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Intramolecular Proton Transfer

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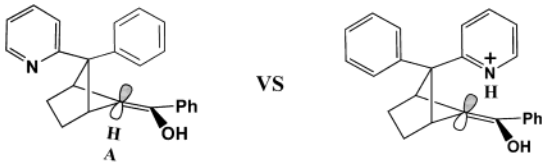
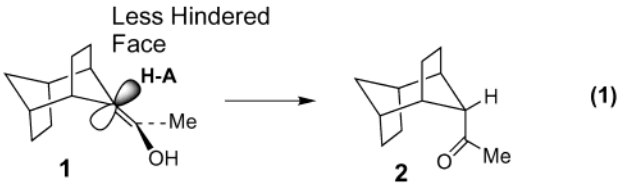
ABSTRACT



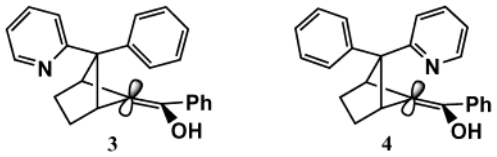
Reversal of the normal kinetic protonation stereochemistry results as a consequence of intramolecular delivery.

A very large number of organic reactions proceed via enols and enolates that then tautomerize to carbonyl products. In 1956 it was recognized that prediction of the stereochemistry of kinetic protonation of these intermediates would permit prediction of the stereochemistry of the overall reactions. It was proposed[1] that in the highly exothermic process, the protonation transition step has an α-carbon that is close to sp^2 hybridized with the consequence that the protonation process occurs from the less hindered face of the enolic system. Generally this leads to the less stable of two diastereomers. Since that time we have published a series of papers generalizing and exemplifying the phenomenon.[2] One typical example is shown in eq 1.



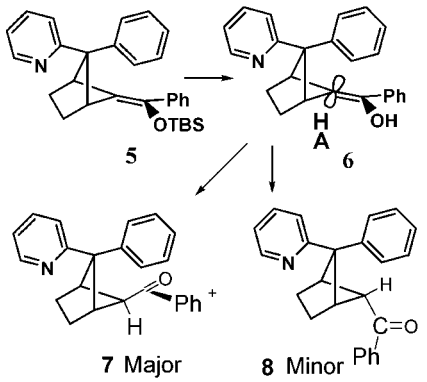
(1)

Recently the question arose whether the stereochemistry could be reversed by intramolecular delivery of the proton to the more hindered face of the enolic system, and one example was uncovered.[3] It now appears that the phenomenon is general, and we report an example in a new molecular system, utilizing the exo and endo 2-pyridyl enols **3** and **4**.



Precursors used to generate these enols were the corresponding *tert*-butyldimethyl silyl enol ethers, which reacted smoothly with tetrabutylammonium fluoride to generate the enols.[4] In the case of the endo-phenyl stereoisomer **3**, with acetic acid as the proton donor, the reaction proceeded as in eq 2 with the usual less hindered approach stereochemistry preferred with a 7.3:1 selectivity independent of the acetic acid concentration.

Conversely, the reaction of the endo-pyridyl diastereomer afforded varying extents of intramolecular proton transfer depending on the concentration of the proton donor employed.



(2)

(1) Zimmerman, H. E. *J. Org. Chem.* **1955**, *20*, 549−557.
(2) (a) Zimmerman, H. E. *Acc. Chem. Res.* **1987**, *20*, 263−268. (b) Zimmerman, H. E.; Linder, L. W. *J. Org. Chem.* **1985**, *48*, 1637−1646.
(3) Zimmerman, H. E.; Ignatchenko, A. *J. Org. Chem.* **1999**, *64*, 6635−6645.

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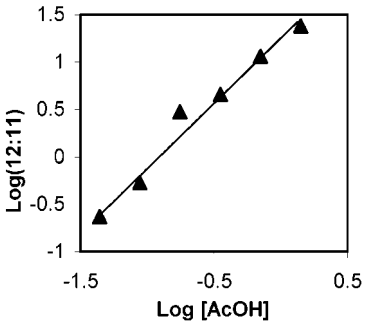
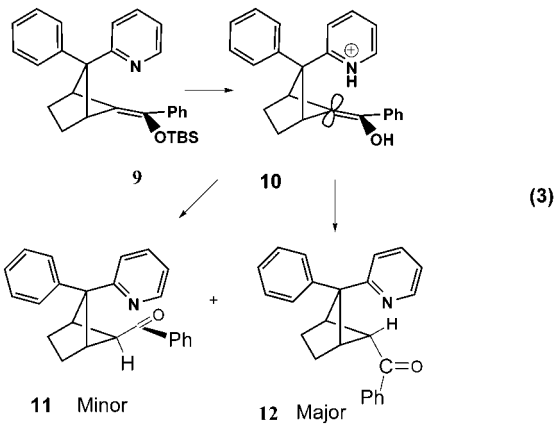


Figure 1. Regioselectivity of enol **4** with HOAc.

Strikingly, in these endo pyridyl acetic acid runs the major process is intramolecular protonation to afford diastereomer **12** as long as the acid concentration was at least 0.17 M. Note eq 3. We note that here, as in all cases in the present study where thermodynamic products resulted, control runs established that the reaction was kinetic and equilibration was not occurring.



It has been noted[3] that the ratio of intra- to intermolecular proton-transfer products is given by eq 4. Here P_{int} and P_{ext} are the products resulting from intra- and intermolecular proton transfer. The *k*'s are the rate constants and [HA] is the proton donor concentration; *n* and *m* are the number of proton donor molecules required in the intra- and intermolecular reactions, respectively:

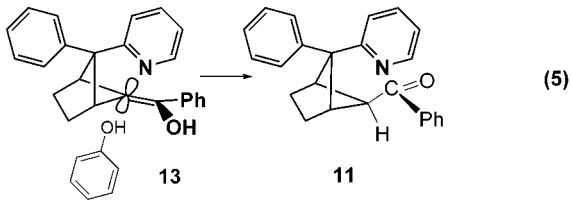
$$\log\left(\frac{P_{int}}{P_{ext}}\right) = (n - m)\log[HA] + \log\left(\frac{k_{int}}{k_{ext}}\right) \qquad (4)$$

The data obtained are plotted in Figure 1. The slope $n - m$ is 1.2, or within reasonable experimental error of unity. We note that the slope of the plot only gives the difference in the reaction orders for the two processes.

(4) (a) A 15-step synthesis was employed to obtain the silyl enol ethers and will be described in our full publication. (b) In a typical run, 4.0 mg of the silyl enol ether in 0.40 mL of acetonitrile was treated with 2 equiv of acetic acid and 2 equiv of tetrabutylammonium fluoride (1.0 M in THF). After 4 h, the reaction was 90% complete, and the ketonized diastereomers were analyzed by proton NMR.

While acetic acid is known to cluster, these species are rapidly equilibrated.[5] It is posible that for intermolecular protonation, one acetic acid molecule separates from the cluster and delivers the proton. This, however, is irrelevant. We know only from $n - m$ that one extra acetic acid molecule is involved in the intramolecular process. If it is an aggregate in the inter mode, it is the same aggregate plus one HOAc molecule in the intra mode. For simplicity of discussion we will assume intermolecular protonation to involve one acetic acid molecule. With $n - m$ being unity, we then conclude that the intramolecular proton-transfer process involves two acetic acid molecules.

Dramatic contrasts were encountered (a) with less acidic proton donors and (b) with hydrochloric acid as the donor. In the case of phenol and the endo-pyridyl isomer **4** we found that the less hindered protonation resulted, giving a preference of 5.7:1, the same stereochemistry as in the case of the endo-phenyl isomer **3**, which however afforded a preference of 19:1.Thus there seems to be minor intramolecular protonation. Nevertheless, the pyridyl group is acting primarily sterically.



In the case of triethylammonium chloride, another weak acid, the endo-pyridyl diastereomer **4** afforded a ratio of 3:1 while the endo-phenyl isomer **3** gave a 9:1 ratio. Thus, again, the weak acid was unable to efficiently protonate the pyridine nitrogen, and the less hindered approach was observed with both diastereomeric enols. The stereochemistry is independent of these donor concentrations, both for this case and that of the phenol protonation, and *m* equals *n*.

A remarkable result was encountered in the hydrochloric acid protonation of enol **4**. With or without fluoride (in this case, fluoride proved unnecessary) there was again a dependence of the stereochemistry on the concentration of proton donor. However, in contrast to the acetic acid example, the slope of the $n - m$ plot was reversed (note Figure 2) with a slope of close to -1 (i.e., -0.96) and an intercept of -0.92.

With HCl as the donor, protonation of enol **3** led exclusively via the less hindered approach to ketone **7**.

It is clear that the stereochemistry of enols **3** and **4** is varied and complex depending on which diastereomer is employed and what proton donor is involved. The pattern is outlined in Table 1.

The first and most striking point to be made is that intramolecular proton delivery now promises to be a general

(5) (a) Smirnov, S. N.; Golubev, N. S.; Denisov, G. S., Bendict, H.; Schah-Mohammdei, P.; Limbach, H.-H. *J. Am. Chem. Soc.* **1996**, *118*, 4094−4101. (b) 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.

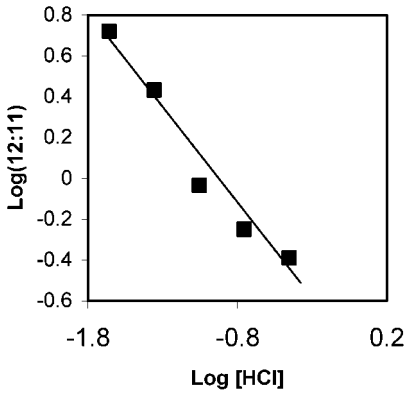


Figure 2. Regioselectivity of enol **4** with HCl.

phenomenon. Thus we have a second example of a 2-pyridyl moiety being able to deliver a proton to the more hindered face of an enolic π-bond just as in ordinary situations proton donors prefer the less hindered enolic face under kinetic conditions.

Table 1. Ratio of External to Intramolecular Protonation[a]

	proton donor			
diastereomer	HOAc[b]	phenol	Et_3NHCl	HCl
endo phenyl	7.3:1	19:1	9:1	1:0
endo pyridyl	1:24	5.7:1	3:1	1:5.3[c]

[a] The ratio of products **7** to **8** for the enol **3** and **11** to **12** for the enol **4**. [b] Ratio given for 1.4 M HOAc. [c] For 0.022 M HCl.

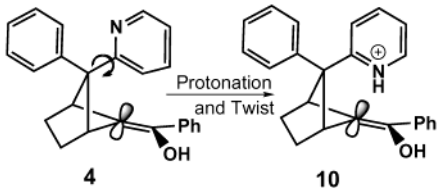
A second conclusion, equally intriguing, derives from the kinetic observation of a unity value for $n - m$. This value signifies that one more acetic acid molecule is required for the intramolecular protonation than for the intermolecular process. The simplest assumption, as noted above, is that a single acetic acid molecule is involved in the intermolecular protonation. Hence two acetic acid molecules are required for the intramolecular transfer. The first acetic acid molecule is required to bond to nitrogen, generating incipient pyridinium and acetate species. The acetate generated is distant from the enolic hydroxyl but can interact with a second acetic acid molecule to provide an acetate anion in proximity of the enolic hydroxyl. It is known[6] that ketonization of enols occurs preferentially by protonation of the enolate rather than the neutral enol. Thus the second acetate can be involved in the enol to enolate conversion.

If acetic acid aggregates are involved with an *n*-aggregate for external protonation, then intramolecular proton transfer must utilize an $n + 1$ aggregate. Thus, for example, protonation of pyridine by a trimer[6] and intermolecular protonation by the dimer would also account of the $n - m$ value of unity.

The case of protonation by phenol is particularly interesting. Phenol with a pK_a of ca. 10 is insufficiently acidic to protonate the 2-pyridyl group (pK_a conj acid ca. 5). Thus, in contrast to the acetic acid ketonizations, the protonation process is aware of pyridyl only as a sterically blocking group equivalent to phenyl. As a consequence, protonation from the less hindered face affords the same regioselectivity as with a phenyl blocker.

The inverse slope observed with hydrochloric acid protonation, with more than an equivalent of the acid, clearly results from complete pyridyl protonation by this strong acid. Thus the intramolecular proton transfer is zero order in concentrations of hydrochloric acid beyond the one equivalent (i.e., $n = 0$), while the intermolecular process is first order in hydrochloric acid ($m = 1$). Hence $n - m$ is minus unity as observed in Figure 2.

A further point of interest is the geometry of the endo-pyridyl protonation process. Thus, it seems likely that the initial pyridyl protonation occurs from a conformation in which the pyridyl nitrogen is more accessible. This, then, is followed by a twist and intramolecular protonation. The twist is depicted in eq 6.



(6)

With kinetic protonation of delocalized systems pervading organic chemistry by virtue of their intermediacy in a very large variety of reactions,[7] it becomes critical to determine in which situations protonation will occur externally and in which cases it will proceed intramolecularly as in the present study. We are proceeding to determine other modes of intramolecular delivery.

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Supporting Information Available: Experimental details. This material is available free of charge via the Internet at http://pubs.acs.org.

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(6) (a) Base-Catalyzed Rearrangements. In *Molecular Rearrangements*; Zimmerman, H. E., Ed.; P. DeMayo, Interscience: New York, 1963; Chapter 6, pp 345−406. (b) Malhotra, S. K.; Ringold, H. J. *J. Am. Chem. Soc.* **1965**, *87*, 3228−3236;

(7) The phenomenon has been proven of value in synthesis, often unexpectedly. Interestingly, the concept has been rediscovered twice,[8] and it seems that the rediscoveries are often cited.

(8) (a) Gerlach, U.; Haubenreich, T.; Hünig, S.; Keita, Y. *Chem. Ber.* **1993**, *126*, 1205−1215. (b) Takano, S.; Kudo, J.; Takahashi, N.; Ogasawara, K. *Tetrahedron 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. *Houben-Weyl, Methods of Organic Chemistry*; G. Thieme: Stuttgart, 1996; Vol. E21D *7*, pp 3851−3911.