H, one of SCH_2CH_2), 2.96–3.00 (m, 1 H, one of SCH_2CH_2), 2.72–2.78 (m, 1 H, one of SCH_2CH_2), 1.75 (t, 1 H, J = 5.8 Hz, O*H*), 1.67–1.72 (m, 1 H, one of SCH_2CH_2), 0.56–0.64 (m, 2 H, two of *Cy*), 0.21–0.25 (m, 1 H, one of *Cy*), −0.17 to −0.21 (m, 1 H, one of *Cy*); HRMS calcd for $C_{13}H_{15}DOS$ (M^+) 220.1032, found 220.1055.

Cyclopropane alcohol 80 (d_1): R_f = 0.20 (20% ethyl acetate in hexanes); IR (neat) 3369 (br, OH), 3079 (w), 2931 (m), 1426 (m), 1151 (w), 1075 (s), 1020 (m), 888 (s), 677 (m); ^{1}H NMR (500 MHz, CD_2Cl_2) 7.55 (s, 1 H, *Ar*-2), 7.45 (s, 1 H, *Ar*-4 or *Ar*-6), 7.27 (s, 1 H, *Ar*-4 or *Ar*-6), 4.66 (d, 2 H, J = 5.7 Hz, $HOCH_2$), 3.17–3.23 (m, 1 H, one of SCH_2CH_2), 3.22 (s, 3 H, CH_3O), 2.96–3.00 (m, 1 H, one of SCH_2CH_2), 2.72–2.78 (m, 1 H, one of SCH_2CH_2), 1.75 (t, 1 H, J = 5.8 Hz, O*H*), 1.67–1.72 (m, 1 H, one of SCH_2CH_2), 0.56–0.64 (m, 2 H, two of *Cy*), 0.21–0.25 (m, 1 H, one of *Cy*), −0.17 to −0.21 (m, 1 H, one of *Cy*); HRMS calcd for $C_{14}H_{17}D_1O_2S$ 253.1327, found 253.1320.

Acknowledgment. We thank Professors Dennis Dougherty and Robert Squires for many helpful discussions. This work was generously supported by the National Institutes of Health. Graduate Fellowship support from the ACS Division of Organic Chemistry (sponsored by the Procter & Gamble Company, P.S.D.) and from the Kodak Company (E.Y.K.) is gratefully acknowledged.

Stereochemical Dissection of a Carbene Fragmentation Reaction†

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Contribution from the Department of Chemistry, Rutgers, The State University of New Jersey, New Brunswick, New Jersey 08903. *Received June 24, 1992*

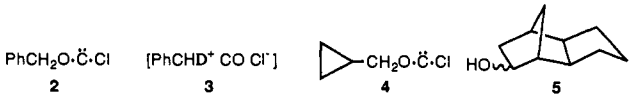
Abstract: The fragmentation of (*S*)-3-(2-butoxy)-3-chlorodiazirine (**9**) in acetonitrile proceeds via N_2 loss to (*S*)-2-butoxychlorocarbene (**10**) and thence via CO scission to a 2-butyl cation/chloride anion pair (**11**) that collapses to (*S*)-2-chlorobutane (**12**) with ~56% net retention. In 1-butanol, ion pair **11** affords 55% chloride **12** by ion pair return with 82% net retention and 45% of (*R*)-2-butyl 1-butyl ether (**13**) by ion pair solvolysis with ~71% net inversion.

In the 1950's Hine[2] and Skell[3] demonstrated that alkoxyhalocarbenes (**1**) formed when dihalocarbenes reacted with alkoxide ions, and Skell found that these derived carbenes fragmented to alkyl cations upon loss of halide and carbon monoxide,[3] eq 1.

$$RO^- + :CX_2 \rightarrow ROCX_2 \xrightarrow{-X^-} \underset{\mathbf{1}}{RO\text{–}\ddot{C}\text{–}X} \rightarrow R^+ + CO + X^- \quad (1)$$

The latter process was termed "deoxideation". Carbon monoxide is isoelectronic to N_2, so that deoxideation resembles the generation of alkyl cations by deaminative reactions,[4] particularly the hydrolysis of alkanediazotates (see below), which also occurs in the presence of strong base.[5] Although the utility of the original deoxideation reaction as a means of generating cations was offset by the accompanying strongly basic conditions, Smith and Stevens subsequently showed that 3-methoxy- and 3-isobutoxy-3-chlorodiazirines gave the corresponding alkoxychlorocarbenes upon thermolysis. Fragmentation of the carbenes could then be studied under neutral conditions.[6]

Exploiting this methodology, we found that the thermolysis of (benzyloxy)chlorodiazirine in acetonitrile at 25 °C gave (benzyloxy)chlorocarbene (**2**), which fragmented to benzyl chloride

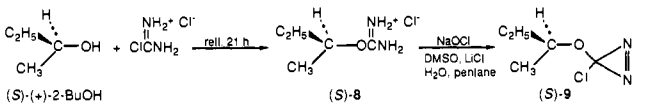


2 **3** **4** **5**

and CO.[7] When this reaction was repeated with (*S*)-[(α-deuteriobenzyl)oxy]chlorodiazirine, leading to the chiral, labeled carbene, (*S*)-**2**-α-d_1, the product benzyl-α-d_1 chloride was obtained with 60–80% net retention, consistent with front-side chloride return in the intermediate ion pair **3**, formed upon fragmentation of **2**-α-d_1.[8]

Importantly, not all examples of carbene **1** fragment readily; the C–X bond must be sufficiently weak to permit fragmentation to compete with the more usual intermolecular reactions that lead to carbene capture. For example, (benzyloxy)bromocarbene fragments easily to benzyl bromide and CO, but (benzyloxy)fluorocarbene resists fragmentation, giving instead typical carbene capture products.[9] (Benzyloxy)cyanocarbene similarly eschews fragmentation in favor of intermolecular reactions.[10]

Scheme I



Within the alkoxychlorocarbene family, however, the carbene fragmentation reaction appears to be rather general. Thus, diazirine-generated (cyclopropylmethoxy)chlorocarbene (**4**) fragmented efficiently, affording a mixture of C_4-alkyl chlorides consistent with the intermediacy of cyclopropylcarbinyl cation/chloride anion pairs.[11] Similarly, the formation of epimeric chlorides (with 70–80% of the exo isomer) upon the CCl_2-mediated deoxideation of either epimer of the 2-norbornyl-type alcohols **5**

† In memoriam: Professor Gerhard Ludwig Closs, 1928–1992.

(1) P. B. is a Visiting Scientist on leave from the Technical University (Politechnika), Warsaw, Poland.
(2) Hine, J.; Pollitzer, E. L.; Wagner, H. *J. Am. Chem. Soc.* **1953**, *75*, 5607.
(3) Skell, P. S.; Starer, I. *J. Am. Chem. Soc.* **1959**, *81*, 4117.
(4) White, E. H.; Woodstock, D. J. In *The Chemistry of the Amino Group*; Patai, S., Ed.; Wiley: New York, 1968; pp 40 f. Moss, R. A. *Chem. Eng. News* **1971**, *49*, Nov. 22, 28.
(5) Moss, R. A. *Acc. Chem. Res.* **1974**, *7*, 421.
(6) (a) Smith, N. P.; Stevens, I. D. R. *J. Chem. Soc., Perkin Trans. II* **1979**, 1298. (b) Smith, N. P.; Stevens, I. D. R. *J. Chem. Soc., Perkin Trans. II* **1979**, 213.
(7) Moss, R. A.; Wilk, B. K.; Hadel, L. M. *Tetrahedron Lett.* **1987**, *28*, 1969.
(8) Moss, R. A.; Kim, H. R. *Tetrahedron Lett.* **1990**, *31*, 4715.
(9) Moss, R. A.; Zdrojewski, T. *J. Phys. Org. Chem.* **1990**, *3*, 694. See also: Moss, R. A.; Zdrojewski, T. *Tetrahedron Lett.* **1991**, *32*, 5667.
(10) Moss, R. A.; Zdrojewski, T.; Krogh-Jespersen, K.; Włostowski, M.; Matro, A. *Tetrahedron Lett.* **1991**, *32*, 1925.
(11) Moss, R. A.; Ho, G.-J.; Wilk, B. K. *Tetrahedron Lett.* **1989**, *30*, 2473.

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Table I. Stereochemical Course of Decomposition of Diazirine (*S*)-**9**[a]

		(*S*)-2-chlorobutane				(*R*)-2-butyl 1-butyl ether			
expt	solvent	α_D, deg[b]	$[\alpha]_D$, deg[c]	opt purity, %[d]	net retn, %[e]	α_D, deg[b]	$[\alpha]_D$, deg[f]	opt purity, %[g]	net inv, %[e]
1	MeCN	+0.244[h]	+16.0	46.0	57[i]				
2	MeCN	+0.255[h]	+16.0	46.0	55[j]				
3	*n*-BuOH	+0.167	+25.3	72.7	83[k]	−0.057	−12.1	64.4	73[k]
4	*n*-BuOH	+0.205	+24.7	71.0	81[k]	−1.11	−11.4	60.6	69[k]

[a] See Schemes I–III for the structures and configurations of precursors and products. Thermolytic conditions were 25 °C, 36 h. See text for the temperatures of optical rotation readings. [b] Path length = 0.1 dm. [c] See text for the concentrations of 2-chlorobutane. [d] Based upon $[\alpha]^{22}_D$ +34.8° for optically pure (*S*)-2-chlorobutane.[22] [e] Corrected for the optical purity of the initial 2-butanol; see below. [f] See text for the concentrations of ether **13**. [g] Based upon $[\alpha]^{24}_D$ +18.8° for optically pure (*S*)-2-butyl 1-butyl ether.[33] [h] Corrected for the presence of 2-butyl formate; see text. [i] Initial 2-butanol was 80.6% optically pure. [j] Initial 2-butanol was 83.5% optically pure. [k] Initial 2-butanol was 87.8% optically pure.

has been attributed to the intervention of tight ion pairs or S_Ni reactions in the fragmentation of the carbenes (RO–C–Cl) derived from **5**.[12]

A sensitive method of studying ion pairs is to monitor the stereochemistry of the products formed from them.[13] In the absence of neighboring group effects, the products of ion pair *return* are formed with overall *retention*, whereas those of ion pair *solvolysis* are formed with *inversion*.[13] This paradigm is particularly well illustrated by the nitrogen-separated ion pairs **6** that

$$[R^+ N{\equiv}N\ X^-] \qquad [R^+ O{\equiv}C\ X^-]$$
$$\mathbf{6} \qquad \mathbf{7}$$

arise in deaminative reactions.[4,5] If the closely related ion pairs **7** are indeed key intermediates in the fragmentations of alkoxychlorocarbenes, then parallel stereochemical phenomena should be observed when **7** is allowed to partition between ion pair return and solvent capture. Here, we report the affirmative results of the first such test, as applied to the fragmentation of 2-butoxychlorocarbene in 1-butanol.[14]

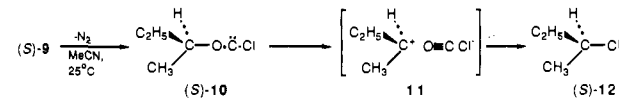
Results and Discussion

Synthesis. 3-(2-Butoxy)-3-chlorodiazirine, the precursor of 2-butoxychlorocarbene, was prepared from 2-butanol (2-BuOH) as shown in Scheme I, where we depict the (*S*)-(+) enantiomer of the starting alcohol. Thus, 2-BuOH was converted to the 2-butylisouronium salt **8** by reflux with chloroformamidinium chloride.[15,16] Chromatography on silica gel gave 42% of **8** as a highly hygroscopic, glassy solid (under vacuum), that fused to a slightly yellow oil in the atmosphere.

Primary alcohols are normally converted to isouronium salts by reaction with cyanamide and *p*-toluenesulfonic acid.[6,8,11] However, this procedure is inefficient with secondary alcohols and leads to significant racemization when applied to (*S*)-(+)-α-deuteriobenzyl alcohol.[8] Both problems are circumvented in the specific example of Scheme 1.

Optically active (*S*)-(+)-2-BuOH, $[\alpha]^{22}_D$ +12.2° (neat) 87.8% optically pure,[17] gave the isouronium salt **8** with $[\alpha]^{24}_D$ +19.0° (*c* = 13.6, MeOH), suggesting a value of $[\alpha]^{24}_D$ ~21.6° for optically pure **8** in MeOH. Parallel preparations using two other lots of 2-BuOH ($[\alpha]^{25}_D$ +11.2° and $[\alpha]^{23}_D$ +11.6°, both neat) afforded samples of **8** with $[\alpha]^{25}_D$ +17.9° (*c* = 33.6, MeOH) and $[\alpha]^{24}_D$ +18.3° (*c* = 38.7, MeOH), respectively. Corrected for the optical purity of the initial 2-BuOH, we obtain $[\alpha]^{25}_D$ +22.2° and $[\alpha]^{24}_D$ +21.9°, leading to an average value of $[\alpha]^{24}_D$ +21.9 ± 0.2° (MeOH) for three independent preparations of **8**. The 2-BuOH *recovered* from these preparations retained 96–97% of the original optical activity, indicating minimal HCl-induced racemization during the formation of **8**. Accordingly, no correction for racemization is applied to **8**.

Scheme II



Graham oxidation[18] of **8** with aqueous NaOCl in DMSO/pentane at 10–13 °C gave 3-(2-butoxy)-3-chlorodiazirine (**9**), λ_{max} 246, 330–360 nm (pentane), λ_{max} 224, 360 nm (MeCN). The NMR spectrum (δ, DMSO-d_6) featured 0.82 (t, *J* = 7.4 Hz, 3 H, CH_2CH_3), 1.25 (d, *J* = 6.2 Hz, 3 H, $CHCH_3$), 1.43–1.50 (m, 2 H, CH_2), and 4.20–4.29 (m, 1 H, CH).

Thermolysis of 9 in Acetonitrile. The thermal decomposition of diazirine **9** in MeCN at 30 °C was monitored by UV spectrometry at 354 nm and proceeded with a first-order rate constant $k = 1.48 \times 10^{-4}$ s^{-1}. This value is similar to those observed in the analogous thermolyses of (benzyloxy)chlorodiazirine (7.4×10^{-5} s^{-1}, 25 °C),[7] (cyclopropylmethoxy)chlorodiazirine (9.0×10^{-5} s^{-1}, 25 °C),[11] and methoxychlorocarbene (1.34×10^{-4} s^{-1}, 30 °C).[6b] Each of these decompositions is believed to directly afford the alkoxyhalocarbene.[6b,7,11]

The preparative thermolysis of 1.9 M **9**, obtained from (*S*)-2-BuOH as shown in Scheme I, was carried out for 36 h at 25 °C in MeCN. We obtained a product mixture that was analyzed by capillary GC and GC-MS and quantitated with the aid of authentic materials. There was formed 89% of 2-chlorobutane (2-BuCl), 2% of 2-butenes,[19] 1.0% of 2-BuOH, and 4% of 2-butyl formate. In a duplicate thermolysis, the respective yields were 86%, 3%, 1%, and 5%.

The formation of 2-BuCl (**12**) can be rationalized with reference to Scheme II, where diazirine **9** affords 2-butoxychlorocarbene (**10**), which fragments to ion pair **11**. Product **12** derives from chloride return in **11**, or in a daughter ion pair (2-Bu$^+$ Cl$^-$) that has lost CO. Scheme II is rendered in analogy to previous analyses of the benzyl[7,8] and cyclopropylmethyl[11] systems; see above, eq 1 and ion pair **3**.

The minor products from the decomposition of **9** deserve brief comment. 2-Butanol probably results from the reaction of the ion pair with traces of water. Reaction of carbene **10** with water would ultimately give 2-butyl formate (4%). The butenes arise by loss of H$^+$ from the 2-butyl cation of the ion pair, but their low yield is noteworthy and reflects both the absence of a strong, external base during the decomposition of **9** and the weak basicity of the chloride anion in **11**. In contrast, ion pairs related to **6**, with R = 2-Bu and X = OAc, afford >50% of 2-butenes, even in CCl_4, illustrating the basicity of the acetate counterion.[20]

The optical activity of the product *mixture* was determined polarimetrically as α^{25}_D +0.255° (0.1 dm, *c* = 15.26, MeCN). If we take this rotation as due only to chloride **12** (see below), then, correcting for path length and concentration,[21] we obtain

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

(13) (a) Lowry, T. H.; Richardson, K. S. *Mechanism and Theory in Organic Chemistry*, 3rd ed.; Harper & Row: New York, 1987; pp 342 f. (b) Carey, F. A.; Sundberg, R. J. *Advanced Organic Chemistry*, Part A, 3rd ed.; Plenum Press: New York, 1990; pp 297 f.

(14) An earlier attempt to study the stereochemical course of solvolysis of **3** in MeOH or EtOH was inconclusive due to the extremely low intrinsic optical activity of PhCHDOMe or PhCHDOEt; see ref 8, notes 12 and 13.

(15) Michand, H.; Prietzel, H.; Lienhard, C. German Patent 1,915,686; *Chem. Abstr.* **1971**, *74*, 124906x.

(16) The conversion of 2-BuOH to **8** by the methodology of Scheme I was first realized in this laboratory by Dr. Joanna Włostowska.

(17) The optical purity is based upon $[\alpha]^{20}_D$ +13.9° (neat): Speziale, A. J.; Freeman, R. C. *J. Am. Chem. Soc.* **1960**, *82*, 909.

(18) Graham, W. H. *J. Am. Chem. Soc.* **1965**, *87*, 4396.

(19) The yield of butenes is a minimum value; no attempt was made to separately trap and quantitate these olefins. By material balance, their maximum yield was ~5%.

(20) White, E. H. *J. Am. Chem. Soc.* **1955**, *77*, 6014. See also: Moss, R. A.; Luchter, K. M. *J. Org. Chem.* **1972**, *37*, 1155.

$[\alpha]^{25}_D$ +16.7°, so that the optical purity of this sample of 2-BuCl is 48%.[22,23] Further correcting for the optical purity (80.6%) of the (*S*)-(+)-2-BuOH, from which the diazirine used in this experiment was made (cf., Scheme I), we would conclude that the (*S*)-(+)-2-BuCl (**12**) was formed with 59.6% *net retention* via the pathway of Scheme II.

However, in assuming that only (*S*)-(+)-**12** is responsible for the optical rotation of the reaction product mixture obtained from **9**, we ignore the 4% of 2-butyl formate that is most likely formed by water-scavenging of carbene **10** (followed by the loss of HCl). The formate, originating from 2-BuOH (Scheme II), would also be (*S*)-(+)[24] and 80.6% optically pure. We calculate that it would contribute +0.0114° to the +0.255° observed rotation of the reaction product.[25] The *corrected* 2-BuCl rotation would then be +0.244°, corresponding to $[\alpha]^{22}_D$ +16.0° (*c* = 15.26, MeCN). The uncorrected specific rotation is 16.7°, so that the difference is small. Carrying the correction through for the overall reaction stereochemistry, we conclude that the conversion of (*S*)-**9** to (*S*)-BuCl occurs with 57% net retention.[26] This value appears in Table I, expt 1.

In a duplicate thermal decomposition, 1.9 M (*S*)-**9**, derived from 2-BuOH of $[\alpha]^{23}_D$ +11.6° (neat), 83.5% optically pure,[17] afforded 86% of 2-BuCl and 5% of 2-butyl formate after 36 h in MeCN at 25 °C. The overall rotation was α^{24}_D +0.271° (0.1 dm, MeCN); Table I, expt 2. Corrected for the contribution (+0.016°) of the formate, the rotation due to the 2-BuCl is α^{24}_D +0.255°, corresponding to $[\alpha]^{24}_D$ +16.0° (*c* = 15.9, MeCN). The chloride is therefore 46% optically pure,[22,23] so that corrected for the optical purity of the initial 2-BuOH, the stereochemical course of this (*S*)-**9** → (*S*)-**12** conversion is 55% net retention, in excellent agreement with the result of expt 1, above.

It is always possible that an unknown optically active impurity has biased these results. However, we consider this to be unlikely. Not only is the mass balance in these experiments 95–96%, with the remainder probably volatile butenes, but capillary GC analysis failed to reveal significant quantities of other side products (except for the 2-butyl formate).

Net stereochemical retention of 55–57% is clearly consistent with the mechanism of Scheme II; ion pair **11**, formed by fragmentation of carbene **10**, would certainly collapse to 2-BuCl with retention. In the parallel case of the α-deuteriobenzyl ion pair **3**, chloride return occurs with 60–80% net retention.[8] In both cases, extremely rapid carbene fragmentations,[27] together with the absence of external nucleophiles, ensures that anion return with retention is the dominant mechanism.

Thermolysis of 9 in 1-Butanol. Diazirine **9** decomposed thermally in 1-butanol with $k = 1.78 \times 10^{-4}$ s^{-1} at 23 °C. This rate constant is slightly larger than that for the thermolysis of **9** in MeCN (1.48×10^{-4} s^{-1} at 30 °C). It is unlikely that this represents direct S_N2-like solvolysis at the *sec*-butyl residue of diazirine **9**, because it has been shown that an added nucleophile does not enhance displacement reactions at the *primary* cyclopropylmethyl carbon of the diazirine precursor of carbene **4**.[11] After 36 h at 25 °C in pure 1-butanol, the major products from **9** were 2-BuCl (44%) and 2-butyl 1-butyl ether (**13**), 36%, corresponding to a chloride/ether molar ratio of 1.25, as determined by calibrated capillary GC.[28]

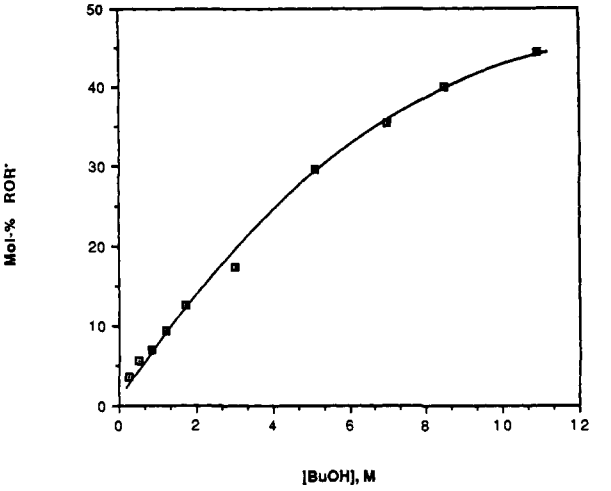
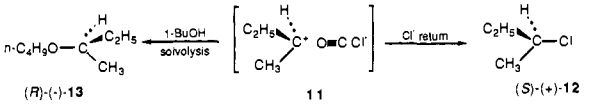


Figure 1. Mole percent ether **13** vs [1-butanol] for the thermolysis of diazirine **9** in acetonitrile at 25 °C. The balance of the product is 2-chlorobutane (**12**) in each run.

Scheme III



Products were identified by GC and GC-MS comparisons with authentic materials. Minor products included ~5% of butenes and 1% of 2-BuOH. Importantly, 2-butyl formate was absent, simplifying the stereochemical studies. As before, we did not quantitate the 2-butenes precisely; to account for mass balance, their yield could have been as high at 20%. Apparently, carbene **10** fragmented too rapidly to be trapped by the 1-butanol solvent;[27] there was no evidence for such products as *sec*-butyl di-*n*-butyl orthoformate, the end product of the reaction of **10** with 1-butanol. Orthoformates are stable under our reaction conditions.[7]

Figure 1 illustrates the dependence of the product distribution, expressed as mole percent of ether **13**, on the concentration of 1-butanol in MeCN. In each case, the balance of the product is chloride **12**, with (**12** + **13**) normalized to 100 mol %. The observed behavior is very similar to that found in the fragmentations of (benzyloxy)chlorocarbene (**2**) in MeOH/MeCN[7] and of (cyclopropylmethoxy)chlorocarbene (**4**) in EtOH/MeCN.[11] In each case, substantial chloride return persists, even in pure alcohol solvent. The limiting mole percent of RCl is 43% from **2** in MeOH,[7] 48% from **4** in EtOH,[11] and 56% from **10** in 1-BuOH.[28] These results can be reasonably interpreted with reference to Scheme III.

Here, fragmentation of carbene **10** again affords the CO-separated ion pair **11**, as in Scheme II. Now, however, in 1-butanol, the ion pair will partition between the return of chloride with retention and *solvolysis* by 1-butanol with net stereochemical *inversion* (see below).

Our observation that there is always a substantial fraction of cations within the ion pairs that are fated to undergo cation/anion recombination, that cannot be scavenged by a nucleophilic solvent, is consistent with the idea that some of the ion pairs are formed from cis-configured precursor carbenes (e.g. **14**).[7] These fragment so as to leave the Cl^- counterion in an appropriate relative ge-

(21) The [2-BuCl], here 0.526 g/mL in MeCN, was determined by capillary GC, calibrated with authentic 2-BuCl.

(22) Based upon $[\alpha]^{22}_D$ +34.8° (neat): Suga, S.; Segi, M.; Kitano, K.; Masuda, S.; Nakajima, T. *Bull. Chem. Soc. Jpn.* **1981**, *54*, 3611. See also: Goodwin, D. G.; Hudson, H. R. *J. Chem. Soc. B* **1968**, 1333. In our hands, (−)-2-BuOH, $[\alpha]^{23}_D$ −12.8°, 92.1% optically pure,[17] was converted by Suga's method to (*S*)-(+)-2-BuCl, $[\alpha]^{22}_D$ +32.0° (neat); see Experimental Section. This gives $[\alpha]^{22}_D$ +34.74° as the maximum rotation of 2-BuCl (after correction for the optical purity of the 2-BuOH), in very good agreement with the value cited by Suga.

(23) Control experiments with authentic optically active 2-BuCl showed that its specific rotation was essentially identical either neat or diluted to 0.15 g/mL in MeCN; viz., $[\alpha]^{22}_D$ +32.0° vs $[\alpha]^{23}_D$ +31.8°.

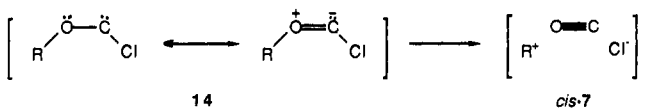
(24) Barroeta, N.; Maccoll, A.; Cavazza, M.; Congiu, L.; Fava, A. *Gazz. Chim. Ital.* **1972**, *102*, 467 report $[\alpha]^{25}_D$ +18.74° (neat) for (*S*)-2-butyl formate. See also: Pickard, R. H.; Kenyon, J.; Hunter, H. *J. Chem. Soc.* **1923**, 1.

(25) From GC analysis, the reaction product solution in MeCN contained 152.6 mg/mL of 2-BuCl and 7.56 mg/mL of the corresponding formate. The latter, on the basis of 80.6% optical purity and $[\alpha]^{25}_D$ +18.74°,[24] would contribute α = +0.0114° in a 0.1-dm polarimeter cell.

(26) We make no correction for the 1% yield of 2-butanol because the optical rotation of this product is unknown. At most, it could contribute less than ±1% to the observed rotation.

(27) (Benzyloxy)chlorocarbene cannot be trapped by alkenes; fragmentation is faster: Ho, G.-J.; Moss, R. A. Unpublished work.

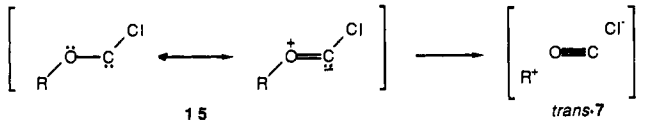
(28) In the present work, we used 1-BuOH, rather than MeOH or EtOH, to permit the complete separation of the chloride and ether products necessary for polarimetric studies.



14 cis-7

ometry for efficient recombination with retention with the R^+ cation.

Alternatively, a trans-configured carbene precursor (**15**) would fragment to ion pair *trans*-**7**, where the CO molecule would inhibit



15 trans-7

immediate recombination and favor solvolytic, rear-side, inverting capture of the cation.

There is good evidence for the existence of "isomeric" cis and trans oxachlorocarbenes in cold matrices[29] and for the persistence of alkylalkoxycarbenes on the subnanosecond time scale,[30] so that the fragmentations of RO–C–Cl could well engender CO-separated ion pairs with geometrical "memories" of their origins. Moreover, the present results with CO-containing ion pairs **7** are strikingly similar to previous findings with the related *nitrogen*-separated ion pairs **6** derived from alkanediazotates.[5] Not only do the latter, in parallel to **7**, exhibit return of the counterion with stereochemical retention and, in a nucleophilic solvent, competitive solvolysis with stereochemical inversion,[5] but they can also display geometry-based "memory effects". For example, the diazo ether R—N=N—OR′, where R = PhCH*Me and R′ = Et, can be generated in syn or anti forms. Decompositions via ion pairs **6** (X^- = EtO^-) afford ROEt with much more net retention (57%) when **6** arises from the *syn*-diazo ether than when it originates from the *trans*-diazo ether (9% net retention).[31]

The stereochemistry attending the thermolysis of **9** in *n*-butyl alcohol was ascertained after decomposing 11 mmol of the diazirine in 10 mL of the alcohol at 25 °C for 36 h. The diazirine was obtained (Scheme I) from (*S*)-2-butanol with $[\alpha]^{24}_D$ +12.2° (neat), 87.8% optically pure,[17] via isouronium salt (*S*)-**8**, $[\alpha]^{21}_D$ +19.1 (*c* = 9, MeOH). After decomposition, the product mixture, which contained 44% of chloride **12** and 36% of ether **13** by GC, was cooled to 0–5 °C and then fractionated over a 20-cm Vigreux column. The fraction collected at 10 °C/13 Torr consisted of **12** in 1-butanol; **13** in 1-butanol distilled at 18–20 °C/13 Torr. These distillates consisted only of **12** or **13** in 1-butanol, and their compositions were quantitated by capillary GC, calibrated with authentic materials.

The sample of chloride (*S*)-**12** had α^{24}_D +0.167° (*l* = 0.1 dm), corresponding to α^{24}_D +25.3° (*c* = 6.6, 1-butanol),[32] and an optical purity of 72.7%.[22] Correcting for the optical purity of the precursor (*S*)-2-butanol, the formation of **12** occurred with 83% *net retention*.

The accompanying sample of (*R*)-2-butyl 1-butyl ether (**13**) had α^{24}_D −0.057° (*l* = 0.1 dm), corresponding to $[\alpha]^{24}_D$ −12.1° (*c* = 4.7, 1-butanol), and an optical purity of 64.4%.[33] Correcting for the optical purity of the initial (*S*)-2-BuOH leads to a stereochemical result of 73% net *inversion* in the conversion of (*S*)-**9** to (*R*)-**13**. These data appear in Table I as expt 3.

In a duplicate experiment, (*S*)-**9** in 1-BuOH afforded 44% of chloride (*S*)-**12**, α^{25}_D +0.205°, $[\alpha]^{25}_D$ +24.7° (*c* = 8.3, 1-butanol), 71.0% optically pure,[22] corresponding to 81% net retention after correction for the optical purity (87.8%) of the initial (*S*)-2-BuOH. The companion ether, (*R*)-**13**, was formed in 34% yield and had α^{25}_D −1.11°, $[\alpha]^{25}_D$ −11.4° (*c* = 9.7, 1-butanol), 60.6% optically pure,[33] corresponding to 69% net inversion after correction for the optical purity of the initial 2-BuOH. These results appear as expt 4 in Table I.

The data in Table I agree well with the mechanistic concepts that underlie Schemes II and III. In the polar, but non-nucleophilic solvent, acetonitrile,[34] carbene **10** fragments to ion pair **11**, or perhaps a mixture of cis and trans ion pairs **7**. Cation/anion recombination occurs with ~56% net or ~78% overall retention, expts 1 and 2. As indicated above, this accords with the stereochemical behavior of the $PhCHD^+$ cation in the analogous fragmentation of [(α-deuteriobenzyl)oxy]chlorocarbene. Moreover, the results are consonant with both the general observations of ion pair return with retention[13] and with specific examples of this phenomenon with nitrogen-separated ion pairs **6**,[4,5] which are closely related to the present CO-separated ion pairs **7** or **11**.

Most importantly, expts 3 and 4 of Table I show that ion pair **11**, when generated by carbene fragmentation in a nucleophilic solvent (Scheme III), does indeed partition between return with retention and solvolysis with inversion. The ion pair return pathway to chloride **12** is characterized by ~82% net (~91% overall) retention and is preferred over solvolysis by a factor of 1.25. The solvolytic pathway affords 2-butyl 1-butyl ether (**13**) with ~71% net (~86% overall) inversion.

These results parallel the behavior of (e.g.) the nitrogen-separated ion pair **6**, where R^+ is the 2-octyl cation and X^- is hydroxide. In ^{18}O-labeled water, this ion pair yields 2-octanol-^{16}O by hydroxide return with 73% overall retention and 2-octanol-^{18}O by hydrolysis with 76% overall inversion.[5,35]

We also note that the stereochemical retention associated with anion return to chloride **12** from ion pair **11** is more complete (82% net) in the less polar solvent 1-butanol (expts 3 and 4) than in acetonitrile (56%, expts 1 and 2).[36] This is consistent with a shorter ion pair lifetime in 1-butanol, which affords a diminished opportunity for either escape to a solvent-separated ion pair[13] or cation rotation[4] within **11**. These processes would each favor racemization. Alternatively, one could argue that any 2-butyl cation that does reach the solvent-separated ion pair stage in the 1-butanol solvent is more likely to be scavenged as ether **13** than to return to chloride **12**. The chloride would therefore be more completely a product of (internal) return (hence formed with greater retention) in 1-butanol than in acetonitrile, where even the solvent-separated (racemic) ion pairs must largely return to chloride.

The sensitive stereochemical tests described here are thus fully in keeping with the anticipated properties of ion pair intermediates. In turn, this lends further support to the generality of the carbene fragmentation–ion pair mechanism (Scheme II) for the decompositions of alkoxychlorocarbenes **2**, **4**, and **10**.

Experimental Section

Instrumentation. Polarimetric readings were determined with a Perkin-Elmer Model 141 polarimeter, accurate to ±0.002° for 0.1-dm cells. Gas chromatography employed a Varian Model 3200 flame ionization unit and a Varian Model 4270 integrator. The capillary column was 25 M × 0.25 μM Chrompack, CP-Sil 5CB, chemically bonded dimethyl polysiloxane. Decomposition product mixtures were analyzed at column temperatures of 26 °C (Table I, expts 1 and 2) and 80 °C (expts 3 and 4). NMR spectra were determined on a Varian VXR 200 instrument, and chemical shifts are reported in δ, relative to Me_4Si.

2-Butylisouronium Chloride (8). This material was prepared as outlined in Scheme I. Chloroformamidinium chloride (mp 180 °C) was prepared from aqueous cyanamide and concentrated HCl at −10 °C,

(29) Kesselmayer, M. A.; Sheridan, R. S. *J. Am. Chem. Soc.* **1986**, *108*, 99, 844.

(30) Sheridan, R. S.; Moss, R. A.; Wilk, B. K. Shen, S.; Włostowski, M.; Kesselmayer, M. A.; Subramanian, R.; Kmiecik-Ławrynowicz, G.; Krogh-Jespersen, K. *J. Am. Chem. Soc.* **1988**, *110*, 7563.

(31) Moss, R. A.; Powell, C. E. *J. Am. Chem. Soc.* **1976**, *98*, 283. These reactions were carried out in CH_2Cl_2/Et_2O. In the absence of a nucleophilic solvent, only the ROEt recombination product was formed.

(32) Control experiments with authentic (*S*)-**12**, $[\alpha]^{25}_D$ +32.0° (neat) showed that the specific rotation was essentially unchanged upon dilution in 1-butanol: $[\alpha]^{22}_D$ +32.3° (*c* = 10, 1-butanol) and $[\alpha]^{25}_D$ +32.1° (*c* = 20, 1-butanol).

(33) Based upon $[\alpha]^{24}_D$ +18.8° for optically pure (*S*)-**13** synthesized by the reaction of (*S*)-2-BuOH, NaH, and 1-BuBr. See the Experimental Section for details.

(34) We observed no Ritter-like products that could have come from reactions of the 2-butyl cation with acetonitrile.

(35) Moss, R. A.; Fritz, A. W.; Emery, E. M. *J. Org. Chem.* **1971**, *36*, 3881. Moss, R. A.; Reger, D. W.; Emery, E. M. *J. Am. Chem. Soc.* **1970**, *92*, 1366.

(36) The dielectric constants of 1-butanol and acetonitrile are 17.5 and 37.5, respectively: *Lange's Handbook of Chemistry*, 13th ed.; Dean, J. A., Ed.; McGraw-Hill: New York, 1985; pp 10–103 f.

followed by filtration of the desired salt and vacuum drying.[37] Then, 4.5 g (61 mmol) of 2-butanol and 2.3 g (20 mmol) of the formamidinium salt were stirred under reflux for 21 h. The mixture was cooled to room temperature, washed with 15 mL of Et_2O, and concentrated under vacuum. The residue was dissolved in 2 mL of MeOH and chromatographed over silica gel with 1.5:1 CH_2Cl_2/MeOH eluent. We obtained 1.29 g (8.4 mmol, 42%) of isouronium salt **8** as a highly hygroscopic, glassy solid (under vacuum), that fused to a slightly yellow oil in the atmosphere.

^{1}H NMR (DMSO-d_6): 0.84 (t, J = 7 Hz, 3 H, CH_2CH_3); 1.21 (d, J = 6 Hz, $CHCH_3$); 1.45-1.65 (m, 2 H, CH_2); 4.75-4.95 (m, 1 H, CH); 8.67 (br s, 4 H, $2N^+H_2$).

Anal. Calcd for $C_5H_{13}ClN_2O{\cdot}0.1H_2O$: C, 38.9; H, 8.62; N, 18.2; Cl, 23.0. Found: C, 38.4; H, 8.56; N, 18.5; Cl, 23.4.

Conversions of (*S*)-2-butanol to (*S*)-**8** were carried out analogously. Detailed descriptions of the optical rotations of these materials appear in the text.

3-(2-Butoxy)-3-chlorodiazirine (9). The Graham oxidation[18] was carried out on 1.29 g (8.4 mmol) of isouronium salt **8**. The salt was dissolved in 5 mL of DMSO; then, 15 mL of pentane and 0.1 g (2.4 mmol) of LiCl were added. The mixture was stirred and cooled to 5 °C while 220 mL of 12.5% aqueous NaOCl was added dropwise. The reaction temperature was kept at 10-13 °C during the addition. Stirring was continued for 20 min at 13 °C after addition of the hypochlorite. Then, 150 mL of ice water was added, the pentane layer was separated, the aqueous layer was extracted with 10 mL of pentane, and the organic extracts were combined. The resulting pentane solution of **9** was washed with 50 mL of brine and then dried over $CaCl_2$. Higher boiling solvents (MeCN, 1-butanol) could then be added and pentane removed at 0 °C under aspirator vacuum, to afford solutions of diazirine **9** in other solvents. The UV and NMR spectra of **9** are described above; it was too unstable to chromatograph. (*S*)-**9** was prepared from (*S*)-**8** in the same way.

(*S*)-2-Chlorobutane (12). (*R*)-(-)-2-Butanol (Aldrich, $[\alpha]^{23}_D$ -12.8° (neat)), 6.2 mL (5.0 g, 67.5 mmol), and 4.6 mL of dichlorophenylphosphine (Aldrich, 6.1 g, 34 mmol) were combined and stirred for 1 h at 0 °C. The product was isolated by vacuum distillation at 0.5 Torr from the solid residue, followed by conventional distillation (bp 68 °C). We obtained 1.75 g (19 mmol, 56% based on phosphine) of (*S*)-2-chlorobutane, $[\alpha]^{22}_D$ +32.0.[22]

(*S*)-2-Butyl 1-Butyl Ether (13). To a cooled (~10 °C) suspension of 1.68 g (70 mmol) of NaH in 20 mL of THF was added 5.2 mL (6.6 g, 48 mmol) of 1-bromobutane. Then, 5.6 mL (4.5 g, 61 mmol) of (*S*)-2-butanol (Aldrich, $[\alpha]^{24}_D$ +12.2° (neat)) was added dropwise with stirring. The mixture was warmed to room temperature and then stirred under reflux for 16 h. The product mixture was then cooled in an ice bath, and 25 mL of water was slowly added. The organic phase was separated, combined with 2 × 10 mL ether extracts of the aqueous phase, washed with water, and dried over $CaCl_2$. Volatiles were stripped at <18 °C using an aspirator vacuum, and the residue was distilled over a 20-cm Vigreux column. The desired **13** was collected at 121-122 °C. We obtained 5.5 g (42 mmol, 88% based on bromobutane) of **13** $[\alpha]^{24}_D$ +16.5° (c = 20, 1-butanol). Corrected for the optical purity of the initial 2-butanol[17] (87.8%), the specific rotation of optically pure **13** should be 18.8° in 1-butanol.

NMR (DMSO-d_6): 0.75-0.9 (m, 6 H, 2 superimposed CH_2CH_3); 0.98 (d, J = 6 Hz, $CHCH_3$); 1.2-1.5 (m, 6 H, $3CH_2$); 3.05-3.3 (m, 2 H, C^*OCH_2); 3.3-3.45 (m, 1 H, CH).

Anal. Calcd for $C_8H_{18}O$: C, 73.8; H, 13.9. Found: C, 74.0; H, 13.9.

Decomposition Reactions of 9. The conditions and analyses for the decompositions of **9** in acetonitrile or 1-butanol are described in detail in the Results and Discussion. Both solvents were Aldrich, spectroscopic grade. In addition, the acetonitrile was dried over P_2O_5 and distilled prior to use. All polarimetric work is also presented above, the results are collected in Table I.

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(37) The precise description is given in Example 5 of ref 15.

Main Chain and Side Chain Chiral Methylated Somatostatin Analogs: Syntheses and Conformational Analyses

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Abstract: We have developed an integrated approach for investigating the "bioactive conformations" of the main chain and side chains for the somatostatin analog c[Pro^6-Phe^7-D-Trp^8-Lys^9-Thr^{10}-Phe^{11}]. A series of analogs have been synthesized incorporating α-methylated and β-methylated residues at positions 7, 8, and 11. These analogs display dramatic differences in in vitro binding affinities for somatostatin receptors. Using 500-MHz ^{1}H NMR and computer simulations, we have assessed the effect of main chain and side chain chiral methylations on the overall structure. The analyses of the changes of side chain topologies and subsequent binding affinities in the β-methylated analogs have provided definitive evidence about the "bioactive conformation" of the side chains of Phe^7, Trp^8, and Phe^{11}. The analyses of the α-methylated analogs have defined a "folded" feature for the peptide backbone. From this study, we have proposed a binding "pocket" for somatostatin analogs which consists of the side chains of Trp^8 and Lys^9, the peptide backbone, and the side chain of Phe^{11} in a "folded" topochemical array. In this "folded" conformation, the Trp^8 side chain assumes the trans rotamer, while the Lys^9 side chain assumes the gauche-rotamer, thus allowing a close proximity between these two side chains. The Phe^{11} side chain assumes the trans rotamer. The peptide backbone adopts a β II' turn about Trp^8-Lys^9 and a β VI turn about Phe^{11}-Pro^6. The overall structure is folded about Phe^7 and Thr^{10} residues assuming a C_7 conformation for their ϕ and ψ torsions. This model should have important implications on the future design of peptide or nonpeptide ligands with somatostatin-like activities.

Introduction

Initially, somatostatin was known for its ability to inhibit the release of growth hormone.[1] Since then, somatostatin has also been shown to suppress the release of many other bioactive molecules, including glucagon, insulin, gastrin, and secretin.[2-5]

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