lifetime (greater than the time required for a single vibration) is precluded from consideration here since a racemic mixture of enantiomers would be expected subsequent to thermal substitution because of the intermediate's enhanced lifetime at lower energy. The present results do not support this.

The results also show that *only* energetic F atoms can undergo front-side attack to yield stereochemical retention. This suggests that the energy barrier for front-side attack must be substantially higher than that for back-side attack since thermal atom approach in this fashion is prevented. It also appears that the chemical energy released from reaction (ΔH = 26 kcal mol^{-1})[12] has little or no effect on the stereochemical outcome. This leads us to conclude that the principal factor directing the stereochemistry of these substitution reactions is the kinetic energy of the displacing atom. This factor directly affects the atom's ability to approach the molecule in one fashion or another.

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(6) Wolf, A. P.; Schueler, P.; Pettijohn, R. P.; To, K.-C.; Rack, E. P. *J. Phys. Chem.* **1979**, *83*, 1237-1241.

(7) To, K.-C.; Rack, E. P.; Wolf, A. P. *J. Chem. Phys.* **1981**, *74* (2), 1499-1500.

(8) To, K.-C.; Wolf, A. P.; Rack, E. P. *J. Phys. Chem.* **1983**, *87*, 4929-4932.

(9) Firouzbakht, M. L.; Ferrieri, R. A.; Wolf, A. P.; Rack, E. P. *J. Phys. Chem.* **1986**, *90*, 5339.

(10) Fu, S.-C. J.; Birnbaum, S. M.; Greenstein, J. P. *J. Am. Chem. Soc.* **1954**, *76*, 6054-6058.

(11) Fickett, W.; Garner, H. K.; Lucas, H. J. *J. Am. Chem. Soc.* **1951**, *73*, 5063-5067.

(12) Estimated from group additivity data on heats of formation from: Benson, S. W. *Thermochemical Kinetics*, Wiley: New York, 1976.