Reversal of the Stereochemistry of Kinetic Protonation by Intramolecular Proton Delivery and a Remarkable Dependence of Selectivity on Donor Concentration[1]

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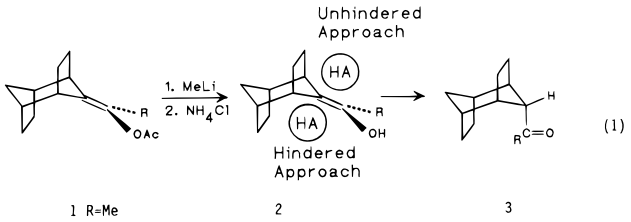
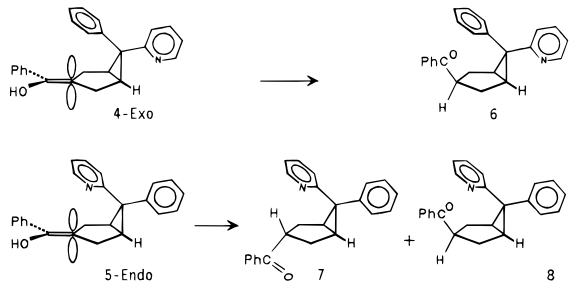
A very large number of reactions proceed by way of transient enolic intermediates and related carbanion species. Nearly four decades ago we reported[2] that the carbon being protonated has a transition state which is close to sp^2 hybridized. Also it was noted that as a consequence the preferred attack of the proton donor is from the less hindered side of the delocalized species to afford the less stable of two alternative stereoisomeric products. A long series of our publications on the subject followed that initial report.[3] One relatively recent and typical example is given in eq 1.[3f]



In the present paper we report a unique example where intramolecular proton delivery permits reversal of the ubiquitous phenomenon and a remarkable dependence of the stereoselectivity on proton donor concentration. The reactivity of the two enols, **4-Exo** and **5-Endo**, was the object of this study. The corresponding silyl enol ethers[4] were employed as precursors. Generation of the enols with tetrabutylammonium fluoride led to the anticipated stereochemistry in the case of **4-Exo** where the less hindered protonation with ammonium ion or acetic acid led to the *endo*-benzoyl ketone **6**.

In contrast, parallel ketonization of the *endo*-pyridyl counterpart **5-Endo**, under conditions sufficiently acidic to permit prior partial protonation of the pyridyl nitrogen, led to reversal of the reaction stereochemistry. Thus, while ketonization of the *endo*-enol **5-Endo** with ammonium ion gave the *endo*-benzoyl−*endo*-pyridyl ketone **8** resulting from the normal, less hindered approach of the proton donor, with 1.4 *M* acetic acid in THF, the stereoselectivity favoring formation of the *exo*-benzoyl−*endo*-pyridyl ketone **7** was 97:3 (Scheme 1). Similar results were obtained in isopropyl alcohol and DMSO solvents as well as with formic acid in THF.

Scheme 1



That the formation of the more stable of the two stereoisomeric ketone products did not result from epimerization of an initially formed *endo*-benzoyl ketone was evidenced by the lack of reactivity of the *endo*-benzoyl ketone under conditions used for the ketonization runs. Thus, with the highest concentration of acetic acid used, less than 4% epimerization was observed.

A remarkable observation was that the stereoselectivity of reaction of the *endo*-pyridyl enol was a function of the concentration of proton donor acetic acid employed, whereas the selectivity of ketonization in the *exo*-pyridyl enol **4-exo** was independent of the donor concentration. This signifies that in the *endo*-pyridyl ketonization, the formation of the two stereoisomers cannot have the same kinetic order in (e.g.) acetic acid.

In ketonization of the *endo*-pyridyl enol, in 1.4 *M* acetic acid the *exo*-benzoyl:*endo*-benzoyl product ratio was 97:3, whereas in the more dilute 0.08 *M* acid a ratio of 1:3 resulted. We conclude that more acetic acid molecules participate in the intramolecular protonation than in the intermolecular process. We designate the amount of the *endo*-benzoyl product **8**, formed by the ordinary intermolecular protonation, as P_1 and the amount of *exo*-benzoyl product **7**, as P_n. Equations 2 give the extent of formation of the

$$dP_1/dt = k_1[HA][Enol] \text{ and } dP_n/dt = k_n[HA]^n[Enol] \quad (2a,b)$$

two stereoisomers after total ketonization.[5] Division of the two equations gives, in logarithmic form, eq 3. Here we note the slope

$$\log(P_n/P_1) = (n-1)\log[HA] + \log(k_n/k_1) \quad (3)$$

of a plot of $\log(P_n/P_1)$ versus the log of acid concentration [HA] is $(n-1)$ and affords the difference in number of acid molecules in the transition state for the intramolecular compared with the ordinary intermolecular process.

(1) (a) This is paper 250. (b) For paper 249, see: Zimmerman, H. E. *J. Phys. Chem. A* **1997**, *102*, 5616−5621.

(2) (a) Zimmerman, H. E. *J. Org. Chem.* **1955**, *20*, 549−557; (b) Zimmerman, H. E.; Nevins, T. E. *J. Am. Chem. Soc.* **1957**, *79*, 6559−6561.

(3) (a) For a review, see: Zimmerman, H. E. *Acc. Chem. Res.* **1987**, *20*, 263−268; A few references of the fourteen follow: (b) Zimmerman, H. E.; Mariano, P. S. *J. Am. Chem. Soc.* **1968**, *90*, 6091−6096; (c) Zimmerman, H. E. *J. Am. Chem. Soc.* **1957**, *79*, 6554−6558; (d) Zimmerman, H. E.; Chang, W.-H. *J. Am. Chem. Soc.* **1959**, *81*, 3634−3643; (e) Zimmerman, H. E.; Cutshall, T. W. *J. Am. Chem. Soc.* **1958**, *80*, 2893−2896; (f) Zimmerman, H. E.; Linder, L. W. *J. Org. Chem.* **1985**, *48*, 1637−1646. (g) Interestingly ref 3a and d contain an algebraic predecessor to the computer molecular mechanics analysis of acyclic conformational analysis of electrophilic attack on an sp^2 hybridized carbon, a subject of considerable subsequent interest in studies arriving at the same conclusions.

(4) Runs were made at 30 °C. All compounds were properly characterized using elemental analysis, HRMS, NMR, IR, and X-Ray analysis in selected cases. Kinetic details will be given in our full publication.

(5) (a) Pyridine and acetic acid have been reported[6] in relatively non-polar solvents to exist in rapidly equilibrated[7] clusters. Thus, eqs 2 and 3 assume dissociation of the clusters prior to transition-state formation. However, if clustering persists, eqs 2 and 3 are replaced by

$$dP_m/dt = k_m[HA]^m[Enol] \text{ and } dP_n/dt = k_n[HA]^n[Enol] \quad (4a,b)$$

$$\log(P_n/P_m) = (n-m)\log[HA] + \log(k_n/k_m) \quad (5)$$

and the slope again gives the difference in number of acid molecules in the alternative transition states. We note that ketonization rates are slow by comparison[8] and thus cluster formation is not rate-limiting. However, the relation between difference in reaction order and slope is independent of this. (b) In eqs 2−5, as a consequence of the complexity of the media with uncertain extents of hydrogen bonding and protonation, the constants k_1, k_n, k_m may not be true rate constants but may incorporate equilibrium constants. However, these constants are uninvolved in the slope obtained.

(6) Akiyama, Y.; Wakisaka, A.; Mizukami, F.; Sakaguchik, K. *J. Chem. Soc. Perkin Trans. 2* **1998**, 95−99.

(7) Golubev, N. S.; Smirnov, S. N.; Gindin, V. A.; Denisov, G. S.; Benedict, H.; Limbach, H.-H. *J. Am. Chem. Soc.* **1994**, *116*, 12055−12056.

(8) Andraos, J.; Kresge, A. J.; Obraztsov, P. A. *J. Phys. Org. Chem.* **1992**, *5*, 322−326.

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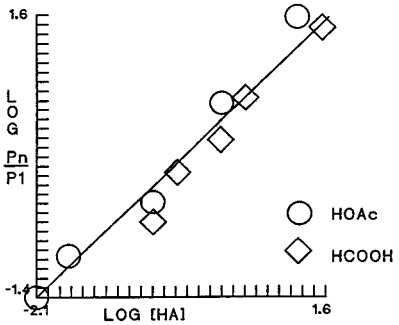


Figure 1. Plot of log(product ratio) versus log(proton donor concn); solvent THF.

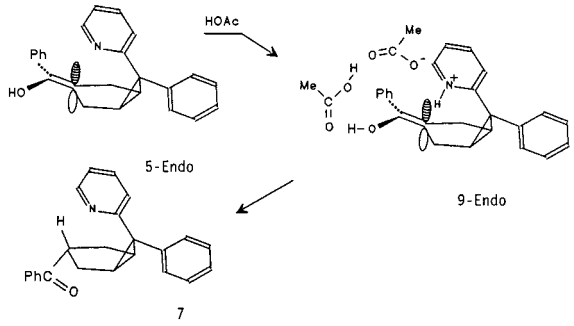
To determine *n* for a number of solvents and for acetic acid as well as for formic acid, "differential plots" of $\log(P_n/P_1)$ versus log[HA] were employed. The average value of *n* for acetic acid in THF, acetic acid in isopropyl alcohol and for formic acid in THF was 2.2 ± 0.3. For acetic acid in DMSO, *n* was 3 (note Figure 1). Thus, under all conditions studied using acetic or formic acid as the proton donor in THF and isopropyl alcohol the *endo*-pyridyl enol (**5-Endo**) incorporates one more acetic acid molecule in the transition state for "inside" intramolecular protonation than in the transition state for "outstide" intermolecular protonation. If the first acetic acid molecule is needed to protonate the pyridyl nitrogen to give an ion pair, the role of the second acetic acid molecule is subject to conjecture.

Nevertheless, we do know that enolates protonate with greater facility than their enol counterparts.[9] One possibility is that the extra acetic acid molecule serves to hydrogen bond and then donate a proton to the acetate of the ion pair, finally converting the enol to the more reactive enolate in a cyclic fashion as depicted in Scheme 2. This picture is in accord with the observation that the "outside protonation" to give the *endo*-benzoyl ketone **8**, where an extra acetic acid molecule cannot reach, does not use this extra molecule and shows no *exo*−*endo* product ratio dependence on acid concentration.

Also, protonation by ammonium ion seems likely to proceed by way of the unprotonated pyridyl isomers and is subject only to the usual steric hindrance to approach of the donor.

(9) (a) Zimmerman, H. E. Base-Catalyzed Rearrangements. In *Molecular Rearrangements*; DeMayo, P., Ed.; Interscience: New York, 1963; Chapter 6, pp 345−406. (b) Malhotra, S. K.; Ringold, H. J. *J. Am. Chem. Soc.* **1965**, *87*, 3228−3236; (c) R. M. Paufler, Ph.D. Thesis presented to Northwestern University, 1960.

Scheme 2



Kinetically controlled protonation of delocalized carbanions in general not only is of mechanistic interest but is also involved in a myriad of organic reactions. This list includes (inter alia) the lithium−ammonia reduction of α,β-enones, the decarboxylation of malonic acids, the protonation of nitronate anions, the conjugate addition to conjugated enones, the debromination of α-bromoketones, deprotonation−protonation, and nucleophilic attack on ketenes.[3]

The phenomenon also has been of considerable use in obtaining the desired stereochemistry in synthesis and has arisen unexpectedly in a variety of studies, and thus, it is not surprising that the concept has been rediscovered several times.[10] In any event, the phenomenon has been of considerable use.[11]

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(10) (a) Gerlach, U.; Haubenreich, T.; Hünig, S.; Keita, Y. *Chem. Ber.* **1993**, *126*, 1205−1215; (b) Takano, S.; Kudo, J.; Takahashi, N.; Ogasawara, K. *Tetrahedon Lett.* **1986**, 2405−2408; (c) Takano, S.; Uchida, W.; Hatakeyama, S.; Ogaswara, K. *Chem. Lett.* **1982**, 733−737; (d) Takano, S.; Goto, E.; Ogasawara, K. *Tetrahedron Lett.* **1982**, 5567−5569; (e) Takano, S.; Yamada, S.; Numata, H.; Hatakeyama, S.; Ogasawara, K. *Heterocycles* **1983**, *20*, 2159−2162. (f) Takano, S.; Tananka, M.; Seo, M.; Hirama, M.; Ogasawara, K. *J. Org. Chem.* **1985**, *50*, 931−936. (g) Note also Hünig, S. Protonation of Carbanions and Polar Double Bonds. In *Methods of Organic Chemistry*; Houben-Weyl, G. Thieme: Stuttgart, 1996; Vol. E21D 7, pp 3851−3911 (where our concept is employed without citation of the source. Of our examples, two cases are included but only with citation of our recent review (ref 3a).

(11) Krause, N. *Angew. Chem., Int. Ed. Engl.* **1994**, *33*, 1764−1765; (b) Baker, W. R.; Pratt, J. K. *Tetrahedron* **1993**, *49*, 8739−8856; (c) Knölker, Ecker, H.-J.; Ecker, A.; Struwe, P.; Steinmeyer, A.; Müller, G. Neef, G. *Tetrahedron* **1997**, *53*, 91−108; (d) Davies, S. G.; Ichihara, O.; Walters, I. A. S. *Syn. Lett.* **1993**, 461−462; (e) Tamura, R.; Watanabe, K., Ono, N.; Yamamoto, Y. *J. Org. Chem.* **1992**, *57*, 4895−4899; (f) Rehders, F.; Hoppe, D. *Synthesis* **1992**, *57*, 859−861. (g) Rehders, F.; Hoppe, D. *Synthesis* **1993**, *58*, 4471−4472.