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Bridgehead Carbocations via Carbene Fragmentation: Erasing a 10^{10} Kinetic Preference

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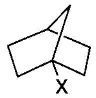
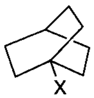
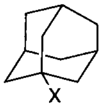
Typical bridgehead substrates form carbocation/anion ion pairs very slowly due to the high energetic costs of increased strain imposed on the cations which cannot become planar. The more the structurally imposed departure from planarity, the greater the activation energy associated with cation formation and the energy of the resultant cation. Consequently, the relative solvolysis rates of 1-substituted adamantyl, bicyclo[2.2.2]octyl, and norbornyl tosylates (HOAc, 70 °C)[1a] or bromides (80% EtOH, 25 °C)[1b] span an interval of 10^{10}; cf.; **1**−**3**.[2−4]



1
(1-Nor)



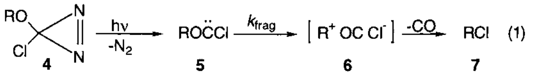
2
(1-Bco)



3
(1-Ad)

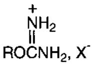
More recent studies afford gas phase ΔG differences of ∼27 and ∼8 kcal/mol, respectively, for the formation of the 1-norbornyl (1-Nor) and 1-bicyclo[2.2.2]octyl (1-Bco) cations, relative to the 1-adamantyl (1-Ad) cation.[5] Moreover, ΔG is proportional to log k_{solv} for these and other bridgehead substrates.[5]

We reported that the fragmentation of alkoxychlorocarbenes generates alkyl cations as components of ion pairs; eq 1.[6]



Experimentally[7] and computationally,[8,9] E_a's for these reactions are quite low (<10 kcal/mol). Here, we demonstrate that the low activation energy of carbene fragmentation permits the ready generation of bridgehead carbocations within ion pairs and obviates the classical 10^{10} kinetic difference between the solvolysis of 1-Nor-X and 1-Ad-X. Most impressively, the fragmentation of 1-NorOCCl to **6** ($R^+ = $ 1-Nor$^+$) at 25 °C occurs *3 × 10^{15} times faster* than the acetolysis of 1-NorOTs at 70 °C.[3]

1-Norbornanol[10] and 1-bicyclo[2.2.2]octanol[11] were converted[12] to isouronium triflates **8**, whereas 1-adamantanol was transformed to the *N*-isourea mesylate **9** by sequential reaction with KH/BrCN (to 1-AdOCN), hydroxylamine, and $MeSO_2Cl$.[13]



$\overset{\overset{+}{NH_2}}{\parallel}$ $ROCNH_2$, X^-

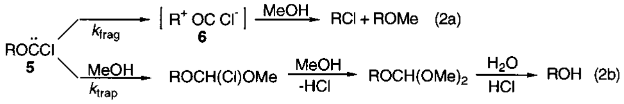
8

$\overset{NH}{\parallel}$ 1-AdOCNHOSO$_2$Me

9

Precursors **8** and **9** were then converted to alkoxychlorodiazirines **4** by oxidation with 12% aqueous NaOCl.[14] The diazirines were characterized by NMR and UV spectroscopy.[15]

Photolysis of diazirines **4** in dichloroethane (DCE) at 25 °C (λ > 320 nm) afforded *only* chlorides **7**, which were identified spectroscopically or by GC and GC−MS comparisons to authentic samples.[10,11,16] That chlorides **7** stem from ion pairs **6** is supported by the competitive interception of the carbocations by methanol.[6,17] Photolyses of diazirines **4** in MeOH−DCE mixtures led to three products derived from ROCCl: RCl, ROH, and ROMe; compare eq 2.



Products RCl and ROMe represent competition between chloride return to R^+ and MeOH capture of R^+ in ion pair **6**; both products represent fragmentation of **5** (eq 2a). ROH, on the other hand, represents MeOH capture of the *carbene*, ultimately followed by acid-catalyzed hydrolysis with adventitious water[18,19] (eq 2b).

Product distributions for eq 2 at several MeOH concentrations appear in Tables S1−S3 (Supporting Information). We note the following trends. (a) In pure MeOH, carbene trapping (ROH formation) is in the order R = 1-Nor (42%) > R = 1-Bco (32%) > R = 1-Ad (9%); that is, the order of R^+ energies.[1,5] The competition between carbene capture (eq 2b) and carbene fragmentation (eq 2a) increasingly favors capture as the alternative fragmentation generates a less stable carbocation. (b) At very low mol fractions (0.01−0.02) of MeOH in DCE, ROH formation is already substantial and remains relatively constant over the remaining [MeOH] range. Presumably, the likelihood of increased ROH yield due to increased carbene capture is balanced by an increasing carbene fragmentation rate as the solvent polarity rises with increasing [MeOH].[20] (c) In pentane, where fragmentation is further retarded by low solvent polarity,[19] low concentrations of MeOH elicit much larger yields of the ROH trapping products. Again, the yields of ROH follow the "instability" order of R^+: at $\chi_{\text{MeOH}} = 0.02$, 1-Nor (82%) > 1-Bco (43%) > 1-Ad (19%). (d) The product ratios of ROMe/RCl increase with increasing [MeOH] for each carbene, but even in pure MeOH, substantial quantities of RCl form via ion pair return within ion pair **6**.[21]

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For ambiphilic ROCCl, k_{trap} is probably $\sim 10^4$ s^{-1} in pure methanol.[22] The corresponding (ROH)/(RCl + ROMe)[23] distributions, which reflect $k_{\mathrm{trap}}/k_{\mathrm{frag}}$, indicate that the k_{frag} values for **5** fall in the anticipated order, 1-Nor < 1-Bco < 1-Ad, but the differences between k_{frag} must be rather small. To quantitate this conclusion, we measured k_{frag} directly by laser flash photolysis (LFP).[6,7,9]

LFP at 351 nm and 25 °C of diazirine **4** (R = 1-Nor) in DCE ($A_{356} = 0.5$) in the presence of pyridine produced an ylide absorption at 416 nm due to pyridine trapping of ROCCl. A correlation of the apparent rate constants for ylide formation ($k_{\mathrm{obs}} = 1.6-5.0 \times 10^5$ s^{-1}) versus [pyridine] (1.65−7.42 M) was linear (8 points, $r = 0.997$) with a slope of 5.47×10^4 M^{-1} s^{-1}, equivalent to the rate constant for ylide formation (k_y), and a *Y*-intercept of 2.91×10^4 s^{-1}, equivalent to k_{frag} for 1-NorOCCl;[7,24] see Supporting Information, Figure S-1. Repetition afforded $k_{\mathrm{frag}} = 3.78 \times 10^4$ s^{-1} ($k_y = 5.46 \times 10^4$ M^{-1} s^{-1}), leading to an average $k_{\mathrm{frag}} = 3.3 \pm 0.4 \times 10^4$ s^{-1}. Similarly, we measured $k_{\mathrm{frag}} = 1.5 \pm 0.2 \times 10^5$ s^{-1} for 1-BcoOCCl (two runs). One example ($k_{\mathrm{frag}} = 1.34 \times 10^5$ s^{-1}, $r = 0.998$ for seven points) is included in the Supporting Information as Figure S-2.

k_{frag} was determined for 1-AdOCl by LFP of **4** (R = 1-Ad, $A_{355} = 0.4$) with time-resolved infrared (TRIR) monitoring of the CO formed as the carbene fragmented.[7,25] We thus obtained $k_{\mathrm{frag}} = 5.9 \times 10^5$ s^{-1} in DCE. The time dependence of CO formation at 2132 cm^{-1} is illustrated in the Supporting Information, Figure S-3.

k_{frag} for ROCCl does increase with decreasing strain energy of the derived carbocation, but the dependence is very compressed: 1-NorOCCl, 3.3×10^4 s^{-1} < 1-BcoOCCl, 1.5×10^5 s^{-1} < 1-AdOCCl (5.9×10^5 s^{-1}). One must be wary of small differences between k_{frag} values obtained by variant methodologies,[7,9] but there is no doubt that the *range* of k_{frag} values for these bridgehead ROCCl is small. In particular, the 10^{10} spread of k_{solv} for **1**−**3** (X = OTs) is reduced to $\sim$18 for k_{frag} when X = OCCl.

This enormous compression of k_{frag} must reflect low activation energies and early transition states for the **5** → **6** transformation; eq 1. We determined $E_a = 9.0 \pm 0.2$ kcal/mol, $\log A = 11.2 \pm 0.1$ s^{-1} (two experiments) for the fragmentation of 1-NorOCCl in DCE. Rate constants were measured from 0 to 50 °C ($r = 0.996$ for nine points); an example appears as Figure S-4 in the Supporting Information. Similarly, E_a for the fragmentation of 1-BcoOCCl in DCE was determined as 4.4 kcal/mol, $\log A = 8.44$ s^{-1} ($r = 0.987$, five points).

The 9 kcal/mol activation energy for the fragmentation of 1-NorOCCl is the highest yet measured for this type of reaction.[6,7] E_a for the fragmentation of 1-NorOCCl is, as expected, larger than that for 1-BcoOCCl, but the difference in log *A* (which favors 1-NorOCCl) narrows the difference in k_{frag} to a factor of only 4.5 at 25 °C.

Using B3LYP/6-31G* methodology,[26a] in analogy to our previous studies,[7−9] we computed E_a's for the fragmentations of carbenes **1** − **3** (X = OCCl) as differences between ground- and transition-state energies.[26b] We obtained E_a (kcal/mol, gas phase): 1-NorOCCl, 25.2; 1-BcoOCCl, 10.8, 1-AdOCCl, 7.4; and in simulated DCE: 1-NorOCCl, 14.6; 1-BcoOCCl, 2.2; 1-AdOCCl, −0.95.

The computed E_a's are in the appropriate order, and the DCE values are in reasonable agreement with experiment for 1-NorOCCl and 1-BcoOCCl. Computed ground-state and transition-state geometries for 1-NorOCCl appear as Figure S-5 in the Supporting Information.

In conclusion, fragmentations of ROCCl readily afford bridgehead carbocations as [R$^+$ OC Cl$^-$] ion pairs. The low activation energies associated with these reactions dramatically compress the kinetic range for 1-norbornyl, 1-bicyclo[2.2.2]octyl, and 1-adamantyloxychlorocarbene fragmentations.

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Supporting Information Available: Tables of product distributions; kinetics and Arrhenius correlations; ground- and transition-state geometries for 1-NorOCCl; thermodynamic data for ground states and transition states of **1**−**3** (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

References

(1) (a) Lowry, T. H.; Richardson, K. S. *Mechanism and Theory in Organic Chemistry*, 3rd ed.; Harper and Row: New York, 1987; pp 391−393. (b) Carey, F. A.; Sundberg, R. J. *Advanced Organic Chemistry, Part A: Structure and Mechanism*, 4th ed.; Kluwer Academic/Plenum: New York, 2000; pp 287−289.

(2) k_{rel} (X = OTs):[1a] **1** (10^{-10}), **2** (10^{-4}), **3** (1.0); (X = Br):[1b] **1** (10^{-10}), **2** (10^{-3}), **3** (1.0).

(3) Bingham, R. C.; Schleyer, P.v. R. *J. Am. Chem. Soc.* **1971**, *93*, 3189.

(4) Review: Fort, R. C., Jr. In *Carbonium Ions*; Olah, G. A., Schleyer, P. v. R., Eds.; Wiley: New York, 1973; Vol. IV, Chapter 32.

(5) Abboud, J.-L. M.; Herreros, M.; Notario, R.; Lomas, J. S.; Mareda, J.; Müller, P.; Rossier, J.-C. *J. Org. Chem.* **1999**, *64*, 6401. Abboud, J.-L. M.; Castano, O.; Della, E. W.; Herreros, M.; Müller, P.; Notario, R.; Rossier, J. C. *J. Am. Chem. Soc.* **1997**, *119*, 2262.

(6) Moss, R. A. *Acc. Chem. Res.* **1999**, *32*, 969.

(7) Moss, R. A.; Johnson, L. A.; Yan, S.; Toscano, J. P.; Showalter, B. M. *J. Am. Chem. Soc.* **2000**, *122*, 11256.

(8) Yan, S.; Sauers, R. R.; Moss, R. A. *Org. Lett.* **1999**, *1*, 1603.

(9) Moss, R. A.; Zheng, F.; Sauers, R. R.; Toscano, J. P. *J. Am. Chem. Soc.* **2001**, *123*, 8109.

(10) Bixler, R. L.; Niemann, C. *J. Org. Chem.* **1958**, *23*, 742. Della, E. W.; Cotsaris, E.; Hine, P. T. *J. Am. Chem. Soc.* **1981**, *103*, 4131.

(11) Kostova, K.; Dimitrov, V. *Synth. Commun.* **1995**, *25*, 1575. Bixler and Niemann, ref 10. Wiberg, K. B.; Lowry, B. R. *J. Am. Chem. Soc.* **1963**, *85*, 3188.

(12) Moss, R. A.; Kaczmarczyk, G. M.; Johnson, L. A. *Synth. Commun*. **2000**, *30*, 3233.

(13) Moss, R. A.; Perez, L. A.; Wlostowska, J.; Guo, W.; Krogh-Jespersen, K. *J. Org. Chem.* **1982**, *47*, 4177. Grigat, E.; Pütter, R.; Konig, C. *Chem. Ber.* **1965**, *98*, 144.

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

(15) λ_{max} (nm) for **4**: R = 1-Nor, 350, 364 (DCE); R = 1-Bco, 353, 366 (DCE); R = 1-Ad, 353, 370 (pentane).

(16) About 10% of 1-bicyclo[3.2.1]octyl chloride was also formed in the experiments involving **4** and **5** (R = 1-Bco) due to contamination.[11]

(17) Moss, R. A.; Balcerzak, P. *J. Am. Chem. Soc.* **1992**, *114*, 9386. Moss, R. A.; Ho, G. J.; Wilk, B. K. *Tetrahedron Lett.* **1989**, *30*, 2473.

(18) Smith, N. P.; Stevens, I. D. R. *J. Chem. Soc. Perkin Trans. II* **1979**, 1298.

(19) Moss, R. A.; Wilk, B. K.; Hadel, L. M. *Tetrahedron Lett.* **1987**, *28*, 1969.

(20) The dielectric constants of MeOH and DCE are 32.6 and 10.36, respectively. MeOH may also catalyze the fragmentation of **5** by specific solvation of the chloride leaving group; cf.; the solvolysis of 1-AdCl: Gajewski, J. J. *J. Am. Chem. Soc.* **2001**, *123*, 10877.

(21) Adamantene is not a precursor of 1-AdOMe in the fragmentation and methanolysis of 1-AdOCCl; photolysis of **4** (R = 1-Ad) in MeOD produces 1-AdOMe containing no deuterium (GC−MS). 1-Norbornene is similarly excluded as an intermediate in the fragmentation/methanolysis of 1-NorOCCl.

(22) Du, X.-M.; Fan, H.; Goodman, J. L.; Kesselmayer, M.A.; Krogh-Jespersen, K.; LaVilla, J. A.; Moss, R. A.; Shen, S.; Sheridan, R. S. *J. Am. Chem. Soc.* **1990**, *112*, 1920.

(23) (ROH)/(RCl + ROMe) = 0.71 (1-Nor), 0.48 (1-Bco), 0.096 (1-Ad).

(24) For this methodology, see: (a) Jackson, J. E.; Soundararajan, N.; Platz, M. S.; Liu, M. T. H. *J. Am. Chem.. Soc.* **1988**, *110*, 5595. (b) Moss, R. A.; Ge, C.-S.; Maksimovic, L. *J. Am. Chem.* Soc. **1996**, *118*, 9792.

(25) Wang, Y.; Yuzawa, T.; Hamaguchi, H.; Toscano, J. P. *J. Am. Chem. Soc.* **1999**, *121*, 2875 and references therein. Toscano, J. P. *Adv. Photochem.* **2000**, *26*, 41. For comparisons of TRIR and LFP-UV k_{frag} data, see ref 9.

(26) (a) *Gaussian 98*, revision A.7; Gaussian, Inc.: Pittsburgh, PA, 1998. DFT calculations used Becke's three-parameter hybrid method with the LYP correlation functional: Becke, A. D. *J. Chem. Phys.* **1993**, *98*, 5648. (b) Single-point calculations were based on fully optimized gas-phase geometries with ZPE and thermal corrections from B3LYP/6-31G* results. Simulated DCE solvent calculations employed $\in = 10.36$, and the pcm and scipcm protocols.

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