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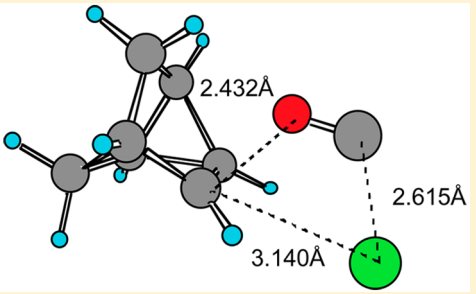
Adventures in Reactive Intermediate Chemistry: A Perspective and Retrospective

Robert A. Moss*

Department of Chemistry and Chemical Biology, Rutgers University, The State University of New Jersey, New Brunswick, New Jersey 08903, United States

ABSTRACT: I review aspects of my research on reactive intermediates, specifically the physical organic chemistry of carbenes and carbocations. The topics treated include carbenoids, carbenic philicity, absolute rates of carbene/alkene additions, the diazirine exchange reaction and derived carbenes, carbene equilibria, carbocations from diazotates, and carbocations from alkoxychlorocarbenes. The essay concludes with observations on the protean nature of physical organic chemistry.



1. GRATITUDE

The James Flack Norris Award in Physical Organic Chemistry of the American Chemical Society was established in 1963, the same year that I received my Ph.D. in chemistry from the University of Chicago. The first three recipients, Christopher K. Ingold, Louis P. Hammett, and Saul Winstein, were my early heroes, founders of physical organic chemistry whose work I had studied as a graduate student. Later, my doctoral and postdoctoral mentors, Professors Gerhard L. Closs and Ronald Breslow, received this award. More recently, my good friends Nick Turro, Josef Michl, Peter Stang, Barry Carpenter, Wes Borden, and Matt Platz were similarly honored. It is with a large dose of humility and a dash of quiet pride that I now find my name added to theirs.

Although my chemical lineage traces back to Liebig, a more immediate ancestry focuses on Professors J. P. Collman, Gerhard L. Closs, and Ronald Breslow. In the summer of 1959, as a NSF undergraduate scholar in Jim Collman's lab at Chapel Hill, I first experienced the suspense and rewards of chemical research. Next, as a graduate student in Gerhard Closs's group at the University of Chicago, I learned and survived the rigors of mechanistic analysis. Lastly, as a postdoctoral in Ron Breslow's lab at Columbia, I absorbed an enthusiasm for chemistry that has lasted for decades. My gratitude to these mentors does not diminish with time.

Of course, little of my scientific work could have been accomplished without the constant and continuing contributions of my graduate students and postdoctoral associates. There have been more than a hundred of them, over half a century, too numerous to list (other than in the references) but absolutely essential to the research described herein. My debt to these associates is boundless.

Three collaborators do require special mention: Dr. Lei Wang, Research Assistant, who has been with my laboratory over the past decade, and my Rutgers colleagues, Professors Karsten Krogh-Jespersen and Ronald R. Sauers. Many years ago, Gerhard Closs told me that he doubted I would become a theoretical chemist. He was certainly correct. Fortunately, close coordination with Karsten and Ron has compensated for this lack and undergirded our experimental efforts with theoretical and computational insights and infrastructure.

Research is expensive. I have been fortunate to secure financial support from the National Institutes of Health, The Petroleum Research Fund, The Army Research Office, and NATO, for which I am most grateful. To the National Science Foundation, which has continuously funded my laboratory since 1965, I extend my deepest thanks.

My heartfelt appreciation goes to Rutgers University, my colleagues, and the Department of Chemistry & Chemical Biology for their unfailing support over nearly six decades. Finally, I am grateful to my wife, Dr. Sandra Moss, and to our sons, Kenneth and Daniel, for many years of love and understanding.

2. INTRODUCTION

Søren Kierkegaard observed: "Life can only be understood backwards, but it must be lived forwards." In a more modern formulation of this insight, Steve Jobs noted that "You can't connect the dots looking forward: you can only connect them looking backwards."

I believe these dicta of Kierkegaard and Jobs apply equally well to scientific research. One goes forward from experiment to experiment, from project to project, but only by looking backward do we discern the logic that drove the forward motion. In retrospect, the stages are arrayed like stepping-stones across a stream, but the forward direction often required leaps of faith.

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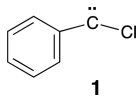
In this essay, I focus mainly on our work in reactive intermediate chemistry, especially carbenes and carbocations. In the interest of concision, I omit discussions of our extensive research on micelles,[1] liposomes,[2] and phosphate ester cleavage,[3] offering only several references as examples. Also, there is necessarily some overlap with a "scientific autobiography" published in early 2016.[4]

I was introduced to carbenes in 1961, while a graduate student at the University of Chicago, when Professor Michael Dewar asked me to write a review of Jack Hine's splendid studies of haloform hydrolysis.[5] Hine's analysis of the reactivity and fleeting intermediacy of the dihalocarbenes fascinated me. Subsequently, for a required research proposition, I suggested a study of substituent effects on carbenic selectivity in additions to alkenes. I discussed this proposal with Professor Gerhard Closs, who had already undertaken a study of the selectivity of chlorocarbene generated by the reaction of butyllithium with methylene chloride.[6] He agreed to let me pursue my ideas in his laboratory, and so I began my graduate research under his direction.

3. EARLY RESEARCH AND CARBENOIDS

Initially, I examined the generation of phenylchlorocarbene (PhCCl, **1**) from benzal chloride and potassium *tert*-butoxide or methyllithium.[7] Reasonable yields of cyclopropanes could be obtained by the addition of PhCCl to alkenes, but we soon discovered that the addition of arylcarbenes was better suited to our purpose because they could be generated from both halide and diazo precursors (see below). Nevertheless, as we shall see, PhCCl was destined to play a recurring role in my research.



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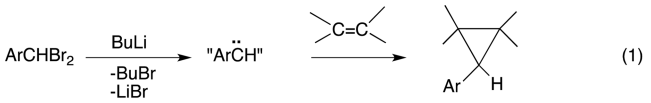
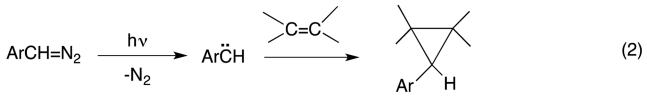
Reactions of ring-substituted benzal bromides with butyllithium in pentane apparently generated arylcarbenes, which added to alkenes, affording cyclopropanes (eq 1).[8] The same





cyclopropanes were produced when the analogous aryldiazomethanes were photolyzed in the alkenes (eq 2).[8] However, the alkene *selectivity* of the reactive intermediates depended on their source; the intermediates of eq 1 and eq 2 manifested different selectivities and had to be different. We suggested that photolyses of the aryldiazomethanes afforded free arylcarbenes, ArCH, whereas the reactions of $ArCHBr_2$ with alkyllithiums proceeded through α-halolithium *carbenoids* (ArCHLiBr). We envisioned the reaction of an alkene with ArCHLiBr as a process in which the alkene's π-electrons displaced Br---Li from ArCHLiBr, much as in a S_N2 reaction. We then introduced "carbenoid" as a *noun*, "for the description of intermediates which exhibit reactions qualitatively similar to those of carbenes without necessarily being free divalent carbon species,"[8] cf. Figure 1.

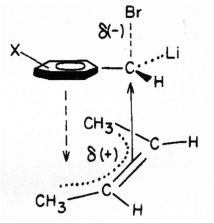
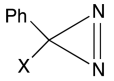


Figure 1. Proposed transition state for addition of ArCHLiBr carbenoid to *cis*-butene. Reprinted from ref 8. Copyright 1964 American Chemical Society.

The carbene/carbenoid dichotomy spiraled back to phenylchlorocarbene in the following way. In 1965, Bill Graham reported that various amidines could be converted to halodiazirines by treatment with aqueous sodium hypochlorite or hypobromite and sodium chloride or bromide.[9] Thus, benzamidine afforded phenylchlorodiazirine or phenylbromodiazirine, **2**, X = Cl or Br. Photolysis of, e.g., phenylbromodiazirine (**2**, X = Br) in alkenes gave good yields of the appropriate cyclopropanes, attributed to the intermediacy of PhCBr.[10] However, the olefinic selectivity of *this* PhCBr was *not* identical to that of the α-elimination PhCBr produced by the reaction of benzal bromide (**3**) with potassium *tert*-butoxide.[10,11] We suggested that the latter species might be a weak complex of PhCBr with either KBr or KO-*t*-Bu.[10] In other words, a carbenoid. A similar duality afflicted "phenylchlorocarbene" generated by photolysis of the diazirine (**2**, X = Cl) or from benzal chloride (**4**) and KO-*t*-Bu. Again, the carbenic intermediates differed in their selectivities toward alkenes, although the differences were relatively minor.[12]



2

$PhCHBr_2$ $PhCHCl_2$

3 **4**

Resolution was found in the use of the macrocyclic polyether 18-crown-6 to scavenge and complex[13] K^+ during the KO-*t*-Bu α-elimination reactions of the benzal halides.[14] In the presence of 18-crown-6, alkene selectivities of the PhCBr and PhCCl produced by either the photolyses of phenylhalodiazirines **2** or the reactions of KO-*t*-Bu with benzal halides **3** or **4** became identical: the same species was produced by either generative method.

There were two important implications of these results. (1) Free carbenes could be obtained by base-mediated α-eliminations in the presence of cation-scavenging crown ethers. (2) The phenylhalocarbenes photogenerated from the diazirines were not in excited states, nor were they excited states of diazirines or derived diazo compounds masquerading as carbenes. Later, after we had learned how to prepare phenylfluorodiazirine (**2**, X = F), we were similarly able to show that the PhCF generated by photolysis of this diazirine or by the action of KO-*t*-Bu on PhCHBrF became identical when the α-elimination reaction was performed in the presence of 18-crown-6. In the absence of the crown ether, however, the intermediates differed.[15]

4. CARBENIC PHILICITY

In the era before the advent of laser flash photolysis (LFP), absolute rate constants for carbene−alkene addition reactions were generally unavailable. Instead, *relative* rate constants, derived from competition reactions between pairs of alkenes,

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provided quanititative data on carbenic reactivity, selectivity, and philicity.[16] This methodology, first applied to CCl_2 by Doering[17] and to CBr_2 by Skell,[18] indicated that both of these dihalocarbenes were electrophilic, reacting most rapidly with the most highly alkylated olefins.

We desired a more general measure of carbenic philicity and set about constructing it in the following manner. We first selected a "standard" set of olefinic substrates: 2,3-dimethyl-2-butene, 2-methyl-2-butene, isobutene, *cis*-2-butene, and *trans*-2-butene. CCl_2 was chosen as the "standard" carbene. We then defined the *carbene selectivity index*, m_{CXY}, as the least-squares slope of log $(k_i/k_{isobutene})$ for CXY versus log $(k_i/k_{isobutene})$ for CCl_2, with all data measured for "free" singlet carbenes at 25 °C.[19] Increasing values of m_{CXY}, relative to m_{CCl2} (defined as 1.00), indicated increasing electrophility of CXY.

The m_{CXY} values of nine carbenes could be correlated by the dual-substituent parameter (eq 3)[20] derived by multiple linear regression analysis[21] of m_{CXY} on σ_i and σ_{R+}, the inductive and resonance substituent parameters of X and Y. Figure 2 illustrates the correlation afforded by eq 3.

$$m_{CXY} = -1.10\Sigma_{X,Y}\sigma_{R^+} + 0.53\Sigma_{X,Y}\sigma_I - 0.31 \quad (3)$$

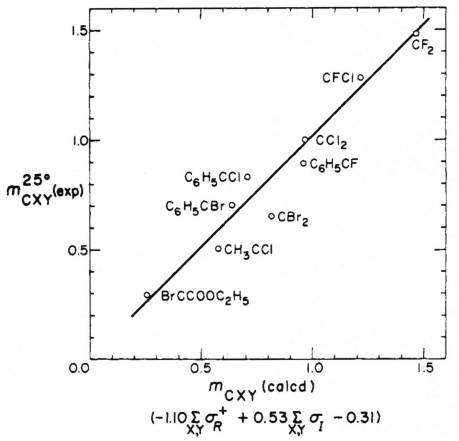

Figure 2. Correlation of experimental and calculated values of m_{CXY}. The correlation coefficient, r = 0.971. Reprinted from ref 20. Copyright 1977 American Chemical Society.

Equation 3 links the carbene's structure with its selectivity, enables the categorization of the philicities of known carbenes, and helps predict the philicity of new carbenes. However, this equation is an empirical correlation that has been "trained" with electrophilic carbenes and normalized to the electrophilic CCl_2. What would it predict for the known nucleophilic dimethoxycarbene, $(MeO)_2C$,[22] which adds only to electron-deficient alkenes and does not add to the alkylethylenes of our standard set? Inserting the σ_I and σ_{R+} values for MeO into eq 3 yields $m_{(MeO)2C}$ = 2.22. This high value suggests that $(MeO)_2C$ should be much more selective than CCl_2 (m = 1.00), but it is only a "virtual" selectivity index because $(MeO)_2C$ does not add to the simple alkylethylenes of our standard set. CF_2, which does add to the standard alkenes, has m = 1.48. What can we say about the philicity of carbenes with 1.48 < m_{CXY} < 2.22?

We imagined that carbenes in this realm might be *ambiphiles*, exhibiting electrophilic selectivity toward electron-rich alkenes and nucleophilic selectivity toward electron-poor alkenes. Indeed, methoxychlorocarbene, MeOCCl, with m_{calcd} = 1.59, proved to be an ambiphile.[23] Table 1 contrasts the relative rates of addition of electrophilic CCl_2 and ambiphilic MeOCCl to electron-rich and electron-poor alkenes.[24]

Table 1. Relative Addition Rates of Carbenes

alkene	k_{rel} MeOCCl[a]	k_{rel} CCl_2[b]
$Me_2C{=}CMe_2$	12.6	78.4
$Me_2C{=}CH_2$	5.43	4.89
tr-MeCH=CHMe[c]	1.00	1.00
$CH_2{=}CHCOOMe$	27.7	0.060
$CH_2{=}CHCN$	54.6	0.047

[a]Generated by photolysis of the diazirine at 25 °C; ref 23. [b]Generated thermally at 80 °C from $PhHgCCl_2Br$; ref 24. [c]Standard alkene.

Note that the reactivity of CCl_2 steadily decreases as the alkenes morph from electron-rich $Me_2C{=}CMe_2$ and $Me_2C{=}CH_2$ to electron-poor $CH_2{=}CHCOOMe$ and $CH_2{=}CHCN$. In contrast, the reactivity of MeOCCl exhibits an inflection at *trans*-butene and then sharply *increases* with the electron-poor alkenes. Experimentally, MeOCCl is an ambiphile.[23] The closely related phenoxychlorocarbene (m_{calcd} = 1.49) also behaves as an ambiphile in additions to alkenes.[25]

Despite its utility in unifying the carbene selectivity spectrum,[23] eq 3 remains an empirical correlation.[20] Therefore, characterizations of carbenic philicity extrapolated from eq 3 should be considered qualitative, and not definitive. For example, when provoked by the very electron-deficient alkene α-chloroacrylonitrile, CCl_2 manifests latent nucleophilic properties,[26] and fluoromethoxycarbene (FCOMe) with m_{calcd} = 1.85 is predominantly nucleophilic rather than ambiphilic.[27]

A more incisive analysis of carbenic philicity is available via frontier molecular orbital theory.[28−31] For singlet carbene−alkene additions, the principal orbital interactions involve the vacant carbene p (LUMO) with the filled alkene π (HOMO) and the filled carbene σ (HOMO) with the vacant alkene π^* (LUMO); cf. Figure 3.[28,30,32] Stabilization of the addition

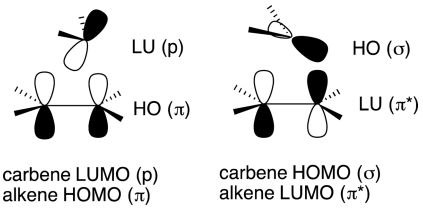

Figure 3. Frontier molecular orbital interactions in carbene/alkene additions. Reprinted from ref 31. Copyright 2012 American Chemical Society.

reaction's transition state (TS) depends *inversely* on the magnitude of $\Delta\varepsilon$, the *differential* energies of these two sets of interacting orbitals: the lower $\Delta\varepsilon$, the more the TS is stabilized, the lower the activation energy for addition, and the faster the reaction.[31]

Quantitative expression can be given to these ideas by eqs 4 and 5, which represent the differential energies of the orbital interactions.[31,32] If the "electrophilic" term, ΔE_E, is smaller than the "nucleophilic" term, ΔE_N, then the TS will be dominated by the carbene p/alkene π orbital interaction, and the carbene's expressed philicity will be electrophilic (e.g., CCl_2). Conversely, if ΔE_N is less than ΔE_E, the TS will be dominated by the carbene σ/alkene π^* orbital interaction, and

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the carbene's expressed philicity will be nucleophilic (e.g., $(MeO)_2C$). Finally, if $\Delta E_E \sim \Delta E_N$, neither orbital interaction will dominate and the carbene will be ambiphilic, able to react with electron-rich alkenes as an electrophile or electron-poor alkenes as a nucleophile (e.g., MeOCCl). Carbene and alkene orbital energies can be calculated or measured and inserted into eqs 4 and 5, thus enabling a broad and general analysis of carbenic philicity in additions to alkenes.[33]

$$\Delta E_E = \varepsilon_{CXY}{}^{LU} - \varepsilon_{C=C}{}^{HO} = p - \pi \quad (4)$$

$$\Delta E_N = \varepsilon_{C=C}{}^{LU} - \varepsilon_{CXY}{}^{HO} = \pi^* - \sigma \quad (5)$$

5. ABSOLUTE RATES OF CARBENE/ALKENE ADDITIONS

Here I encountered one of those turning points in a research career that is best understood in retrospect. In the autumn of 1978, I was diagnosed with Hodgkin's disease. After two months of radiotherapy in early 1979, I was at low ebb, both physically and emotionally. A *deus ex machina* appeared in the person of Columbia University's Nick Turro. At a Gordon Conference that summer, Nick told me that his group had constructed a nanosecond laser flash photolysis (LFP) system with which he thought carbenes could be directly observed in solution. Which carbene would I recommend to test this conjecture?

I immediately suggested PhCCl because it could be photochemically generated from phenylchlorodiazirine,[12] with the latter readily available from benzamidine.[9] Moreover, the phenyl group of PhCCl would provide a spectroscopic "handle" to monitor the carbene. Thus, began a delightful and (for me) a revivifying collaboration.

LFP of phenylchlorodiazirine provided PhCCl (λ_{max} = 295 nm in isooctane solution at 23 °C). Quenching of the carbene by added alkenes afforded absolute rate constants for the carbene additions. For example, k_{addn} varied from 1.3×10^8 M^{-1} s^{-1} with tetramethylethylene (TME) to 1.3×10^6 M^{-1} s^{-1} with 1-hexene, demonstrating that the addition rates were both slower than diffusion and responsive to changes in alkene structure.[34]

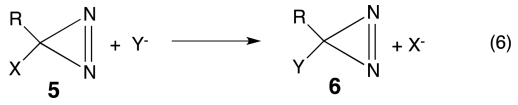
Of course, our ability to measure k_{addn} meant that we could also determine the activation parameters for these additions by studying k_{addn} as a function of temperature. We found that E_a for the addition of PhCCl to 1-hexene was ~1 kcal/mol.[35] Surprisingly, E_a measured for PhCCl addition to the more reactive TME was *negative* at −1.7 ± 0.5 kcal/mol.[35] A more general study of k_{addn} for additions of ArCX (X = Br, Cl, or F) to TME and 1-hexene reinforced our initial findings: negative values of E_a and $\Delta H^{\ddagger}$ were observed for carbene additions to TME, while positive values were found with 1-hexene. All the reactions were dominated by $\Delta S^{\ddagger}$ (ranging from −22 to −29 eu), leading to positive values of $\Delta G^{\ddagger}$ (ranging from 5 to 11 kcal/mol).[36]

Determinations of carbene/alkene addition rate constants and activation parameters are now routine and fundamental to the correlation of carbenic structure and reactivity, but what is the origin of the negative activation energies and enthalpies? Our preferred explanation was developed by Houk et al., who argued that the carbene/alkene additions were so exothermic that enthalpy decreased all along the reaction coordinate, leading to negative values of E_a and $\Delta H^{\ddagger}$. On the other hand, unfavorable entropic factors led to very negative values of $\Delta S^{\ddagger}$ and, therefore, to maxima on the free energy surface and positive values of $\Delta G^{\ddagger}$.[37]

Deriving from this interpretation, a recipe for enhanced negative activation energy would comprise a very reactive, highly electrophilic carbene and a similarly reactive, highly nucleophilic alkene. Indeed, the addition of 3,5-dinitrophenylchlorocarbene to tetramethoxyethylene exhibits $E_a \approx -10$ kcal/mol.[38]

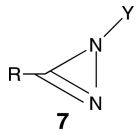
6. DIAZIRINE-EXCHANGE REACTION AND DERIVED CARBENES

The hypochlorite or hypobromite oxidation of amidines readily affords chloro- or bromodiazirines,[9] but the corresponding fluorodiazirines are not analogously available. We were fortunate to find that the halodiazirines obtained from the Graham reaction could undergo nucelophilic substitution, affording new diazirines via a *diazirine exchange* reaction (eq 6).[39]



5 6 (6)

Thus, reaction of **5** (e.g., R = aryl, X = Br) with tetrabutylammonium (TBA) fluoride afforded fluorodiazirine **6** (Y = F).[40] Similarly, reaction of **5** (R = Ph, X = Br) with NaOMe gave phenylmethoxydiazirine **6** (R = Ph, Y = OMe).[41] With hard nucleophiles, such as fluoride or methoxide, the mechanism of these diazarine-exhange reactions appears to involve successive S_N2' attacks on **5**, initially affording an intermediate isodiazirine **7** and subsequently diazirine **6**.[42] With softer nucleophiles, such as acetate or azide, diazirine exchange involves radical intermediates.[43,44]



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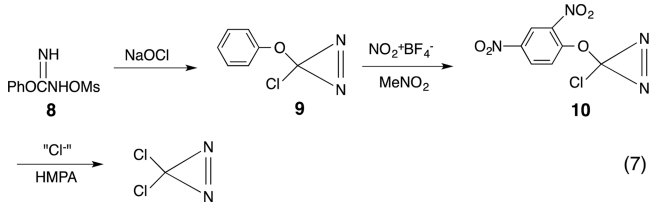
The diazirine exchange reaction yields photochemical precursors for many previously unvisualized carbenes.[40] For example, methoxychlorodiazirine[9] (**5**, R = MeO, X = Cl) reacts with NaOMe to give dimethoxydiazirine (**6**, R = Y = OMe), precursor of the archetypal nucleophilic dimethoxycarbene $(MeO)_2C$.[45] This carbene, which could be generated by LFP, absorbs at λ_{max} = 255 nm in pentane. Its rates of reaction with methanol and electron-deficient alkenes were determined.[45]

The diazirine exchange process provided access to other key carbenes, cf. eq 7. Here, Graham oxidation of phenylisourea



8 9 10 (7)

mesylate (**8**) gave phenoxychlorodiazirine (**9**). Nitration of the phenyl moiety with nitronium tetrafluoborate then gave the 2,4-dinitrophenoxychlorodiazirine (**10**), where the dinitrophenoxy unit is primed to function as a leaving group. Indeed, reaction of **10** with a blend of chloride nucleophiles yielded

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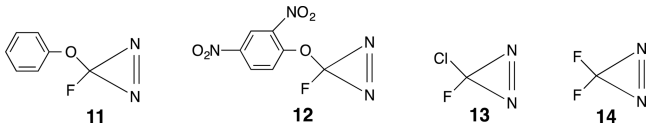
dichlorodiazirine,[46] precursor of dichlorocarbene, the iconic intermediate of Hine; cf. eq 7.[5]

Furthermore, diazirine exchange of **9** with fluoride gave phenoxyfluorodiazirine, **11**. Dinitration to **12**, followed by treatment with TBACl gave chlorofluorodiazirine **13**,[47] whereas analogous diazirine exchange with TBAF afforded difluorodiazirine, **14**.[48]



We thus obtained precursors to chlorofluorocarbene (CClF)[47] and difluorocarbene (CF_2), a paradigmatic electrophilic carbene.[48] By LFP of the appropriate diazirines we obtained CCl_2, CClF, and CF_2, enabling the first measurements of absolute rate constants and activation parameters for their additions to alkenes.[47−49]

Additions of these dihalocarbenes to several alkenes with varying degrees of alkylation were all rapid. For example, the fastest reaction (CCl_2 + $Me_2C{=}CMe_2$) had k_{addn} = 4.7 × 10^9 M^{-1} s^{-1}, whereas the slowest (CF_2 + $CH_2{=}CHC_4H_9$) exhibited k_{addn} = 2.4 × 10^6 M^{-1} s^{-1}, a "spread" of ∼2000. With these electrophilic carbenes, k_{addn} increased as expected with increasing alkene alkylation, although differences toward a given carbene were small. Carbene reactivity followed the order CCl_2 > CFCl > CF_2, inverse to computed measures of carbenic stability.[39b]

Measurements of k_{addn} as a function of temperature gave activation parameters for the dihalocarbene−alkene additions;[48,49] some of this data appears in Table 2.

Examination of Table 2 confirms several expectations. (1) With each alkene, E_a and $\Delta H^{‡}$ increase in the order of carbenic stability: CF_2 > CFCl > CCl_2. (2) With a given dihalocarbene, E_a and $\Delta H^{‡}$ decrease as olefin alkylation increases, in keeping with the electrophilic nature of these carbenes. (3) Additions of the carbenes to TME are dominated by entropy ($-T\Delta S^{‡}$ > $\Delta H^{‡}$), whereas additions to cyclohexene and 1-hexene are dominated by enthalpy ($\Delta H^{‡}$ > $-T\Delta S^{‡}$).

An unexpected and potentially important observation is the appearance of *compensation*:[50] a persistent increase in $\Delta S^{‡}$ that partners a corresponding increase in $\Delta H^{‡}$ for the additions of the three carbenes to each alkene. A similar phenomenon attends the additions of arylchlorocarbenes[51] and (*N*-methyl-3-pyridinium)chlorocarbene[52] to alkenes. As a result, $-T\Delta S^{‡}$ counters the influence of $\Delta H^{‡}$ on $\Delta G^{‡}$, which varies relatively little.

For example, from the top to the bottom of Table 2, $\Delta H^{‡}$ increases by 9.2 kcal/mol, but $\Delta G^{‡}$ increases only by 4.4 kcal/mol. Compensation might originate in dynamic effects peculiar to these carbene−alkene additions and be better understood in terms of reaction trajectories rather than classical transition state theory.[32,51,52]

7. CARBENE EQUILIBRIA

The signature reaction of Hine's mechanism for the hydrolysis of chloroform is eq 8.[5]

$$CCl_3^- \overset{K}{\rightleftharpoons} :CCl_2 + Cl^- \tag{8}$$

LFP of dichlorodiazirine in 1:1 MeCN−CH_2Cl_2 solution containing 0.9 M TBACl affords a weak absorbance for CCl_3^- at 328 nm in accord with the reverse of eq 8.[53,54] Unfortunately, the equilibrium constant (K) could not be determined because the absorbance of CCl_2 in the solution is too weak under our LFP conditions. An *indirect* determination of K ∼ 10 M^{-1} is possible for the equilibrium of eq 9 involving CCl_2Br^- (388 nm).[53]

$$:CCl_2Br^- \rightleftharpoons CCl_2 + Br^- \tag{9}$$

The *direct* extraction of K for halocarbene−halocarbanion equilibria is greatly simplified if we study phenylhalocarbenes, which exhibit strong absorbances involving their phenyl moieties. Here again, PhCCl played an important role in my research. Using the strong absorptions of PhCCl at 292 nm and $PhCCl_2^-$ at 404 nm (in 1,2-dichloroethane, DCE), we extracted K = 4.0 M^{-1} for equilibrium (10) at 294 K.[55]

$$Ph\ddot{C}Cl + Cl^- \rightleftharpoons PhCCl_2^- \tag{10}$$

From similar studies at various temperatures, we obtained ΔH° = −5.7 kcal/mol, ΔS° = −16.8 eu, and ΔG° = −0.71 kcal/mol.[55] K for the analogous equilibrium of PhCBr and $PhCBr_2^-$ was determined to be 3.01 M^{-1}.

Manipulation of the concentration ratios of $PhCCl/PhCCl_2^-$ or $PhCBr/PhCBr_2^-$ by modulating the halide concentration has synthetic utility. In the *concurrent* cyclopropanation of alkenes by halocarbenes and halocarbanions, we can selectively favor additions of electrophilic PhCX to electron-rich alkenes or nucleophilic $PhCX_2^-$ to electron-poor alkenes.[56,57] Halide ions can *catalyze* the additions of PhCX via $PhCX_2^-$ to electron-poor alkenes. For example, the addition of PhCF to acrylonitrile is enhanced by a kinetic factor of 17.5 by added

Table 2. Activation Parameters for Dihalocarbene Additions[a]

carbene	alkene[b]	E_a	$\Delta H^{‡}$	$\Delta S^{‡}$	$-T\Delta S^{‡}$	$\Delta G^{‡}$
CCl_2	TME	−1.2 (0.02)	−1.8	−20 (0.2)	6.0	4.2 (0.2)
CClF	TME	0.9 (0.02)	0.3	−16 (0.2)	4.7	5.0 (0.2)
CF_2	TME	3.0 (0.05)	2.5	−10 (0.3)	3.0	5.5 (0.3)
CCl_2	cyclohex	3.8 (0.02)	3.3	−10 (1.3)	3.1	6.4 (0.4)
CClF	cyclohex	5.6 (0.3)	5.0	−7.8 (1.1)	2.3	7.3 (0.4)
CF_2	cyclohex	6.9 (0.2)	6.3	−4.3 (0.5)	1.3	7.6 (0.5)
CCl_2	1-hexene	4.7 (0.02)	4.1	−12 (1.1)	3.4	7.5 (0.4)
CClF	1-hexene	6.0 (0.06)	5.4	−7.8 (1.1)	2.3	7.7 (0.3)
CF_2	1-hexene	8.0 (0.07)	7.4	−3.9 (0.2)	1.1	8.6 (0.1)

[a]Data from refs 48, 49, and 39b. Units are kcal/mol for E_a, $\Delta H^{‡}$, $-T\Delta S^{‡}$, and $\Delta G^{‡}$; cal(deg-mol) for $\Delta S^{‡}$. $\Delta H^{‡}$ is calculated at 283 K; $\Delta G^{‡}$ is calculated at 298 K. Errors (in parentheses) are average deviations of two determinations. [b]TME = tetramethylethylene, cyclohex = cyclohexene.

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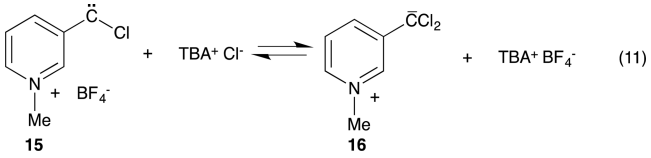
bromide ion, which promotes the intermediacy of $PhCFBr^-$.[58] A Hammett study of the chloride-mediated equilibrium between ArCCl and $ArCCl_2^-$ exhibited $\rho = +3.18$, indicating that electron-withdrawing substituents on the aryl group stabilize the carbanion ($ArCCl_2^-$) and destabilize the carbene (ArCCl), thus driving the equilibrium to the right.[59]

In consonance with this idea, we note that inclusion of a positive charge on the aryl unit, as in methylpyridinium-chlorocarbene, **15**, greatly destabilizes the carbene and drives the equilibrium even more markedly toward chloride addition, here forming zwitterion **16**, cf. eq 11. Now, $K = 4.5 \times 10^3$ M^{-1}, about 1100 times greater than K for the corresponding equilibrium with PhCCl in eq 10.[60]



The UV absorptions of PhCCl and arylcarbenes in general are easily followed because of their strong $\pi \rightarrow$ p transitions originating in the aryl π systems. The $\sigma \rightarrow$ p absorptions of alkylchlorocarbenes (RCCl), however, are much weaker; cf. Figure 4.

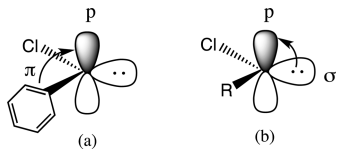


Figure 4. (a) π to p transition of PhCCl; (b) σ to p transition of RCCl.

Indeed, these species were once considered "invisible carbenes" under LFP conditions.[61] Nevertheless, the $\sigma \rightarrow$ p absorptions of RCCl can be detected and have been acquired for species with R = methyl, benzyl, *tert*-butyl, cyclopropyl, and 1-adamantyl.[62] These carbenes can thus be directly observed, enabling studies of carbene solvation, π complexation to aromatic molecules, and analyses of equilibria between carbenes and carbene complexes.[54,62]

For example, the $\sigma \rightarrow$ p transition of methylchlorocarbene (MeCCl), which appears at 544 nm in pentane, shifts to 520 nm in anisole, indicative of anisole solvation.[62] After 1500 ns, the 520 nm absorption disappears in favor of a new absorption at 368 nm that we attribute to weak MeCCl/anisole complexes. Examples of computed π and *O*-ylidic MeCCl/anisole complexes are shown in Figure 5.[62] Here, there is electron donation from either the anisole π-system or oxygen atom to the "vacant" carbene p orbital. The complexes are stabilized by enthalpy, but the free energy is unfavorable (see the caption to Figure 5), so that the equilibrium between the solvated carbene and the carbene/anisole complexes favors the former. Nevertheless, there are many other complexes that are minima on the carbene/anisole energy surface, and their strong absorptions in the 368 nm region ultimately replace that of the solvated carbene at 520 nm.[62]

There are also reactivity consequences to the solvation/complexation of MeCCl by anisole. Additions of MeCCl to TME or 1-hexene are about four times slower in anisole than in pentane. In anisole, carbene complexes may be stabilized or

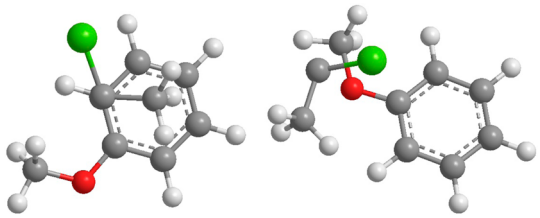


Figure 5. PBEPBE/6-311+G(d)-computed structures of an *o*-MeCCl/anisole complex ($\Delta H^\circ = -3.35$ kcal/mol, $\Delta G^\circ = 5.13$ kcal/mol) and an ylidic MeCCl/anisole complex ($\Delta H^\circ = -1.79$ kcal/mol, $\Delta G^\circ = 6.36$ kcal/mol) (gas phase).[62]

encumbered by solvent and react more slowly than the unsolvated or uncomplexed carbenes in pentane. We found analogous MeCCl solvation by 1,3-dimethoxybenzene with similar spectroscopic and kinetic effects. The retardation of MeCCl addition to TME in 1,3-dimethoxybenzene was 10 times greater than in anisole. Parallel spectroscopic and kinetic observations were made with benzylchlorocarbene ($PhCH_2CCl$) solvated by anisole or dimethoxybenzene.[62]

Complexation between phenylchlorocarbene (PhCCl) and 1,3,5-trimethoxybenzene (TMB) led to an equilibrium mixture of carbene and complex where each component exhibited its unique spectroscopic signature.[63] In TMB/pentane, PhCCl was visible at 324 ($\pi \rightarrow$ p) and 596 nm ($\sigma \rightarrow$ p), whereas the PhCCl/TMB complex absorbed at 484 nm. By variation of the TMB concentration, an equilibrium constant, $K = 1264$ M^{-1}, was obtained for complex formation, indicating that the complex was quite stable (in contrast to the MeCCl/anisole complex, above). Indeed, temperature variation afforded thermodynamic parameters for the equilibrium: $\Delta H^\circ = -7.1$ kcal/mol, $\Delta S^\circ = -10.2$ eu, and $\Delta G^\circ = -4.1$ kcal/mol. Theoretical studies suggested that there were several PhCCl/TMB complexes present; the most stable ones involving charge transfer from TMB to the "vacant" carbenic p orbital.[63] A Hammett study of K for *p*-X-substituted PhCCl gave $\rho = 2.48$, indicating that electron-withdrawing substituents destabilize the carbene but stabilize the TMB/carbene complex.[64] Not surprisingly, therefore, the equilibrium between pentafluorophenylchlorocarbene and TMB was characterized by $K = 3.21 \times 10^5$ M^{-1}, $\Delta H^\circ = -10.2$ kcal/mol, $\Delta S^\circ = -9.5$ eu, and $\Delta G^\circ = -7.4$ kcal/mol. The more electron-deficient aryl group of pentafluorophenylchlorocarbene, relative to the phenyl group of PhCCl, leads to ~250 times stronger complexation with TMB.[65] Similarly, the equilibrium between the cationic carbene, (*N*-methyl-3-pyridinium)chlorocarbene (**15**) and TMB lies far to the right, with $K = 2.86 \times 10^4$ M^{-1}, $\Delta H^\circ = -11.1$ kcal/mol, $\Delta S^\circ = -17$ eu, and $\Delta G^\circ = -6.1$ kcal/mol. Again, an electron-poor (hetero)aromatic moiety strengthens TMB complex formation with ArCCl relative to PhCCl.[60]

It was quite satisfying to find that the iconic dichlorocarbene, CCl_2, formed spectroscopically detectable (though unstable) π and *O*-ylidic complexes with a variety of aryl ethers and that these complexes modulated the rates of CCl_2 additions to TME.[66,67]

CCl_2/aryl ether complexes were observed with anisole, 1,3-dimethoxybenzene, TMB, dibenzofuran, dibenzo-18-crown-6, and various methylanisoles. Figure 6 shows two (computed) CCl_2/TMB complexes in which the carbene sits over an electron-rich aromatic carbon atom, and there is charge transfer from the TMB to the carbenic p orbital.[66] Although these complexes are calculated to be stabilized by enthalpy,

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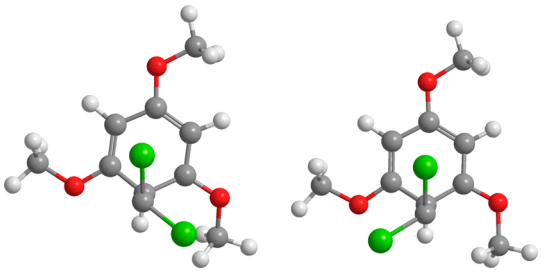
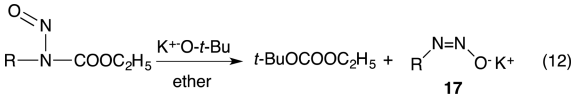


Figure 6. PBE/6-311+G(d)-computed structures of complexes between CCl_2 and trimethoxybenzene. Calculated values of $\Delta H^\circ \approx -9$ kcal/mol and $\Delta G^\circ \approx 2$ kcal/mol.[66]

unfavorable entropic factors lead to positive values of ΔG° and $K < 1$.[66] Compared to CCl_2 addition to TME in pentane, complexation by 0.3 M TMB retards the rate by a factor of 152,[66] while complexation by 2,3,5,6-tetramethylanisole evokes retardation by a factor of 96.[67]

8. CARBOCATIONS FROM DIAZOTATES[68]

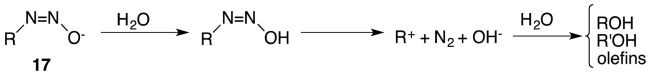
When I was a postdoctoral student, I needed to prepare a diazoalkane, and so I treated the requisite *N*-alkyl-*N*-nitrosourethane with K^+O-*t*-Bu in (diethyl) ether. Unfortunately, I omitted a source of protons (e.g., ethanol), thus eliding the prototropy needed to convert the intermediate alkanediazotate (**17**) to the desired diazoalkane, $RCH{=}N_2$; cf. eq 12.



(12)

I obtained a precipitate of potassium alkanediazotate **17** instead of a red ethereal solution of diazoalkane. With the intemperance of youth, I tossed the "failed" experiment into the sink, whereupon a copious evolution of gas (nitrogen) ensued. Aha! I repeated the experiment, this time effecting the hydrolysis in a flask, analyzing the products, and concluding that they were consistent with the intermediacy of a carbocation.

The cleavage of *N*-alkyl-*N*-nitrosourethanes to alkanediazotates with K^+O-*t*-Bu in ether is general. When the alkyl group is primary, subsequent hydrolysis affords the diazoalkane as a major product, but when R is secondary, nitrogen loss and carbocation intermediacy dominates;[69] cf. eq 13. Moreover, the

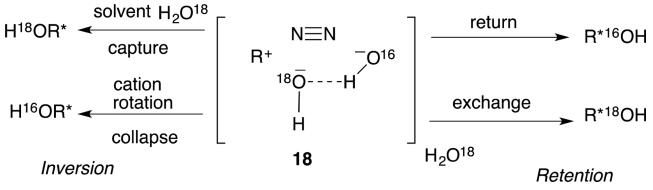


(13)

hydrolysis of *sec*-alkanediazotates occurs under highly basic or nucleophilic conditions affording carbocations that arise as components of ion pairs or ion triplets.[68,69] A particularly informative example appears in Scheme 1 and represents the hydrolysis of octane-2-diazotate. Here, a double-labeling approach permits dissection of the product 2-octanol among four channels of formation.[70]

One label is the chirality of the 2-octyl group in 2-Oct*N=N−O^-, while the second is the oxygen isotope. Optically active octane-2-diazotate (R*−N=N−$^{16}O^-$) is hydrolyzed with H_2O^{18}, leading to the nitrogen-separated ion triplet **18**. The four channels of decay for **18** are (1) return of $^{16}OH^-$ with

Scheme 1

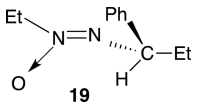


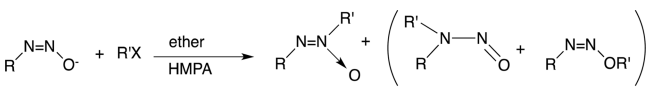
retention and *conservation* of ^{16}O, yielding R*^{16}OH, (2) collapse with *retention* and frontside isotope *exchange* to R*^{18}OH, (3) rearside solvolysis forming H^{18}OR* with *inversion* and isotope *exchange*, and (4) cation rotation and collapse within **18**, yielding *inverted* H^{16}OR* (and H^{18}OR*).

In the event, an HMPA solution of R*−N=N−$^{16}O^-$ was added to 20% isotope-enriched $H_2{}^{18}O$. Product 2-octanol was isolated and resolved, and the $^{16}O/^{18}O$ content of each enantiomer was determined by mass spectroscopy.[70a,c] From the overall stereochemistry of the diazotate to octanol conversion and the isotopic composition of each octanol enantiomer, the contribution of each decay channel was determined: (1) retention with ^{16}O conservation or return, 16.5%; (2) retention with ^{18}O exchange, 18.9%; (3) inversion with ^{18}O exchange, 58.5%; and (4) inversion with ^{16}O conservation, 6.0%.[70]

We see that even in this unusually degenerate hydrolysis the overall behavior of intermediate **18** conforms to that generally expected of ion pairs: solvolysis with inversion (channel 3, the principal fate of **18**) and return with retention (channels 1 and 2). Many other solvolytic reactions of alkanediazotates were examined, and their chemistry has been reviewed.[68]

A useful sidelight on alkanediazotates is their utility in a general, stereospecific synthesis of azoxyalkanes.[68,71,72] Alkylation of, e.g., 1-phenylethanediazotate with $Et_3O^+BF_4^-$ converts the diazotate's O^- to an ethoxide anion, nitrogen is expelled, and the [PhEtCH$^+$$^-$OEt] ion pair collapses to the ether product by frontside return with 70% net retention.[71] Accompanying this process is the alkylation of the "middle" nitrogen of the N=N−O^- triad, yielding 46% of azoxyalkane **19**.[71] In fact, alkylation with R′I of alkanediazotates, derived from aminoalkanes via *N*-nitrosourethanes, constitutes a flexible, directed synthesis of azoxyalkanes that affords a single, structurally predictable product and accommodates chirality at both of the azoxyalkane's α and α' carbon atoms; cf. eq 14.[72] Yields of the unsymmetrical azoxyalkane range from 30% to 60%. In 95:5 ether/HMPA, the *N*-nitrosoamine is the major byproduct.





(14)

The alkylation of the diazotate at N is a S_N2 reaction, so that chirality is readily introduced at the (proximal) α carbon atom adjacent to the azoxy nitrogen by use of a chiral alkylating reagent.[73] Chirality at the other (distal) α carbon atom follows from initial use of a chiral aminoalkane. Moreover, "photothermal" isomerization[74] moves the azoxy oxygen from one

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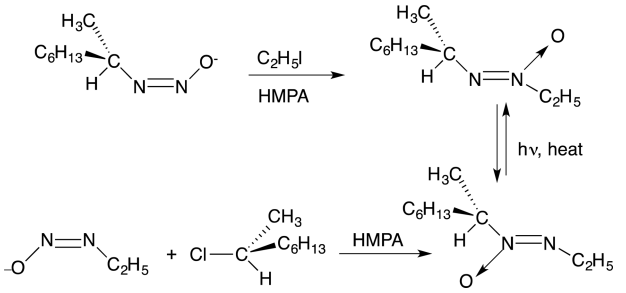
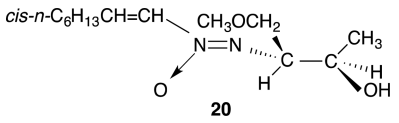
nitrogen to the other, thus interconverting the two isomeric azoxyalkanes; cf. Scheme 2.[73]

Scheme 2



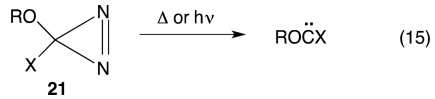
Our excursions into azoxyalkane chemistry concluded with an unusual foray for physical organic chemists: the total synthesis of the naturally occurring, threonine-derived azoxyalkene, elaiomycin, **20**.[75]



20

9. CARBOCATIONS FROM ALKOXYCHLOROCARBENES[76]

Long ago, Hine[77] and Skell[78] reported that the reaction of dihalocarbenes with alkoxides gave alkoxyhalocarbenes (ROCX). When R was secondary or tertiary, the carbene spontaneously fissioned to alkyl cations and halide anions with expulsion of CO.[78] In a modern formulation, we would suggest the intervention of CO-separated ion pairs [R^+ OC X^-], where the resemblance to the nitrogen-separated ion pairs from various reactions of alkanediazotates is patent (see above).[68] These reactions are of intrinsic mechanistic interest, but neither the carbenes nor their daughter alkyl cations will long survive the strongly basic conditions under which they arise. Fortunately, Graham oxidation[9] of *O*-alkyl isoureas affords alkoxyhalodiazirines **21**, whose thermal or LFP decompositions permit detailed examinations of the chemistry of alkoxyhalocarbenes under neutral conditions and in a variety of polar or nonpolar solvents (eq 15).[76] Alkoxyhalocarbenes are situated

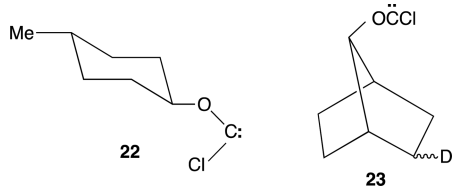


21 (15)

at a confluence of carbene, cation, and substitution (S_N1, S_N2, and S_Ni)chemistry, affording access to many of the iconic carbocations and solvolytically generated ion pairs of classical physical organic chemistry as well as substitution reactions that bypass the ionic intermediates.[76]

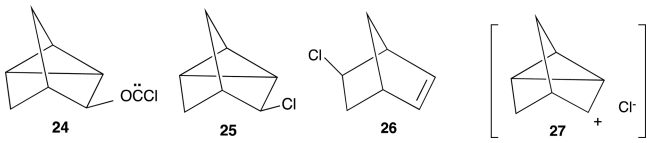
Substitution Reactions. For example, ROCCl where R is primary, e.g., *n*-butyl, undergoes S_N2 decomposition with added chloride ion.[79] Cases in which R is secondary are particularly interesting because the mechanism of carbene fragmentation is solvent-sensitive: S_Ni in pentane, but with increasing intervention of ion pairs (S_N1) in polar solvents like acetonitrile.[76b] Thus, ROCCl (R = cyclohexyl) decomposes in *pentane* to chlorocyclohexane and cyclohexene. Computational studies indicate that the substitution product arises by parallel, nearly isoenthalpic S_Ni processes, which traverse both retention (equatorial, front side) and inversion (axial, back side) transition states, with no intervention of intermediates.[80]

Indeed, *trans*-4-methylcyclohexyloxychlorocarbene (**22**) decomposes in pentane to *trans*-4-methyl-1-chlorocyclohexane and its cis isomer in a ratio of 2.3:1.[80] Analogous results attend the decomposition in $CDCl_3$ of deuterium-labeled *syn*-7-norbornyloxychlorocarbene, **23**, where the *syn*- and *anti*-7-chloronorbornane isotopomeric products form in a ratio of 3.5:1. Computational studies again exclude intermediates on the intrinsic reaction coordinate connecting the carbene with its decomposition products, supporting competing S_Ni pathways.[80]



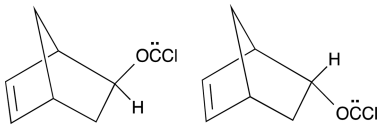
22 **23**

A more revealing study involves the fragmentation of optically active 3-nortricyclyloxychlorocarbene, **24**.[80,81] In pentane, only 3-nortricyclyl chloride (**25**) is formed with 91−96% racemization.[81] However, in the more polar CD_3CN solvent, 10−11% of *exo*-5-norbornenyl chloride (**26**) is also formed, accompanied by **25**, now with 24% stereochemical *retention*.[80,81] A rationalization posits that **24** decomposes by parallel, nearly isoenthalpic retention and inversion S_Ni transition states in pentane (calculated $\Delta G^{\ddagger} \approx 11-12$ kcal/mol, $\Delta H^{\ddagger} \approx 14-15$ kcal/mol), while in CD_3CN partial escape to nortricyclyl chloride ion pair **27** leads to increased retention in the formation of **25**, as well as the appearance of some **26**.



24 **25** **26** **27**

Even more complicated scenarios are required for the decompositions of *exo*-5-norbornenyl-2-oxychlorocarbene (**28**) and its endo isomer (**29**) in nonpolar or polar solvents, but the products and their stereochemistry can also be rationalized as competing S_Ni and S_N1 (ion pair) processes.[82,83] Although S_Ni mechanisms are suggested for these *sec*-alkoxychlorocarbene decompositions in hydrocarbon solvents, the calculations suggest asynchronous, polarized, "loose," transition states, which provide an escape from the formal Woodward−Hoffmann "forbiddeness" of concerted S_Ni processes.[76b]



28 **29**

Ion-Pair Processes. These include reactions in polar solvents of alkoxychlorocarbenes in which the alkyl group is either secondary, tertiary, or otherwise well-suited to carbocationic character.[76] Consider the benzyl cation. Even in pure methanol, thermal fragmentation of benzyloxychlorocarbene affords 43% of benzyl chloride as well as benzyl methyl ether (eq 16).[84] We formulate this reaction as

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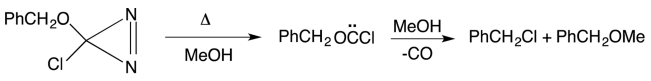
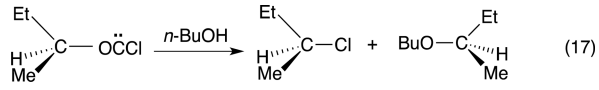


(16)

proceeding via ion pair [$PhCH_2^+$ OC Cl^-], which can either collapse to benzyl chloride or be trapped by methanol, affording the methyl ether. Fragmentation of chiral α-deuteriobenzyloxychlorocarbene in MeCN gives the benzyl chloride with 60−80% net retention, indicative of front-side return (probably in a syn ion pair).[85]

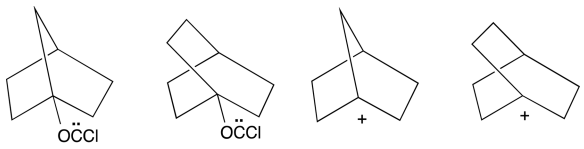
The fragmentation of chiral *sec*-butyloxychlorocarbene in *n*-butanol is particularly informative; cf. eq 17.[86] The ion-pair



(17)

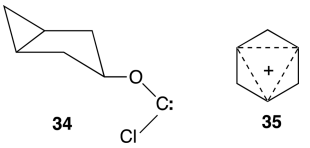
return product, 44% of *sec*-butyl chloride, forms with 81−83% net retention, while the solvolysis product, 36% of *sec*-butyl *n*-butyl ether, forms with 69−73% net inversion. (The residual product is butene.) The observation of return with retention and solvolysis with inversion for CO-separated *sec*-butyl chloride ion pairs is satisfyingly analogous to the stereochemistry of the nitrogen-separated ion pairs derived from alkanediazotates (see above).[68,87]

Activation Energies. Distinguishing features of many alkoxychlorocarbene fragmentations in polar solvents like dichloroethane (DCE) are the unusually low associated activation energies. These can be determined from the kinetics of the disappearance of the carbenes, as generated by LFP of their precursor diazirines, and monitored by the pyridine ylide method.[61] For example, rate constants for the fragmentations of ROCCl where R = 1-norbornyl (**30**) or 1-bicyclo[2.2.2]-octyl (**31**) are in the 10^4−10^5 s^{-1} range,[88] orders of magnitude faster than acetolysis of the corresponding tosylates at elevated temperatures.[89] Thus, [R^+ OC Cl^-] ion pairs containing bridgehead cations **32** and **33** are readily accessible via fragmentations of **30** and **31**, with E_a = 9.0 or 4.4 kcal/mol, respectively.[88] This contrasts with $\Delta H^{\ddagger}$ = 27.8 or 26.2 kcal/mol for the acetolysis of 1-norbornyl triflate or 1-bicyclo[2.2.2]octyl brosylate.[89]



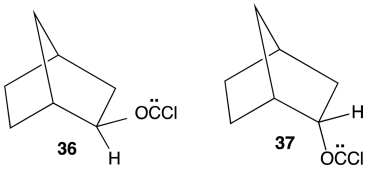
The bridgehead cation/chloride ion pairs collapse to the bridgehead chlorides in DCE, whereas in DCE-MeOH, both bridgehead chlorides and methyl ethers form by return and solvolysis processes.[88] The rates of these reactions are likely comparable to solvent/counterion equilibration of the ion pairs, and carbocation-trapping experiments with trimethoxybenzene[79,88b,90] lead to estimates of ∼70 ps for the lifetimes of the cations in DCE.[91]

Another consequence of the low activation energy for ROCCl fragmentation is the "disconnection" or mitigation of σ electron donation from nearby C−C bonds, compared to analogous classical solvolysis reactions. Thus, fragmentation of *cis*-3-bicyclo[3.1.0]hexyloxychlorocarbene (**34**) largely bypasses the intermediate tris-homocyclopropenyl cation (**35**) familiar from solvolysis of the corresponding tosylate.[92]



Instead, the bicyclo[3.1.0]hexyl cation chloride ion pair formed from carbene **34** in DCE yields an array of products, including the *cis*- and *trans*-chloride return products, cis and trans hydride-shifted chlorides, and even some alkene formed by HCl elimination.[93] Strikingly, carbon "scrambling", a hallmark of solvolysis proceeding through cation **35**, is greatly suppressed in chloride formation from **34**. The low activation energy for carbene fragmentation (measured as 2.4 kcal/mol,[93] compared to $\Delta H^{\ddagger}$ = 24.1 kcal/mol for acetolysis of the analogous tosylate[92]) obviates the need for assistance by the neighboring cyclopropyl C−C bond.

A similar disconnection of neighboring σ-bond delocalization occurs in fragmentations of *exo*- and *endo*-2-norbornyloxychlorocarbenes **36** and **37**.[94]



In the acetolysis of *exo*- and *endo*-2-norbornyl brosylates, electron donation from the C1−C6 σ bond confers a kinetic advantage of 350 on the exo isomer.[95] This disparity disappears with the exo and endo carbenes where k_{frag} = 7.2 × 10^4 and 8.7 × 10^4 s^{-1}, respectively.[94] We could not reliably measure activation parameters for the carbene fragmentations, but computed values at the B3LYP/6-31G* level in simulated MeCN gave $\Delta G^{\ddagger}_{exo}$ = 2.60 kcal/mol and $\Delta G^{\ddagger}_{endo}$ = 2.87 kcal/mol.[94] Analogous values for the brosylate acetolysis reactions are 22.6 and 27.1 kcal/mol, respectively.[95] The exo/endo solvolysis difference of 4.5 kcal/mol is erased in the carbene fragmentations.

Acetolysis of the *exo*- or *endo*-2-norbornyl brosylates affords only *exo*-2-norbornyl acetate, famously due to the intermediacy of the nonclassical 2-norbornyl cation, where the C1−C6 C−C bond donates electron density to the cation arising at C2.[95] With no requirement for similar electron donation in the norbornyl cation chloride ion pairs formed from carbenes **36** and **37**, the products are not formed stereospecifically, are more diverse, and are origin dependent.[94]

Solvent and Counterion Equilibration of Ion Pairs. Two questions about the ion pairs formed by fragmentations of ROCCl: Have they equilibrated with solvent, and how long does this process take? Consider Scheme 3, in which the homoadamantyl chloride ion pair **38** is generated either directly by fragmentation of homoadamantyloxychlorocarbene **39** or by fragmentation−ring expansion of adamantylmethoxychlorocarbene **40**.[96] In DCE/methanol solvent, the products are the homoadamantyl chloride **41** and the corresponding methyl ether **42**. The dependence of the **42**/**41** product ratio on the concentration of MeOH in the DCE solvent is *identical* from either carbene **39** or **40**, suggesting that ion pair **38** has become solvent equilibrated regardless of its source.[96]

An estimate of the lifetime of the solvent-equilibrated ion pair can be made from LFP time-resolved cation trapping experiments using trimethoxybenzene as the cation trap.[90] We

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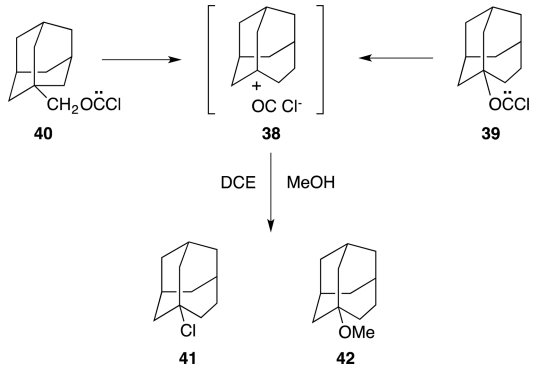
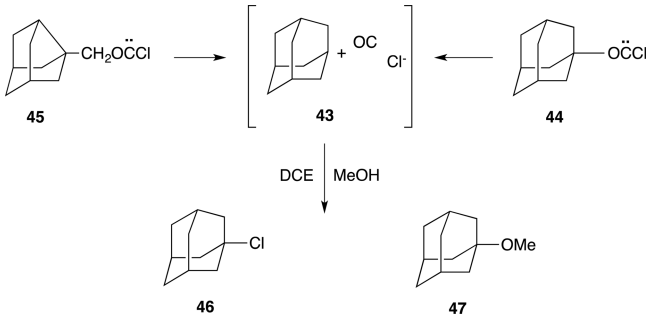
Scheme 3



associate the resulting value of 20−30 ps with decay of a solvent-separated version of ion pair **38** as well as an upper limit for the time required for evolution of an initial (contact) ion pair **38** to the solvent equilibrated form.[96] For perspective, we note that the diphenylmethyl chloride contact ion pair becomes solvent separated in MeCN in 65 ps and collapses to benzhydryl chloride in 92 ps.[97] The greater lifetime of the $[Ph_2CH^+\ Cl^-]$ ion pair vs ion pair **38** is likely due to the greater stability of the former.[98]

In contrast, consider Scheme 4. Here, adamantyl chloride ion pair **43** is generated either directly by fragmentation of

Scheme 4



adamantyloxychlorocarbene **44** or by fragmentation−ring expansion of 3-noradamantylmethoxychlorocarbene **45**.[96] In DCE/methanol solvent, the products are adamantyl chloride **46** and the corresponding methyl ether **47**.

Now, however, the dependence of the **47**/**46** product ratio on the concentration of MeOH in the DCE solvent is *origin dependent*. The ion pairs arising from **44** or **45** are similar but not identical. A residual memory of the carbene parent suggests that product formation is competitive with R^+Cl^- reorganization and solvent equilibration of ion pair(s) **43**. In the gas phase, the 1-adamantyl cation (of **43**) is 4.2 kcal/mol less stable than the homoadamantyl cation of **38**.[98] This decreased stability likely translates into a shorter lifetime for **43**, relative to **38** and probably accounts for the origin dependence of the **47**/**46** product ratio.

10. L'ENVOI

I've described a number of my "adventures" in reactive intermediate chemistry. Others, for example the extrinsic kinetic stabilization of phenoxyfluorocarbene by entrapment within a hemicarcerand,[99] have been omitted due to the limitations of space. I now conclude with several personal impressions and observations. A related discussion recently appeared in the *Israel Journal of Chemistry*.[4]

Leonard Woolf (Virginia's husband) entitled his 1969 memoir: *The journey not the arrival matters*. My journey in physical organic chemistry, from graduate student to Professor Emeritus, has lasted more than half a century and witnessed remarkable changes. The time resolution of experiments, driven by the evolution of spectroscopy, has increased by some 12 orders of magnitude, from ms to fs. Intermediates (even transition states[100]), whose existence and structure we once inferred from product studies, can now be directly visualized. Enormous increases in computational methodology and computer power (with desktop availability) enable us to calculate the geometries of molecules and reactive intermediates, as well as the energy surfaces upon which their transformations occur.

Despite these advances, my experience has been that progress in physical organic chemistry is cyclical, not linear; as our technical infrastructure develops, we return to classic mechanistic or structural problems to "peel another layer off the onion." I also believe that there are personal motifs underlying our approach to science and that these often channel our research. In my case, an early study of phenylchlorocarbene[7] familiarized me with a readily generated intermediate that later assumed key roles in experiments with carbenoids,[14] determinations of absolute rate constants for carbene/alkene additions,[34,35] and the quantitation of carbene/carbanion equilibria.[55]

Organic chemists have been fortunate to practice our science at a time when reasonably available funding permitted a curiosity-driven style of research. As I noted elsewhere, our research "is not like a railway journey, wherein the destination is known once you purchase your ticket and board the train. Our science is more like those voyages of exploration made by our ancestors to the fringes of the world, where unknown islands and new species were to be found beyond the breadth of the chart."[4]

Physical organic chemistry's focus on mechanism informs our sister sciences, biochemistry, bioorganic chemistry, and chemical biology. Mechanisms are portable; deciphered for small molecules, they are often readily applicable to the macromolecules of enzymology or genetics. And physical organic chemistry is protean, continually reinventing itself to probe new problems and unanticipated reactions. It has been a privilege to participate in these last 50 years of progress. The journey, not the arrival, *has* mattered. Indeed, there will likely be no "arrival". Physical organic chemistry will continue to nourish and assist more applied sciences as we move deeper into the twenty-first century.

AUTHOR INFORMATION

Corresponding Author

*E-mail: rmoss@rci.rutgers.edu.

ORCID

Robert A. Moss: 0000-0003-3963-1224

Notes

The author declares no competing financial interest.

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Biography

Robert A. Moss is the Louis P. Hammett Professor of Chemistry Emeritus at Rutgers University in New Brunswick, NJ. He is the author or coauthor of more than 400 articles on the physical organic chemistry of carbenes, carbocations, micelles, liposomes, and phosphate cleavage as well as coeditor of eight books on carbenes and reactive intermediates.

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(87) Additional complexity stems from the stereochemistry of ROCCl, which could be cis and/or trans, leading initially to "isomeric" CO-separated ion pairs, where the cis ion pair would be more apt to collapse or return, while the trans version would be more susceptible to solvent capture. See ref 76 for further discussion. See also: Kesselmayer, M. A.; Sheridan, R. S. *J. Am. Chem. Soc.* **1986**, *108*, 99−107 and 844−845 for examples of ROCCl isomers. In the alkanediazotate cases, the diazotates are syn and should initially furnish "syn" ion pairs (ref 68).
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