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Kinetics of the Reactions of Phenylchlorocarbene with Alkyl Azides

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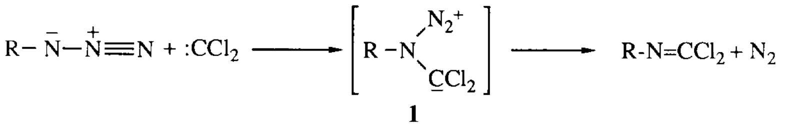
Abstract. The reactions of phenylchlorocarbene with several alkyl azides lead to C-chloroimines (and derived N-alkylbenzamides) with absolute rate constants of ~1-4 × 10^7 $M^{-1}s^{-1}$.

In 1968, Baldwin and Patrick reported that n-octyl azide reacted with dichlorocarbene ($CHCl_3$, KO-t-Bu, 0 °C) to yield 89% of n-octyl isocyanide dichloride, eq. (1).[1] More recently, Szönyi and Cambon utilized solid-liquid phase transfer catalytic generation of CCl_2 ($CHCl_3$, powdered NaOH, 1 mol-% $PhCH_2N^+Et_3\ Cl^-$) to extend reaction (1) to benzyl azide and several 2-F-alkylethyl azides.[2] Under the phase transfer conditions, where a large flux of CCl_2 was generated, subsequent carbene additions to the products' N=C double bonds also afforded tetrachloroaziridines as secondary products.

$$n\text{-}C_8H_{17}N_3 + :CCl_2 \longrightarrow n\text{-}C_8H_{17}N{=}CCl_2 + N_2 \qquad (1)$$

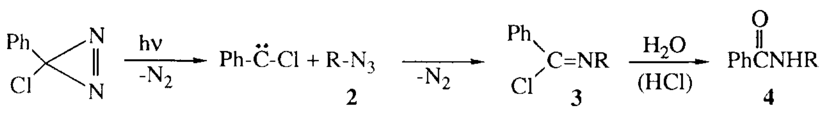
Reaction (1) has been formulated as an electrophilic carbene attack on N(1) of the azide, followed by rapid nitrogen loss from the resulting intermediate, **1**; eq. (2).[1] Our general interest in the application of fast kinetic methods to carbene reactions[3] led us to inquire just how rapid was the process represented by eqs. (1) or (2), and how the reactivity of the alkyl azides toward carbenes would compare to that of alkenes, which are much more common carbenic substrates.



$$R-\overset{-}{N}-\overset{+}{N}\equiv N + :CCl_2 \longrightarrow \underset{\mathbf{1}}{\left[R-N\begin{matrix} N_2^+ \\ \\ \underline{C}Cl_2 \end{matrix} \right]} \longrightarrow R\text{-}N{=}CCl_2 + N_2 \qquad (2)$$

Although CCl_2 has been generated by laser flash photolysis (LFP) for fast kinetic studies,[4] the available phenanthrenoid carbene precursor complicates the kinetic analysis and is not particularly convenient in the synthetic mode. We therefore focused on phenylchlorocarbene (PhCCl), which can be readily generated from 3-chloro-3-phenyldiazirine,[5] and for which much absolute kinetic data is already available.[3] Here we report absolute rate constants for the reactions of PhCCl with 3 alkyl azides, as well as the activation parameters for its reaction with benzyl azide.

Product studies. Benzyl, n-butyl, and α-phenylethyl azides were prepared in 46-78% (unoptimized) yields from the corresponding bromides by S_N2 reactions with NaN_3 in 2:1 DMF/H_2O (50°C, 3 h). The azides were purified by distillation under reduced pressure, and spectroscopically characterized by GC-MS, ^1H NMR, and ir.[6] Photolyses of ~1 mmol samples of 3-chloro-3-phenyldiazirine[5] in pentane solutions of 10-fold excess azides **2a-c** were carried out in sealed Pyrex tubes at 360 nm (25°C, 3 h) using a Rayonet reactor, until the diazirine's absorbance at 372 nm was no longer detectable. GC-MS examination of the concentrated product mixtures revealed the anticipated *C*-chloroimines **3a** and **3b**, as well as the *N*-alkylbenzamides, **4a-c**, derived from the chloroimines by hydrolysis; eq. (3). The imines and amides formed in ~90% aggregate yields, together with by-products typical of the carbene generation (e.g., azine and carbene-pentane insertion products).



(3)

[**a**, R = $PhCH_2$; **b**, R = *n*-C_4H_9; **c**, R = Ph(Me)CH]

Isolation of the chloroimines was difficult due to their facile hydrolysis either by adventitious water or during column chromatography. The hydrolysis was presumably autocatalyzed by liberated HCl. Deliberate hydrolysis of the product mixture from **2a** converted chloroimine **3a** to *N*-benzylbenzamide (**4a**), whereas the product mixture produced from azide **2c** already contained only the corresponding benzamide (**4c**). The benzamides were identified by GC-MS and NMR, in comparison with authentic materials or literature data.[7] The course of the PhCCl/azide reactions, as outlined in eq. (3), indicates that PhCCl behaves analogously to CCl_2; *cf.*, eq. (1).

Kinetics. LFP studies of reaction (3) employed our XeF excimer laser.[8] Samples of 3-chloro-3-phenyldiazirine in pentane (A_{372}~1.0) were flashed with 14 ns, 50 mJ pulses of 351 nm light, generating PhCCl.[3,9] The carbene's transient absorbance, monitored at 310 nm,[9] was quenched upon the addition of alkylazides **2a-2c**. From the slope of the observed rate constants for carbene decay (k_{obs}) vs. the corresponding concentrations of azide, we derived k_2, the bimolecular rate constant for each carbene/azide reaction. These values appear in Table I, together with the concentration range of the alkyl azides examined in the kinetic runs.

An Arrhenius study was carried out for the LFP reactions of PhCCl with benzyl azide in isooctane. Although the temperature was varied over a 75 degree range [243 - 318 K], k_2 did not significantly change (3.73 - 3.81 × 10^7 $M^{-1}s^{-1}$). The derived Arrhenius parameters were $E_a \leq 0.04$ kcal/mol and $A = 4.06 \times 10^7$ s^{-1}, with the low A value translating into a strongly negative entropy of activation, $\Delta S^* = -25.7$ e.u. Error analysis indicated the precision of this value to be within ± 1 e.u.

PhCCl reacts with alkyl azides **2a**-**2c** with rate constants that range from 1.5-3.8 × 10^7 $M^{-1}s^{-1}$ and, as shown in Table 1, little dependence on alkyl group structure is displayed. The azides are seen to be very reactive substrates toward PhCCl, comparable in their reactivity to common alkenes, particularly styrene, for which $k_{addn} = 4.0 \times 10^7$ $M^{-1}s^{-1}$.[10] The azides are somewhat less reactive than trimethylethylene ($k_{addn} = 1.3 \times 10^8$ $M^{-1}s^{-1}$), but more reactive than *trans*-butene ($k_{addn} = 5.5 \times 10^6$ $M^{-1}s^{-1}$) or 1-butene ($k_{addn} = 2.2 \times 10^6$ $M^{-1}s^{-1}$).[3] From a broader perspective, the azides are seen to be 1-2 orders of magnitude less reactive toward PhCCl than is pyridine, where ylide formation occurs with $k_2 \sim 10^8 - 10^9$ $M^{-1}s^{-1}$.[11]

The near-zero activation energy and exceptionally negative ΔS^* for the reaction of PhCCl with benzyl azide again recall the additions of this carbene to alkenes, where activation energies were found to be very low, or even negative, while $\Delta S^* \leq -20$ e.u.[3,12] In both cases, the unusual ΔS^* can be ascribed to the loss of translational, vibrational, and rotational entropy as the reactant molecules traverse the transition state required to form a single molecule; presumably, with an azide substrate, transient **1** in eq. (2). Thus there arise (free energy) barriers to these reactions despite the nonexistant activation energies.[13]

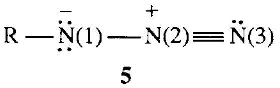
Table 1. Rate Constants for the Reactions of PhCCl with Alkyl Azides[a]

Alkyl azide	Concentration, M	$10^{-7}\,\underline{k}_2$, $M^{-1}s^{-1}$[b]	$\underline{n}$, $\underline{r}$[c]
$PhCH_2N_3$	0.00834-0.0417	3.77	5, 0.996
$\underline{n}$-BuN_3	0.0218-0.1750	1.52	8, 0.985
$Ph(Me)CHN_3$	0.0153-0.0915	1.89	6, 0.999

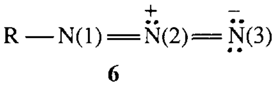
[a] In pentane, at 22°C. [b] Estimated error, ±10%. [c] $\underline{n}$ = number of individual $\underline{k}_{obs}$ determinations in the correlation, $\underline{r}$ = correlation coefficient.

The present results are consistent with the mechanism proffered by Baldwin and Patrick, eq. (2),[1] which features a rate determining electrophilic "addition" of the carbene at N(1) of the alkyl azide's nitrogen triad. The products, rate constants, and activation parameters here obtained with PhCCl accord with an "alkene-like" addition of the carbene at N(1), followed by extremely rapid N_2 loss from a transient analogous to **1**.

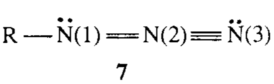
Theoretical considerations generally supported this qualitative picture. A series of ab initio molecular orbital calculations were carried out on RN_3 (R = Me and Ph) at the Hartree-Fock level with the 6-311G** basis set.[14] Natural Bond Orbital[15] analysis of the electronic wavefunction computed for MeN_3 unmistakably showed that the electronic structure was best described as strongly resonance delocalized. Using maximal Lewis structure electron occupancy as the criterion of importance, the dominant structure was **5**, followed by **6**.[16] A third potential Lewis structure, represented by the hypervalent configuration **7**, localized poorly and did not appear competitive.[17]


$R-\underset{\cdot\cdot}{\overset{-}{N}}(1)-\overset{+}{N}(2)\equiv\ddot{N}(3)$

5


$R-N(1)=\overset{+}{\ddot{N}}(2)=\underset{\cdot\cdot}{\overset{-}{N}}(3)$

6


$R-\ddot{N}(1)=N(2)\equiv\ddot{N}(3)$

7

The optimized geometries support considerable formal double and triple bond character in the central N(1)N(2) and terminal N(2)N(3) azide bonds, respectively.[18] Optimized N(1)N(2) and N(2)N(3) bond lengths for MeN_3 are 1.224 Å and 1.096 Å, respectively, and similar values are found for PhN_3 (1.229 Å, 1.093 Å). For comparison, the optimized triple bond length in N_2 is 1.070 Å and the double bond length in N_2H_2 is 1.212 Å, while the single bond length in N_2H_4 is 1.411 Å. The optimized value for the N(1)N(2)N(3) angle is 175.4° in MeN_3 and 174.6° in PhN_3.

Importantly, the dominance of resonance contributor **5** in the electronic structure of RN_3 leads to quite negative computed partial atomic charges (natural population analysis[15]) on N(1): $q = -0.47$ or -0.46 for R = Me or Ph, respectively. Slightly smaller positive charges develop on N(2) [+0.33 for MeN_3, +0.34 for PhN_3], whereas the terminal nitrogen, N(3), remains essentially neutral [-0.07 in MeN_3, -0.02 in PhN_3].

The attack of electrophilic carbenes at N(1) of RN_3, as observed here and previously,[1,2] is therefore in good accord with theory. On the other hand, we did not observe chloroimine or benzamide product formation from an attempted reaction of PhCCl with PhN_3. The computed negative charge on N(1) of PhN_3 is the same as that on N(1) of MeN_3 (see above), and, by extension, on N(1) of azides **2a-2c**, so that the PhCCl/PhN_3 reaction should be electronically favorable. Since we found that the reaction of (phase transfer generated[2]) CCl_2 with PhN_3 did afford $PhN{=}CCl_2$ and the derived tetrachloroaziridine (GC-MS), the failure of the PhCCl/PhN_3 reaction may have been due to steric problems.

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