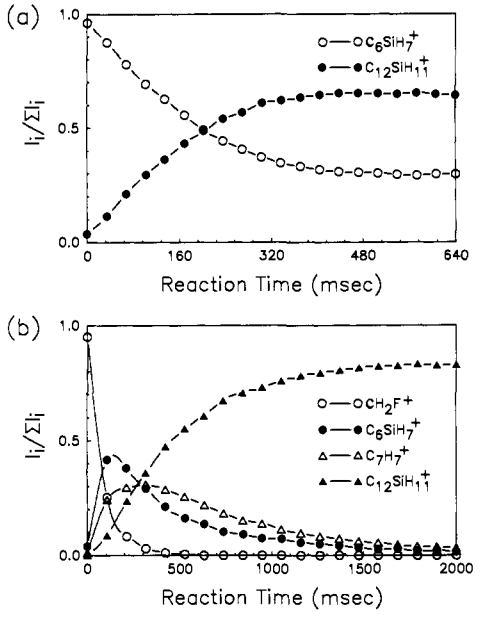

Figure 1. (a) Temporal variation of ion abundances following the isolation of $C_6SiH_7^+$ in phenylsilane at a pressure of 1.8×10^{-7} Torr (approximate value). The electron impact ionization energy was 20 eV. (b) Temporal variation of ion abundances following the isolation of CH_2F^+ in a 1:6 mixture of phenylsilane and CH_3F at a total pressure of 6.2×10^{-7} Torr (approximate value). The electron impact ionization energy was 30 eV. For purposes of clarity, in both the figures minor products arising from side reactions are not shown. These ions are, however, included in the total ion count.

silacycloheptatrienyl (Ib) and the phenylsilyl (IIb) cations.

Figure 1b shows the temporal variation of ion abundances following the isolation of CH_2F^+ in a 1:6 mixture of phenylsilane and CH_3F at a total pressure of $\sim 6 \times 10^{-7}$ Torr. Besides CH_2F^+, the other ions that participate in the reaction processes are $C_7H_7^+$, $C_6SiH_7^+$, and $C_{12}SiH_{11}^+$. Standard double resonance ion ejection techniques[5] enabled reaction processes 1-5 to be identified.

$$CH_2F^+ + C_6H_5SiH_3 \rightarrow C_6SiH_7^+ + CH_3F \quad (2)$$

$$CH_2F^+ + C_6H_5SiH_3 \rightarrow C_7H_7^+ + SiH_3F \quad (3)$$

$$C_7H_7^+ + C_6H_5SiH_3 \rightarrow C_6SiH_7^+ + C_7H_8 \quad (4)$$

$$C_6SiH_7^+ + CH_3F \rightarrow C_7H_7^+ + SiH_3F \quad (5)$$

Isolation of $C_6SiH_7^+$ produced by electron impact ionization of phenylsilane in the same mixture of phenylsilane and CH_3F indicates that the fraction of $C_6SiH_7^+$ which is unreactive with phenylsilane is unreactive with CH_3F as well, while the reactive fraction of $C_6SiH_7^+$ is seen to undergo both reactions 1 and 5. These observations strongly suggest that $C_6SiH_7^+$ generated by reaction 2 is the same reactive species generated from phenylsilane by electron impact. In a mixture of CF_4 and phenylsilane, the reactive isomer of $C_6SiH_7^+$ is exclusively generated by the reaction channel of CF_3^+ with phenylsilane which is analogous to process 2. It is entirely reasonable that "soft" chemical ionization processes such as hydride abstraction (by CH_2F^+, $C_7H_7^+$, and CF_3^+) are likely to generate the phenylsilyl cation. We therefore, propose that the reactive isomer of $C_6SiH_7^+$ is the phenylsilyl cation (IIb).

From Figure 2 it can be seen that the unreactive isomer of $C_6SiH_7^+$, which is the dominant product at electron energies below 14 eV, decreases monotonically until the ratio of the unreactive to reactive isomers attains a constant value of ~ 0.5 at electron energies greater than 20 eV. Such behavior is qualitatively similar to the analogous process in toluene (as studied by ion cyclotron resonance spectrometric techniques[2i,m]), where the ion analogous to the unreactive isomer of $C_6SiH_7^+$ is Ia ($\Delta H_f \approx 206$ kcal mol^{-1}[6])

(5) Anders, L. R.; Beauchamp, J. L.; Dunbar, R. C.; Baldeschweiler, J. D. *J. Chem. Phys.* **1966**, *45*, 1062.

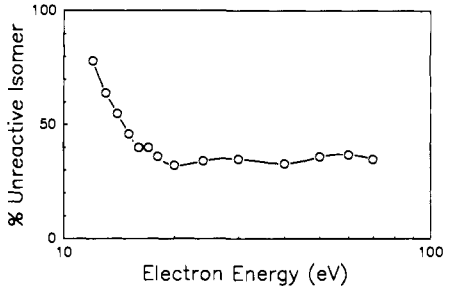

Figure 2. Variation of the percentage of the unreactive $C_6SiH_7^+$ isomer as a function of electron impact ionization energy (uncorrected) of phenylsilane at a pressure of 5.5×10^{-8} Torr (approximate value). The fraction of the unreactive $C_6SiH_7^+$ isomer is defined as the ratio of the steady-state (measured between 1500 and 2000 ms) abundance of $C_6SiH_7^+$ to the abundance of $C_6SiH_7^+$ measured 5 ms after the electron beam pulse. The width of the electron beam pulse was ~ 20 ms.

while the ion analogous to the reactive isomer of $C_6SiH_7^+$ is IIa ($\Delta H_f \approx 217$ kcal mol^{-1}[6]). This leads us to propose that the unreactive isomer of $C_6SiH_7^+$ is the silacycloheptatrienyl cation (Ib). The greater yield of Ib at low electron impact energies indicates that it is perhaps more stable than IIb. Further studies are in progress in our laboratory to quantitatively determine the relative stabilities of the $C_6SiH_7^+$ isomers and the energetics of their interconversion.

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Registry No. Ib, 139732-71-1; IIb, 139732-72-2; $PhSiH_3$, 694-53-1; CH_3F, 593-53-3; CF_4, 75-73-0.

(6) Average of the values listed in the following: Lias, S. G.; Bartmess, J. E.; Liebman, J. F.; Holmes, J. L.; Levin, R. D.; Mallard, W. G. *J. Phys. Chem. Ref. Data* **1988**, *17*, Suppl. No. 1.

An Unusually Rapid Intramolecular General-Base Catalysis. Relevance to Enzymology

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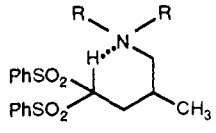
Intramolecular general-base catalyses are notoriously inefficient;[1] "effective molarities" in organic systems rarely exceed 10 M. Contrast this with chymotrypsin, an enzyme that operates via a general-base mechanism worth 10^8 in rate acceleration.[2] Few comparisons in bioorganic chemistry are more humbling.

We have proposed that enzyme-like rates are possible when two reactive species are held rigidly at "contact distances" too short to accommodate intervening solvent.[3] The question arose whether "spatiotemporal" factors could, in part, also explain the general-base disparity between enzymes and their chemical models. An opportunity to explore this possibility arose when an article by R. L. Harlow et al.[4] came to our attention half a decade after its publication.

(1) Kirby, A. J.; Williams, N. H. *J. Chem. Soc., Chem. Commun.* **1991**, 1643.
(2) Bender, M. L.; Kézdy, F. J.; Gunter, C. R. *J. Am. Chem. Soc.* **1964**, *86*, 3714.
(3) Menger, F. M. *Acc. Chem. Res.* **1985**, *18*, 128. Menger, F. M. *Adv. Mol. Model.* **1988**, *1*, 189. Menger, F. M.; Ladika, M. *J. Am. Chem. Soc.* **1988**, *110*, 6794.
(4) Harlow, R. L.; Li, C.; Sammes, M. P. *J. Chem. Soc., Chem. Commun.* **1984**, 818.

0002-7863/92/1514-3574$03.00/0

In 1984 Harlow et al.[4] published the X-ray crystal structure of an amino disulfone, I (R = CH_3). The structure revealed an intramolecular CH···N distance of 2.34 Å (significantly less than the sum of the van der Waals radii, 2.75 Å). It was also known that the ^1H NMR spectrum of I (CD_2Cl_2, 22 °C) has a methine signal at 6.2 ppm (about 2 ppm downfield from the shift in protic solvents where the intramolecular hydrogen bond becomes uncoupled).[5] These striking results led us to examine an intramolecular general-base-catalyzed proton exchange between the amino group of I (R = H) and the methine proton, two entities shackled at a "contact distance".[6]



I

Key NMR observations (from a Nicolet F-360 spectrometer) on 25 mM I in toluene-d_8 or $CDCl_3$ are now summarized: (a) I (R = CH_3) at +20 °C in both solvents gave the expected 6.3 ppm methine multiplet. The methine proton hydrogen-bonds to the dimethylamino group, but the latter, lacking a labile proton of its own, cannot promote intramolecular exchange. (b) I (R = H) in toluene-d_8 at +20 °C has a methine signal that is lost in the base line. Cooling the sample to −40 °C (to impede the NH/CH exchange that was obviously occurring) produced a broad hump (δ = 6.1 ppm, $W_{1/2}$ = 162 Hz). Further cooling narrowed the signal to 53 Hz at −60 °C and 27 Hz at −80 °C. Thus, even reducing the temperature to −80 °C was insufficient to prevent NH/CH exchange and to generate fine splitting. This proton interchange must be intramolecular because all spectra of I (R = H) were concentration-independent (0.4–100 mM). (c) Proton exchange was slower in $CDCl_3$ than in toluene-d_8. This was evident from the fact that at +20 °C the methine signal was now visible ($W_{1/2}$ = 115 Hz) and that at −40 °C the signal had a $W_{1/2}$ of 24 Hz rather than the 162 Hz observed in toluene-d_8.

In order to compare equivalent intra- and intermolecularly-catalyzed exchanges, we also examined the reaction in toluene-d_8 between $(PhSO_2)_2CHCH_2CH(CH_3)_3$ (3.0 mM) and *n*-hexylamine (30 mM). The methine signal appeared here as a triplet at temperatures up to +100 °C. Thus, under the specified conditions, the intramolecular amine at −80 °C manifests a catalysis that the intermolecular amine is unable to accomplish at a temperature 180 °C higher!

When I (R = H) and $(PhSO_2)_2CHCH_2CH(CH_3)_2$ were mixed at 3.0 mM each, the former exchanged whereas the latter did not. This was ascertained from their distinct methine NMR signals. Therefore, the reactivity of I (R = H) cannot be attributed to an adventitious impurity.

An "order-of-magnitude" estimate of the rate difference between intra- and intermolecular processes is possible via a traditional set of assumptions. The observed k_{inter} at 30 mM amine and 100 °C must be no faster than the lower limit of the NMR time scale (10^2 s^{-1}). At 1 M amine, the maximum observed k_{inter} would then be 3×10^3 s^{-1} at 100 °C. Employing a "conservative" activation enthalpy of only 12 kcal/mol,[7] one can calculate that the intermolecularly-catalyzed exchange should be 10^5 slower at −80 °C than at +100 °C, giving an observed $k_{inter} = 3 \times 10^{-2}$ s^{-1}. Since, however, the intramolecular counterpart exchanges rapidly at −80 °C, k_{intra} equals about 10^3 s^{-1}. Accordingly, intramolecular exchange proceeds at least 10^4–10^5 times faster than the intermolecular reaction.

The carbon acid of I has a pK_a value of 13.8,[8] while the pK_a of its amino group is only 10. Consequently, the proton must "swim upstream" against a 3.8 pK_a gradient during its transfer from carbon to the proximate nitrogen. Of course, 3.8 grossly underestimates the actual thermodynamic barrier because the number is based on acidity in water, not in toluene. Ion-generating equilibria are often disfavored by 10^7–10^8 in aprotic solvents relative to water,[9] so that the barrier to $R_3C^-H_3N^+R$ formation could be orders of magnitude greater than $10^{3.8}$. The extremely fast intramolecular proton exchange of I (R = H) seems, in this light, all the more remarkable.

One final set of experiments turned out to be critical to understanding the chemistry of I. Dynamic NMR methods[10] were applied to the reaction between $(PhSO_2)_2CHCH_3$ and *n*-hexylamine in toluene-d_8 under conditions wherein intermolecular exchange became detectable (10 mM carbon acid, 50 mM amine). Line-shape analysis on the methyl group showed that the observed rate constant for exchange increases a mere 30% upon elevation of the temperature a full 52 °C! Intermolecular exchange must, therefore, be a composite of at least three steps: (a) acid–base association to achieve a "contact distance"; (b) actual C-to-N proton transfer to form an ion-pair intermediate;[11] and (c) rapid return of a different amine proton. Step b is, no doubt, accelerated by an increase in temperature. On the other hand, the prequilibrium hydrogen-bonding (step a) should be impeded by a temperature increase, with the result that there exists, overall, only a slight temperature dependence.

The above mechanism invalidates the traditional comparison of intra- and intermolecular rates given above.[12] More importantly, however, the mechanism helps explain why the intramolecular reaction is so fast at −80 °C. Compound I possesses a predisposed "contact distance" (2.34 Å if identical to the solid state). Within such a geometry, proton transfer is fast on the NMR time scale despite the nonpolar solvent, the low temperature, and the sizable pK_a barrier.[13] *A concentration-independent and sustained contact with no intervening solvent: therein lies the source of I's reactivity.*[3]

The faster intramolecular rate in toluene-d_8 relative to $CDCl_3$, mentioned earlier, reflects the dominant role of prereaction association. Thus, a tighter hydrogen bond in toluene-d_8 must dominate over ion-pair stabilization in the more polar $CDCl_3$.

It is tempting to extrapolate our results to enzymes. Accordingly, we propose that enzymes achieve their "uphill" proton transfers[14] by imposing contact distances within hydrophobic pockets at the active site. This proposal expresses, once again, the notion of spatiotemporal control.[3]

Acknowledgment. Work was supported by the National Science Foundation.

(5) Li, C.; Sammes, M. P. *J. Chem. Soc., Perkin Trans. 1* **1983**, 1303.

(6) It has been argued recently that enzymatic α-proton abstraction from a ketone is greatly facilitated by carbonyl protonation. This, however, displaces rather than solves the problem of carbon acid acidity at active sites because one now has to wonder how a carbonyl is protonated at pH = 7. See: Gerlt, J. A.; Kozarich, J. W.; Kenyon, G. L.; Gassman, P. G. *J. Am. Chem. Soc.* **1991**, *113*, 9667.

(7) A computer search for activation parameters in related alcoholate-catalyzed enolizations listed ΔH^* values ranging from 5 to 22 kcal/mol.

(8) Hibbert, F. *J. Chem. Soc., Perkin Trans. 2* **1973**, 1289.

(9) Maran, F.; Celadon, D.; Severin, M. G.; Vianello, E. *J. Am. Chem. Soc.* **1991**, *113*, 9320.

(10) Menger, F. M.; Saito, G. *J. Am. Chem. Soc.* **1973**, *95*, 6838.

(11) For arguments against a concerted four-membered cyclic transition state, see: Menger, F. M.; Smith, J. H. *J. Am. Chem. Soc.* **1972**, *94*, 3824.

(12) The assumed activation energy of 12 kcal/mol[7] was taken from literature values based on protic solvents (the only data available). In accordance with our results, and with spatiotemporal theory,[3] much of this energy requirement derives from the need to desolvate the base prior to actual proton abstraction. In toluene, this step is minimized.

(13) The explanation for the fast reaction is essentially the same as that advanced by Kirby and Williams in ref 1. Their effective molarity, claimed to be the highest yet measured for proton transfer to carbon, is only 300 M.

(14) Stubbe, J.; Abeles, R. H. *Biochemistry* **1980**, *19*, 5505. Xue, L.; Talalay, P.; Mildvan, A. S. *Biochemistry* **1990**, *29*, 7491. Alter, G. M.; Casazza, J. P.; Zhi, W.; Nemeth, P.; Srere, P. A.; Evans, C. T. *Biochemistry* **1990**, *29*, 7557. Davis, J. T.; Moore, R. N.; Imperiali, B.; Pratt, A. J.; Kobayashi, K.; Masamune, S.; Sinskey, A. J.; Walsh, C. T.; Fukui, T.; Tomita, K. *J. Biol. Chem.* **1987**, *262*, 82.