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Origins of Steric Effects in General-Base-Catalyzed Enolization: Solvation and Electrostatic Attraction

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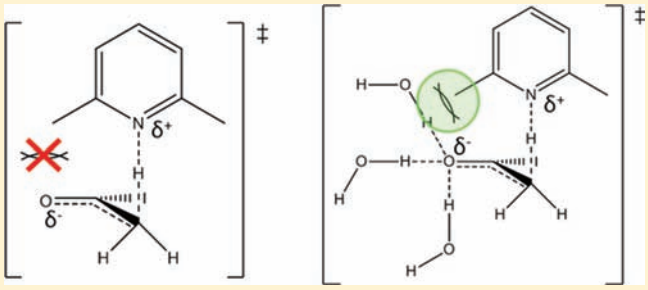
ABSTRACT: Brønsted plots for general-base-catalyzed enolization of aldehydes and ketones show significant negative deviations for the rates of proton removal by sterically hindered amine bases. The origins of the deviations are not apparent from considerations of interactions at the site of the proton transfer. Contrasting behavior is observed in general-base-catalyzed proton removal from an iminium derivative, *N1′*-methyl-2-(1-hydroxybenzyl)thiamin (NMHBnT), which shows no deviations from the Brønsted correlation for sterically hindered amine bases. The difference in behavior for these two systems suggests that the steric effects arise from disruption of solvation of the enolate enforced by the electrostatic requirements of the overall process. This interpretation also can account for reduced steric effects for enolization in the presence of metal ions.



INTRODUCTION

Transfers of protons from carbon acids to Brønsted bases involve transition states with relatively large distances between heavy atoms, where there would be minimal steric effects on reaction rates in comparison with the steric effects seen in nucleophilic additions. In one practical application, directing reactions toward elimination rather than substitution (E2 vs S_N2) is accomplished by using "sterically hindered" bases, with which proton transfers occur readily while nucleophilic reactions are blocked.[1] Contrary to these expectations, steric-induced rate reductions are well-established features in the general-base-catalyzed formation of enolates from simple ketones[2,3] and aldehydes.[4] Feather and Gold[2,3] proposed that the effects are the result of unprecedented transition-state interactions (Figure 1), but this model was not supported in more detailed analyses by Hine and co-workers.[4−7]

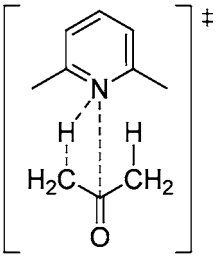


Figure 1. Proposed coplanar transition state.[2]

In considering alternative explanations, Hine[4] noted the proposal of Lewis and Allen[6] that steric effects in proton transfer reactions could be due to disruption of solvation of the conjugate base. If the observed steric effects do arise from interference with solvation of the developing enolate, then proton removal from a comparably acidic carbon acid that has a reduced solvation requirement would not be affected by alkyl substituents on the base. Transfer of the C2α proton of *N1′*-methyl-2-(1-hydroxybenzyl)thiamin (NMHBnT) (Scheme 1) leads to a carbanion that is internally neutralized upon delocalization, where loss of charge produces a decreased solvation requirement. The solvation hypothesis would predict that no steric effect should be observed in this general-base-catalyzed process. In this paper, we report that the rates of removal of the C2α proton from NMHBnT by a series of hindered and unhindered Brønsted bases produce a Brønsted plot with no deviations. This result contrasts as predicted with the plots showing steric deviations in the formation of enolates.

EXPERIMENTAL SECTION

Materials and Methods. Reagents were purchased and used without further purification. All UV spectra and kinetic data were collected with a UV−vis spectrometer equipped with a temperature-regulated cell compartment. The system was interfaced to a computer for data collection and analysis.

NMHBnT. 2-(1-Hydroxybenzyl)thiamin (HBnTh) was prepared according to the reported process.[8] ^{1}H NMR (400 MHz, DMSO-d_6): δ 9.00 (br, 2H), 7.88 (d, 1H, J = 3 Hz), 7.48−7.44 (m, 2H), 7.30−7.23 (m, 3H), 7.13 (s, 1H), 6.42 (s, 1H), 5.73 (d, 1H, J = 18 Hz), 5.44 (d, 1H, J = 18 Hz), 3.72−3.62 (m, 2H), 3.04 (t, 2H, J = 5 Hz), 2.49 (s, 3H), 2.28 (s, 3H).

Methylation of the pyrimidine ring at the N1′ position was carried out by a procedure adapted from that of Zoltewicz and Baugh.[9] ^{1}H NMR (400 MHz, DMSO-d_6): δ 9.24 (s, 1H), 8.41 (s, 1H), 7.69 (d, 1H), 7.40−7.37 (m, 2H), 7.29−7.20 (m, 3H), 6.71 (s, 1H), 6.30 (d, 1H), 5.30 (s, 2H), 3.79−3.65 (m, 2H), 3.51 (s, 3H), 3.12−2.99 (m,

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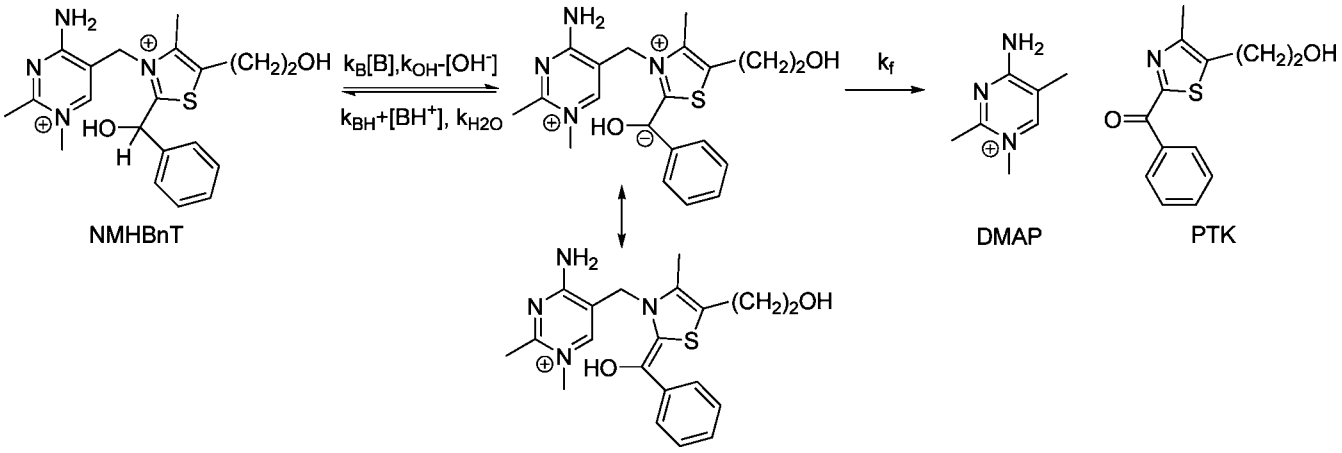
Scheme 1. Enamine Formation and Fragmentation from NMHBnT



2H), 2.48 (s, 3H), 2.28 (s, 3H). ESI-MS $[C_{20}H_{25}N_4O_2S]^{2+}$: m/z 192.6 (M/2).

NMHBnT-C2α-*d*. The isotopic derivative of NMHBnT was synthesized as previously reported.[10] Condensation of thiamin hydrochloride with benzaldehyde-1-*d* yielded HBnT-C2α-*d*. NMHBnT-C2α-*d* was produced by methylation of the pyrimidine ring at the N1′ position of HBnT-C2α-*d* with dimethyl sulfate as above. ^{1}H NMR (300 MHz, DMSO-d_6): δ 9.30 (s, 1H), 8.51 (s, 1H), 7.72 (s, 1H), 7.44−7.30 (m, 5H), 6.80 (s, 1H), 5.38 (s, 2H), 3.77 (m, 2H), 3.58 (s, 3H), 3.11 (m, 2H), 2.52 (s, 3H), 2.32 (s, 3H). ESI-MS $[C_{20}H_{24}DN_4O_2S]^{2+}$: m/z 193.3 (M/2).

pK_a Determinations. The method of Andon and Cox[11] was used to determine the acid dissociation constants of the pyridine derivatives under conditions similar to those of our kinetic measurements. Spectral scans were recorded for acidic, basic, and neutral-buffered solutions of each pyridine derivative. The λ_{max} of the pyridine in acid was determined, and the absorbances under acidic (A_{acid}), basic (A_{base}), and buffered (A_{buffer}) conditions at that wavelength were used to calculate the dissociation constant according to eqs 1 and 2:

$$pK_a = pH + \log\left(\frac{A_{Buffer} - A_{Base}}{A_{Acid} - A_{Buffer}}\right) + \log \gamma_{BH^+} \quad (1)$$

$$\log \gamma_{BH^+} = -0.5262\left(\frac{\sqrt{I}}{1 + \sqrt{I}}\right) = 0.2631 \quad (2)$$

The acid dissociation constant of protonated bis-tris at 40 °C and I = 1.0 was approximated using a temperature coefficient (dpK_a/dT) of −0.022/°C and the Debye−Hückel relation (eq 3), in which z is the charge of the conjugate acid and A is the temperature constant (A = 0.5262 at 40 °C):[12]

$$pK_a(I = 1\,M) = pK_a(2z - 1)\left[\frac{A\sqrt{I}}{1 + \sqrt{I}} - 0.1I\right] \quad (3)$$

On the basis of determinations conducted in triplicate, the representative error in our reported pK_a values is ±0.1 pH units. The pK_a we used for 2-isopropylimidazole was 7.70, which was based on the temperature coefficient for the pK_a of imidazole.[12,13]

Kinetics. Measurements of the rate of fragmentation of NMHBnT were conducted in buffered solutions (0.1−0.6 M) of substituted pyridines and other nitrogenous bases (pH = pK_a, I = 1.0 M, 40 °C) in the cell compartment of a UV−vis spectrometer with the temperature controlled to ±0.1 °C. The reactions were followed at 328 nm, the λ_{max} of the product PTK (Scheme 1). Observed first-order rate constants k_{obs} were calculated from nonlinear regression analysis using the integrated first-order rate expression. For slower reactions, the rate constants were determined by the method of initial rates to 5% or less conversion. Primary kinetic isotope effects (KIEs) were calculated on the basis of the rates of fragmentation of NMHBnT-C2α-*d*.

The rates of deprotonation of acetone were measured using the procedure of Feather and Gold,[3] which follows the disappearance of triiodide absorbance at 353 nm. First-order rate constants were obtained by dividing $-d[I_2]/dt$ by the concentration of acetone.[14]

RESULTS AND DISCUSSION

The magnitudes of the observed first-order rate constants for proton removal from NMHBnT are linearly dependent upon the concentration of the base component of each buffer. From the mechanism in Scheme 1, we obtain

$$k_{obs} = \frac{(k_B[B] + k_{OH^-}[OH^-])k_f}{k_{BH} + [BH^+] + k_{H_2O} + k_f} \quad (4)$$

Since the rate constant for fragmentation of the conjugate base, k_f, is ~10^5 s^{-1}, proton removal is rate-determining (in terms of competing reactions of the intermediate, $k_f \gg k_{BH} + [BH^+] + k_{H_2O}$).[15] This is consistent with the observed dependence of the reaction rate on the buffer concentration and further information from related studies.[16,17] Thus,

$$k_{obs} = k_B[B] + k_{OH^-}[OH^-] \quad (5)$$

From eq 5, we see that k_{obs} is linearly dependent on the concentration of the base component of the buffer; the second-order rate constant (k_B) can be obtained from the slope of a plot of k_{obs} versus [B]. The resulting second-order rate constants and pK_a values are summarized in Table 1. A Brønsted plot obtained from these data gave β = 0.85 with r^2 = 0.98 (Figure 2a).

Second-order rate constants for the deprotonation of NMHBnT-C2α-*d* by 4-picoline and bis-tris were also determined (Table 2). The primary KIEs (k_H/k_D) were calculated from these results.

The Brønsted plot for transfer of the C2α proton of NMHBnT to amine bases shows no deviations for hindered bases (Figure 2a). This contrasts with the established steric effects in general-base-catalyzed enolization of acetone (Figure 2b).[2,3] Both processes involve rate-determining removal of a proton from a carbon acid. Since all of the amine bases leading to steric effects in the work of Feather and Gold were aromatic,[2,3] we further tested the generality of these observations using a tertiary amine that is not a pyridine derivative (bis-tris). Again, there is no deviation from the Brønsted plot for NMHBnT, but there is a significant deviation

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Table 1. Effect of Catalyst Basicity on the Second-Order Rate Constant for the Fragmentation of NMHBnT

catalyst	pK_a[a]	$10^5 k_B$ (M^{-1} s^{-1})
pyridine	5.0	0.62 ± 0.03
3-picoline	5.4	1.0 ± 0.1
4-picoline	5.9	4.0 ± 0.3
2-picoline	5.5	0.87 ± 0.07
3,5-lutidine	5.8	3.0 ± 0.3
bis-tris	6.4	5.8 ± 0.2
2,6-lutidine	6.5	6.0 ± 0.4
2,4,6-collidine	7.0	19 ± 1
2-isopropylimidazole	7.7[b]	150 ± 2

[a]The error in the pK_a values is ±0.1. [b]Estimated from ref 13 and temperature coefficient (dpK_a/dT) for imidazole.

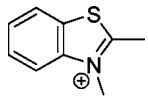
from the plot for acetone, consistent with the model we have proposed.

The primary KIEs observed with 4-picoline and bis-tris confirm that deprotonation of NMHBnT is rate-limiting in the formation of PTK and DMAP (Scheme 1). This value falls within the range of primary KIEs reported for other enolization reactions ($k_H/k_D \approx 2-7$).[18] Proton transfer is clearly rate-limiting.

Zoltewicz and O'Halloran studied the general-base-catalyzed deprotonation of 2,3-dimethylbenzothiazolium ion (DMBT).[19] Their analysis was based on a Brønsted plot that was fit to five data points. Two of the points were rate constants for catalysis by oxyanionic bases. The other three points were for catalysis by neutral amine bases: pyridine, 3-chloropyridine, and phthalazine. The rate constant for catalysis by 2,6-lutidine is 3.7 times lower than the value that would fit the line. However, we have noted that Brønsted correlations for catalysis by carboxylates and pyridines with NMHBnT fall on different plots, presumably because of electrostatic differences between these classes of bases.[15] Thus, the deviation for 2,6-lutidine with DMBT is more likely to be the result of uncertainty in the Brønsted plot. Zoltewicz and O'Halloran had noted that their conclusions were not certain because of the limited data set.[19]

Table 2. Second-Order Rate Constants for the Deprotonation of NMHBnT-C2α-*d*

catalyst	$10^5 k_B$ (M^{-1} s^{-1})	KIE
4-picoline	0.86 ± 0.04	4.6 ± 0.5
bis-tris	1.3 ± 0.2	4.5 ± 0.5



DMBT

Steric Effects and Solvation. As mentioned in the Introduction, Lewis and Allen[6] suggested that disruption of solvation of transition states in the formation of a conjugate base would be a basis for the appearance of steric effects. Oxyanions produced as a consequence of proton transfers from the α-carbon of ketones and aldehydes should be stabilized by solvation through hydrogen bonding with water. The solvation shell surrounding the oxyanion is composed of a primary sphere of water molecules. A secondary sphere encapsulates the primary sphere and also forms an extensive hydrogen-bonding network.[20] The alkyl groups of hindered amine catalysts would disrupt the formation of this large, structured shell, causing a substantial increase in the free energy barriers leading to the transition states. Since enolates and phenoxide are similarly basic,[21] we can approximate an upper limit for the solvation stabilization energy to be 10 kcal/mol, with much larger values having been suggested in an overview by Jencks.[20] The 10-fold depression in the observed rate constant for the enolization of acetone implies a loss of 1.4 kcal/mol (14% of the solvation energy). Since the iminium in NMHBnT cannot act as a hydrogen-bond acceptor, proton removal is less affected by disruption of the solvation shell in the transition state.

Synchronicity and the Magnitude of Steric Effects. According to Bernasconi's principle of nonperfect synchronization,[22,23] delocalization can lag C–H bond cleavage, leaving anionic character localized on carbon in the transition state.[24,25] While there is evidence to suggest significant imbalance in the deprotonation of 2-(1-methoxybenzyl)thiazolium at C2α-H,[26]

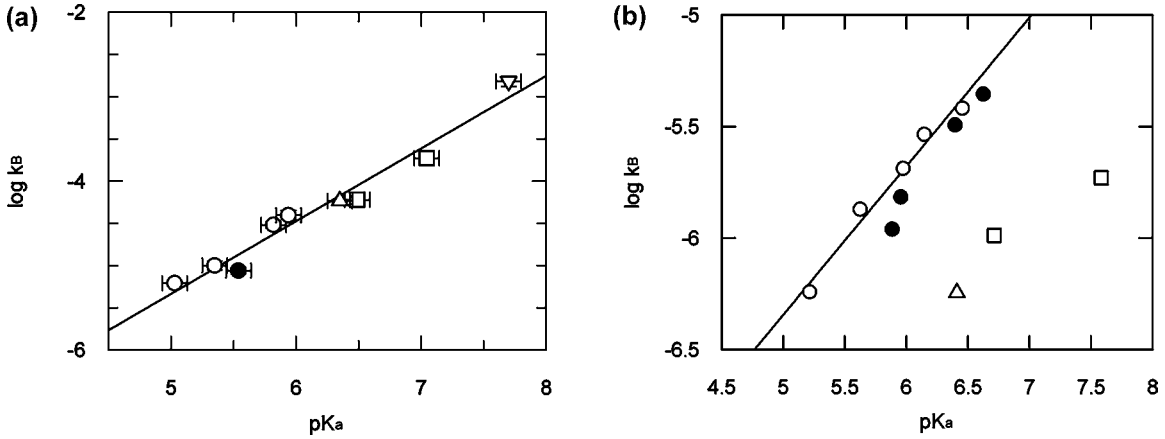


Figure 2. Brønsted plots for deprotonation of (a) NMHBnT ($\beta = 0.85$, $r^2 = 0.98$; 40 °C, pH = pK_a, $I = 1.0$ M) and (b) acetone (25 °C, $I = 0.1$ M; as reported by Feather and Gold[3]) by nonhindered pyridines (○), 2-alkyl-substituted pyridines (●), 2,6-alkyl-substituted pyridines (2,6-lutidine and 2,4,6-collidine) (□), bis-tris (△), and 2-isopropylimidazole (▽). Nonhindered pyridines include pyridine, 3-picoline, 4-picoline, 3,4-lutidine, and 3,5-lutidine. 2-Alkyl-substituted pyridines include 2-picoline, 2-ethylpyridine, 2,4-lutidine, and 2,5-lutidine. All are listed in order of pK_a for each group. The Brønsted line in (a) was fit to all of the data. The Brønsted line in (b) was reproduced as reported by Feather and Gold[3] (error bars were not reported).

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in this case steric effects that arise from disruption of solvation would be minimal regardless of the degree of delocalization. In the case of enolate formation, the extent of charge delocalization could affect the importance of oxyanion solvation. In particular, if delocalization and deprotonation are not synchronized, the carbonyl oxygen would have minimal negative character, and solvation would not contribute significantly to transition-state stabilization. This would lead to variability in the observed magnitude of steric effects in enolizations. However, computations by Saunders[27] suggested that charge on the carbonyl oxygen remains significant even in nonsynchronous enolizations. Thus, solvation of the oxyanion should not be dependent upon the synchronization of movements of the reaction partners.

Steric Effects in the Gas Phase. The rates of proton transfers between pyridines in the gas phase are sensitive to the degree of substitution adjacent to nitrogen atoms of the reactants.[28] This establishes that disruption of solvation is not the only factor contributing to steric effects. However, these gas-phase proton transfer reactions are subject to relatively small steric effects that occur only with very bulky reactants. The similarity of the acids and bases requires a symmetrical transition state with the alkyl substituents directed toward the reaction center, where a single positively charged species is transferred between reactants (Figure 3). This suggests that the

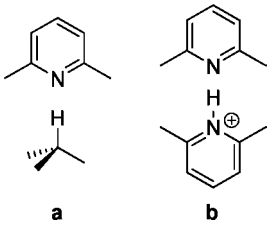

Figure 3. (a) Proton transfer from a tetrahedral site. The alkyl substituents of the pyridine are not proximal to heavy atoms of the acid. (b) Proton transfer from a planar site. The alkyl substituents of the acid and base are directed toward one another.

transition state can tolerate elongation to accommodate the steric bulk of large substituents in these reactions. In contrast, the formation of enolates in solution by proton transfer to amines from carbonyl compounds creates opposite charges whose electrostatic attractions compress the transition state, increasing both the short-range steric effects and the disruption of solvation of the oxyanion.

Metal Ion Cocatalysts Reduce the Solvation Requirement and Reduce Steric Effects. The hypothesis of disruption of the solvation shell is consistent with the decrease in steric effects induced by metal ion cocatalysts. The enolization of methyl acetonylphosphonate (MAcP) by amine bases is subject to significant steric effects, as expected. Significantly, those effects are attenuated in reactions that are further catalyzed by divalent cations (Figure 4).[14,29] Association

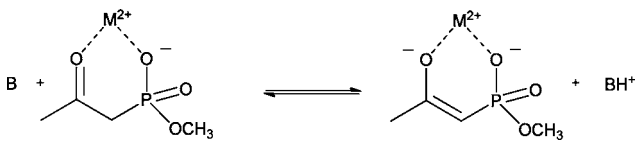

Figure 4. Steric hindrance in MAcP deprotonation is alleviated in the presence of divalent metal.

of the metal ion with the carbonyl oxygen during the transfer of the proton reduces the solvation requirements and the electrostatic demands of the resulting enolate.

Importance of Solvation in Enzymic Catalysis. The proposed sources of differential steric patterns in proton removal from carbon acids are also consistent with what is seen in enzyme-catalyzed reactions. The very low acidity of typical carbon acids in those reactions is a clear indication that the environment alters the barrier to the reaction in such a way that formation of the carbanion overcomes an inherent electrostatic stress in the transition state for proton removal.[30] In enzymic reactions, the carbonyl compound may be coordinated to a metal ion, forming an ion pair that is stabilized electrostatically as in the model presented for the enolization of MAcP (Figure 4). Therefore, enzyme catalysts can accelerate proton transfer reactions by controlling both solvation and the distance between the reactive partners.[31] Another common mode for enzymic activation involves the formation of an iminium derivative of the carbonyl compound,[32] where a positive charge pre-exists on the protonated nitrogen center that may be derived from a carbonyl oxygen.[33]

■ CONCLUSIONS

Our results strongly support the hypothesis that the apparent steric hindrance observed in enolization reactions arises from the disruption of transition-state solvation in bases with adjacent alkyl substituents and is enforced by electrostatic effects. The contrast with related reactions with clearly different solvation requirements is a key observation that is consistent with this hypothesis.

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■ REFERENCES

(1) Smith, M. B.; March, J. *Advanced Organic Chemistry*, 5th ed.; Wiley: New York, 2001.
(2) Feather, J. A.; Gold, V. *Proc. Chem. Soc., London* **1963**, 306.
(3) Feather, J. A.; Gold, V. *J. Chem. Soc.* **1965**, 1752.
(4) Hine, J.; Houston, J. G.; Jensen, J. H.; Mulders, J. *J. Am. Chem. Soc.* **1965**, *87*, 5050.
(5) Bordwell, F. G.; Scamehorn, R. G. *J. Am. Chem. Soc.* **1968**, *90*, 6749.
(6) Lewis, E. S.; Allen, J. D. *J. Am. Chem. Soc.* **1964**, *86*, 2022.
(7) Fife, T. H. *J. Am. Chem. Soc.* **1965**, *87*, 4597.
(8) Doughty, M. B.; Risinger, G. E.; Jungk, S. J. *Bioorg. Chem.* **1987**, *15*, 15.
(9) Zoltewicz, J. A.; Baugh, T. D. *Synthesis* **1980**, 217.
(10) Ikeda, G.; Kluger, R. *J. Phys. Org. Chem.* **2004**, *17*, 507.
(11) Andon, R. J. L.; Cox, J. D.; Herington, E. F. G. *Trans. Faraday Soc.* **1954**, *50*, 918.
(12) Beynon, R. J.; Easterby, J. S. *Buffer Solutions*; IRL Press at Oxford University Press: Oxford, U.K., 1996.
(13) Akiyama, M.; Ihjima, M.; Hara, Y. *J. Chem. Soc., Perkin Trans. 2* **1979**, 1512.

(14) Kluger, R.; Wong, M. K.; Dodds, A. K. *J. Am. Chem. Soc.* **1984**, *106*, 1113.
(15) Kluger, R.; Moore, I. F. *J. Am. Chem. Soc.* **2000**, *122*, 6145.
(16) Moore, I. F.; Kluger, R. *J. Am. Chem. Soc.* **2002**, *124*, 1669.
(17) Ikeda, G.; Kluger, R. *Can. J. Chem.* **2005**, *83*, 1277.
(18) Held, G.; Xie, L. F. *Microchem. J.* **1997**, *55*, 261.
(19) Zoltewicz, J. A.; O'Halloran, J. K. *J. Org. Chem.* **1978**, *43*, 1713.
(20) Jencks, W. P. *Catalysis in Chemistry and Enzymology*; McGraw-Hill: New York, 1969; Chapter 7, Part B.
(21) Bordwell, F. G.; McCallum, R. J.; Olmstead, W. N. *J. Org. Chem.* **1984**, *49*, 1424.
(22) Bernasconi, C. F. *Tetrahedron* **1985**, *41*, 3219.
(23) Bernasconi, C. F. *Adv. Phys. Org. Chem.* **1992**, *27*, 119.
(24) Wu, W.; Shaik, S.; Saunders, W. H. Jr. *J. Org. Chem.* **2010**, *75*, 3722.
(25) Zhong, Z. L.; Snowden, T. S.; Best, M. D.; Anslyn, E. V. *J. Am. Chem. Soc.* **2004**, *126*, 3488.
(26) Barletta, G. L.; Zou, Y.; Huskey, W. P.; Jordan, F. *J. Am. Chem. Soc.* **1997**, *119*, 2356.
(27) Saunders, W. H. *J. Am. Chem. Soc.* **1994**, *116*, 5400.
(28) Jasinski, J. M.; Brauman, J. I. *J. Am. Chem. Soc.* **1980**, *102*, 2906.
(29) Kluger, R.; Wayda, A. *Can. J. Chem.* **1975**, *53*, 2354.
(30) Goryanova, B.; Amyes, T. L.; Gerlt, J. A.; Richard, J. P. *J. Am. Chem. Soc.* **2011**, *133*, 6545.
(31) Guthrie, J. P.; Kluger, R. *J. Am. Chem. Soc.* **1993**, *115*, 11569.
(32) Tagaki, W.; Guthrie, J. P.; Westheimer, F. H. *Biochemistry* **1968**, *7*, 905.
(33) Crugeiras, J.; Rios, A.; Riveiros, E.; Richard, J. P. *J. Am. Chem. Soc.* **2011**, *133*, 3173.