The Stereochemistry of Chloride Exchange in Desyl Chloride[1]

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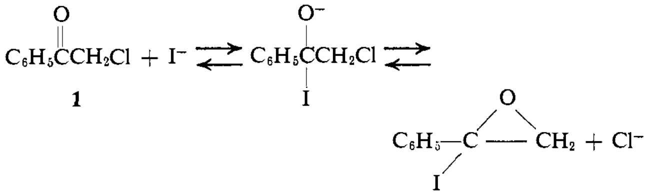
Abstract: Desyl chloride (**2**) is one of a number of α-halo ketones which, with some nucleophiles, gives epoxide products derived from attack of the nucleophile at the carbonyl group followed by intramolecular displacement of halide. To test the hypothesis that the high reactivity of α-halocarbonyl compounds in bimolecular nucleophilic displacements may be due to the operation of a mechanism involving epoxide intermediates, the stereochemistry of chloride exchange in desyl chloride was determined by comparing the rates of racemization and exchange in acetone solutions of lithium chloride-36. The reaction was found to proceed with inversion, a result which is inconsistent with an epoxide intermediate and which establishes the usual SN2 stereochemistry in this case.

The α-halocarbonyl compounds are among the few substrates for bimolecular nucleophilic displacement reactions that are more reactive than their unhindered primary aliphatic counterparts.[2] The enhanced reactivity is dramatically illustrated by α-chloroacetophenone (**1**), which reacts with potassium iodide in acetone at 75° some 32,000 times faster than *n*-butyl chloride.[3] The C_6H_5CO group and its ring-substituted analogs exhibit the largest accelerations reported for any SN2 reaction.[3–5]

The source of the increased reactivity has proved rather difficult to pinpoint.[3a] A stabilizing interaction between the nucleophile, the leaving group, and the carbonyl group in the transition state can be justified by molecular orbital calculations[6a] and on stereochemical grounds,[6b] although steric effects may be important.[3a]

One mechanism that has received brief attention[7] is based on the assumption that the reaction is not a typical SN2 reaction, but that it is actually a multistep process in which the nucleophile first adds to the carbonyl group. The resulting ion then undergoes an internal displacement to yield an intermediate epoxide which reacts with a nucleophile from the medium to give the observed product. The reaction of α-chloroacetophenone with iodide would be as follows.



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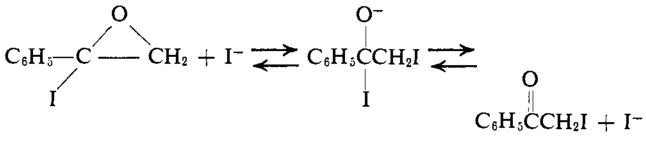
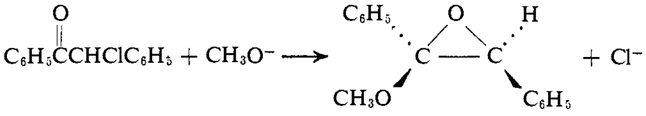


If either of the steps before the epoxide ring opening were rate limiting, typical second-order kinetics[8] would be observed.

The proposal was based on the observation that stable epoxides corresponding to the proposed intermediate could actually be isolated in some systems, for example, in the reaction of desyl chloride (**2**) with sodium methoxide in methanol.[9]



2 **3**

There are now numerous cases where the reaction takes this course,[10] as well as related examples where addition to a carbonyl group followed by ring closure predominates over simple displacement at primary carbon.[11]

Pearson, *et al.*,[7] concluded, largely by a comparison of rate ratios with product ratios in the competitive reaction of a single substrate with a mixture of two nucleophiles in excess, that the displacement reactions of α-bromoacetophenone in particular and carbonyl compounds in general probably did not involve an epoxide intermediate. A more convincing argument for or against the epoxide mechanism can be made by examining the stereochemistry of α-halocarbonyl displacements.[12] This is reported below for chloride

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[1] Most of the experimental work involved in this study was carried out at the Department of Chemistry, Harvard University, Cambridge, Massachusetts.

[2] (a) A. Streitwieser, Jr., "Solvolytic Displacement Reactions," McGraw-Hill Book Co., Inc., New York, N. Y., 1962, pp 11–29; (b) J. Hine, "Physical Organic Chemistry," McGraw-Hill Book Co., Inc., New York, N. Y., 1962, pp 169–178; (c) E. L. Eliel in "Steric Effects in Organic Chemistry," M. S. Newman, Ed., John Wiley and Sons, Inc., New York, N. Y., 1956, pp 84–106.

[3] (a) F. G. Bordwell and W. T. Brannen, Jr., *J. Amer. Chem. Soc.*, **86**, 4645 (1964); (b) *cf.* J. B. Conant, W. R. Kirner, and R. E. Hussey, *ibid.*, **47**, 488 (1925).

[4] W. T. Brannen, Jr., Ph.D. Thesis, Northwestern University, Evanston, Ill., 1962, p 47.

[5] Preliminary kinetic data suggest that displacements in α-bromoacetophenone oxime may be faster than those in α-bromoacetophenone itself; personal communication, Dr. Arthur Ash, Ash-Stevens, Inc., Detroit, Mich.

[6] (a) Reference 2a, p 28; (b) P. D. Bartlett and E. N. Trachtenberg, *J. Amer. Chem. Soc.*, **80**, 5808 (1958).

[7] R. G. Pearson, S. H. Langer, F. V. Williams, and W. J. McGuire, *ibid.*, **74**, 5130 (1952).

[8] Reference 3b and earlier papers cited.

[9] (a) C. L. Stevens, M. L. Weiner, and R. C. Freeman, *J. Amer. Chem. Soc.*, **75**, 3977 (1953); (b) C. L. Stevens and T. H. Coffield, *J. Org. Chem.*, **23**, 336 (1958).

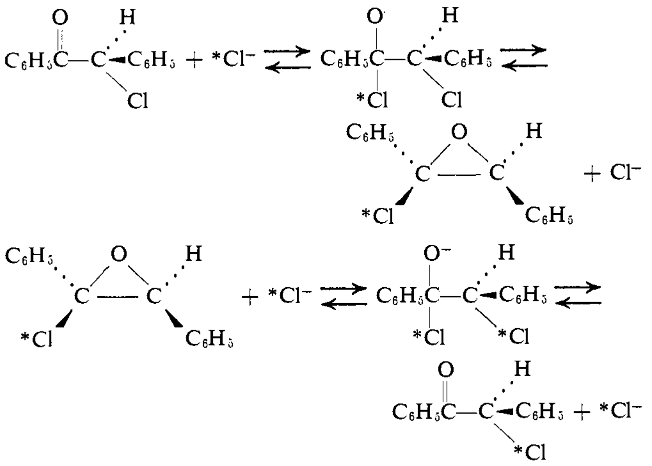
[10] (a) T. I. Temnikova and O. A. Kaurov, *Zh. Obshch. Khim.*, **34**, 3165 (1964), and earlier papers; (b) N. Almasi, L. Szotyori, and M. Domokos, *Rev. Roum. Chim.*, **9**, 531 (1964), and references cited; (c) L. Szotyori, N. Almasi, L. Fey, and M. Domokos, *ibid.*, **9**, 545 (1964); (d) C. L. Stevens, P. Blumbergs, and M. Munk, *J. Org. Chem.*, **28**, 331 (1963); (e) M. Mousseron and R. Jacquier, *C. R. Acad. Sci., Paris*, **229**, 374 (1949); (f) M. Mousseron, R. Jacquier, and A. Fontaine, *ibid.*, **231**, 864 (1950); (g) C. L. Stevens and A. J. Weinheimer, *J. Amer. Chem. Soc.*, **80**, 4072 (1958); (h) A. S. Kende, *Org. Reactions*, **11**, 283 (1960).

[11] (a) H. E. Zaugg, V. Papendick, and R. J. Michaels, *J. Amer. Chem. Soc.*, **86**, 1399 (1964); (b) H. E. Zaugg, F. E. Chadde, and R. J. Michaels, *ibid.*, **84**, 4567 (1962); (c) H. E. Zaugg, R. W. DeNet, and R. J. Michaels, *J. Org. Chem.*, **28**, 1795 (1963); (d) H. E. Zaugg, R. W. DeNet, and R. J. Michaels, *ibid.*, **26**, 4821 (1961); (e) *ibid.*, **26**, 4828 (1961).

[12] The instances where displacement stereochemistry in simple α-halocarbonyl substrates has been examined have involved carboxylic

change in desyl chloride.

The exchange of radioactive chloride with optically active desyl chloride, assuming the epoxide mechanism, would proceed as shown (*Cl$^-$ = chloride-36).[13]



Since the final product is reached by a double inversion at the asymmetric center, radiochloride would be incorporated with over-all retention of configuration. The ratio of rate constants, k_{ex}/k_{inv}, where k_{ex} represents exchange and k_{inv} inversion, would then equal infinity. If the reaction were however a typical SN2 displacement, the ratio would be unity.[14] If the substrate happened to react by both mechanisms, the value of k_{ex}/k_{inv} would lie somewhere between unity and infinity.

Results and Discussion

The rates of racemization and exchange were measured at 25° in anhydrous acetone containing 0.0921 *M* lithium chloride. To ensure that the medium was duplicated in both reactions, the acetone solution of radioactive lithium chloride prepared for the exchange reaction was used for the racemization study. The concentration of (+)-desyl chloride used in the racemization study was 0.0336 *M*. Optically inactive desyl chloride (0.0337 *M*) was used for the exchange.

Tables I and II give the kinetic data for exchange and racemization, respectively. Excellent plots for pseudo-first-order kinetics were obtained using standard treatments,[15] with the line slopes calculated by the method of least squares. Second-order rate constants were calculated assuming that only free chloride ions take part in displacement.[16] The concentration of free chloride was determined from the known dissociation constant of lithium chloride in acetone at 25°.[17] The values were 5.91×10^{-2} l. mol^{-1} sec^{-1} for k_{ex} and 6.00×10^{-2} l. mol^{-1} sec^{-1} for k_{inv}, which give 0.985 for the ratio k_{ex}/k_{inv}.[18,19]

The ratio suggests strongly that desyl chloride reacts with lithium chloride in acetone by the usual SN2 mechanism.[20] This finding should perhaps not be extended casually to other substrates and nucleophiles, however. The many examples of epoxide products isolated under SN2 conditions must still be accounted for, and it may prove that the relative reactivities of some nucleophiles toward carbonyl and saturated carbon atoms are balanced to allow for the operation of an epoxide mechanism.

Experimental Section

(+)-Desyl Chloride. The synthesis procedure was adapted from that of Roger and Wood.[21] (−)-Benzoin[22] (13.0 g, 0.0614 mol) was suspended with magnetic stirring in 250 ml of ether and the mixture cooled to −35°. A solution of 5.1 g (0.065 mol) of pyridine in a few milliliters of ether was added dropwise, then 16.3 g (0.137 mol) of thionyl chloride in 75 ml of ether was added dropwise in 1 hr. The suspension was maintained at −35 to −40° during addition and for 1 hr longer, then was allowed to warm to room temperature and maintained there for 50 hr (the time found necessary for complete reaction). It was poured onto crushed ice, the layers were separated, and the ether layer was washed consecutively with ice-cold 5% sodium bicarbonate, water, and saturated sodium chloride. It was dried over anhydrous sodium sulfate, then the ether was removed on a rotary evaporator to yield 13.5 g of crude product. Recrystallization from *n*-hexane gave 10.4 g (74%) of sample having mp 75–76° and $[\alpha]^{22}_{5461}$ +166° (*c* 0.619, acetone) (lit.[21] mp 75–76°, $[\alpha]_{5461}$ +168° (*c* 0.618, acetone)). Material used in kinetic runs was again recrystallized from *n*-hexane, using decolorizing carbon, then recrystallized a third time from *n*-hexane. The final melting point was still 75–76°.[23]

Radioactive Lithium Chloride. Five grams of lithium chloride (recrystallized three times from water) was dissolved in 50 ml of 0.016 *N* hydrochloric acid containing 10 μCi of chlorine-36. The solution was filtered, evaporated to dryness on a hot plate in a slow stream of dry nitrogen, then dried for 11 hr at 220° to give lithium chloride having a nominal activity of 0.085 μCi/mmol. The actual sample used in kinetic runs was further dried over phosphorus pentoxide for 2 hr at 150–160° (0.1 mm) just before use.

Preparation of Solutions. Dry acetone was prepared by passing reagent-grade acetone through a column of Linde 4A Molecular Sieve into a receiver containing molecular sieves. The acetone was distilled out of the drying agent, and a fraction boiling at a constant 56.2° was used immediately. Acetone dried in a similar fashion has been found to give no reaction to Karl Fisher reagent, indicating a water content of less than 0.005%.[17]

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acids or their derivatives, and the observations need not necessarily apply to aldehydes and ketones. (Results are summarized in C. K. Ingold, "Structure and Mechanism in Organic Chemistry," Cornell University Press, Ithaca, N. Y., 1953, p 388.) Displacements in some steroidal α-halo ketones appear to go with inversion (G. P. Mueller and W. F. Johns, *J. Org. Chem.*, **26**, 2403 (1961)).

(13) The chloro epoxide is shown with the phenyl groups *trans*, in analogy with the known configuration of the epoxy ether **3** derived from desyl chloride and sodium methoxide.[9b] Chloro epoxides are known, albeit thermally labile, compounds; see, for example, R. N. McDonald and T. E. Tabor, *J. Amer. Chem. Soc.*, **89**, 6573 (1967). An attempt to prepare the specific chloro epoxide proposed as the intermediate above, by the peracid oxidation of *trans*-α-chlorostilbene, yielded desyl chloride instead, by a process involving chlorine migration (R. N. McDonald and P. A. Schwab, *ibid.*, **85**, 4004 (1963)).

(14) Reference 2b, pp 25–26.

(15) A. A. Frost and R. G. Pearson, "Kinetics and Mechanism," 2nd ed, John Wiley and Sons, Inc., New York, N. Y., 1961, pp 192–193, for the exchange kinetics.

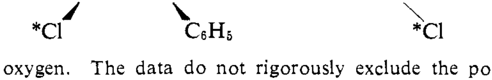
(16) S. Winstein, L. G. Savedoff, S. Smith, I. D. R. Stevens, and J. S. Gall, *Tetrahedron Lett.*, **9**, 24 (1960).

(17) L. G. Savedoff, *J. Amer. Chem. Soc.*, **88**, 664 (1966).

(18) The estimated error in the rate constants is 3%.

(19) The exchange rate in this system may be compared with that of ethyl chloride, measured using radioactive lithium chloride in anhydrous acetone by P. D. B. de la Mare, *J. Chem. Soc.*, 3169 (1955). Ethyl chloride exchanges at 25° with a second-order rate constant of 5.0×10^{-5} l. mol^{-1} sec^{-1}, a value calculated from the reported constant to conform with the assumption made above that only free chloride is reactive. The approximately 1200-fold acceleration with desyl chloride is considerably less than with the previously examined α-chloro ketones, where chloride was usually displaced by iodide in acetone solutions of alkali iodides.[3,4,8]

(20) Displacement with inversion also rules out a mechanism in which an intermediate chloro epoxide rearranges to desyl chloride by intramolecular chlorine migration with back-side displacement of the



epoxide oxygen. The data do not rigorously exclude the possibility that the observed decrease in optical activity takes place by an unrelated process, such as chloride-catalyzed enolization, whose rate is fortuitously related to the exchange rate as indicated above.

(21) R. Roger and R. Wood, *J. Chem. Soc.*, 811 (1954).

(22) A. McKenzie and H. Wren, *ibid.*, **39**, 309 (1908).

(23) All melting points are uncorrected.

Table I. Chloride Exchange in Desyl Chloride; Activity of Kinetic Samples

Time, sec	Activity,[a] cpm/mmol
3,825	22,410
7,280	40,000
10,940	55,600
15,505	71,370
18,275	79,740
21,695	88,330
25,315	95,750
∞[b]	141,800

[a] Relative activities; the counting efficiency was not determined. Based on ~500,000 total counts or a counting time of 100 min. [b] 160 hr.

Table II. Racemization of (+)-Desyl Chloride; Loss of Optical Rotation with Time

Time, sec	α, deg	Time, sec	α, deg
0	1.160	14,625	0.439
1,130	1.077	15,755	0.407
1,785	1.030	17,040	0.374
2,895	0.955	18,090	0.350
3,600	0.912	19,270	0.324
4,454	0.862	20,580	0.297
6,035	0.775	21,665	0.277
7,270	0.713	23,695	0.242
8,320	0.666	25,585	0.214
9,760	0.605	27,625	0.188
11,050	0.557	30,120	0.159
12,290	0.509	∞[a]	0.000
13,265	0.479		

[a] 70 hr.

The acetone solution of radioactive lithium chloride (250 ml of 0.0921 *M*) was prepared in a glovebox under dry nitrogen. The process of dissolution was hastened with magnetic stirring. A portion of the solution was transferred to an ampoule, sealed, and stored in Dry Ice for later use in the racemization experiment. The rest was used immediately to prepare 200 ml of a solution 0.0337 *M* in desyl chloride (optically inactive, recrystallized from *n*-hexane and dried under vacuum, mp 66.8–67.8° (lit.[24] mp 66–67°)).

Exchange Kinetics. The solution of desyl chloride and lithium chloride-36 in acetone was thermostated at 25.00 ± 0.05°. Samples were withdrawn about every hour and worked up as follows. The reaction solution (25 ml) was poured into 25 ml of ice water, and the originally homogeneous mixture was subjected to oil-pump vacuum on a rotary evaporator until only a few milliliters of slurry remained. Water and dichloromethane were then added, and the flask was rotated for several minutes to dissolve the solid and effect contact between the layers. The dichloromethane solution was separated, washed with water, dried over anhydrous sodium sulfate, and evaporated in a stream of dry nitrogen. The oily residue was taken up in a few milliliters of dichloromethane and transferred to a Craig tube.[25] The dichloromethane was evaporated as before and the residue recrystallized at least twice from *n*-hexane. (A third recrystallization of several samples had negligible or no effect on their activity.) The weight of the dried, twice recrystallized samples typically represented 85% of the original sample weight. The procedure gave material whose melting point was identical with that of desyl chloride taken for the exchange reaction, and a control experiment in which nonradioactive desyl chloride in 25 ml of acetone was added to 25 ml of aqueous radioactive lithium chloride showed that no incorporation of chloride-36 took place during the work-up.

The activities of kinetic samples were measured with a Nuclear Chicago scintillation counter and are given in Table I. Each sample (~60 mg) was dissolved in 15 ml of reagent-grade toluene containing 0.5% PPO (2,5-diphenyloxazole) and 0.03% POPOP (2,2-*p*-phenylenebis(5-phenyloxazole)); sample concentrations were kept uniform to minimize quenching effects.

Racemization Kinetics. (+)-Desyl chloride was dissolved in the acetone solution of radioactive lithium chloride prepared for the exchange kinetics. Final concentrations were 0.0336 *M* (+)-desyl chloride and 0.0921 *M* lithium chloride. The optical rotation (α) was followed at 436 mμ in a 5-cm cell placed in the thermostated (25.00 ± 0.05°) compartment of a Rudolph polarimeter equipped with a photoelectric detector. The values of α as a function of time are given in Table II.

Acknowledgments. This work was supported in part by a grant from the Petroleum Research Fund administered by the American Chemical Society. The author is indebted to Dr. F. H. Westheimer for the use of the scintillation counter.

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[24] A. M. Ward, "Organic Syntheses," Coll. Vol. II, John Wiley and Sons, Inc., New York, N. Y., 1943, p 159.

[25] R. S. Tipson in "Technique of Organic Chemistry," Vol. III, A. Weissberger, Ed., 2nd ed, Interscience Publishers, Inc., New York, N. Y., 1956, p 545.