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# Control of Proton Transfer: Intramolecular vs Intermolecular[1,2]

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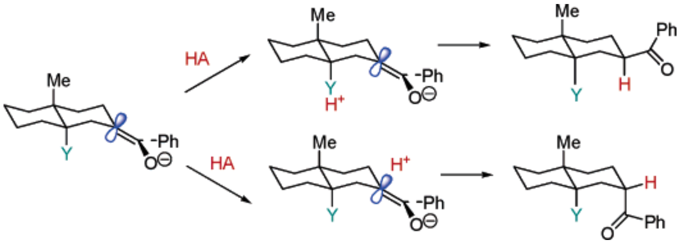
## ABSTRACT



**Proton transfer in ketonization of enolates is a critical step in a myriad of organic reactions. Its stereochemistry has been the object of our studies since we reported kinetic protonation from the less hindered face of the molecule under kinetic control some decades ago. Very recently, we have succeeded in reversing the stereochemistry using 2-pyridyl groups to deliver the proton. We now report intramolecular delivery by other moieties and control of intramolecular versus intermolecular proton delivery.**

Five decades ago, one of us suggested that kinetically controlled ketonization of enolic species proceeds by selective protonation from the less hindered face to afford the less stable of two diastereomers.[3] Since that time, the phenomenon has proven to be of considerable synthetic use since a very large number of organic reactions proceed via transient enolic intermediates.[4] Mechanistically, the stereochemistry results from the highly exothermic transition state having the α-carbon close to its original $sp^2$ hybridization.

A recent challenge was to reverse the stereochemistry. In two systems, we utilized strategically positioned 2-pyridyl groups to deliver the proton to the hindered face of the enolic moiety.[5] This posed the question whether moieties other than pyridyl also could deliver a proton intramolecularly.

The present study utilized the decalyl framework. As delivery groups, we utilized carboxylate, aminomethylene, hydroxymethylene, methoxymethoxymethylene, and formyl.[6] These are the groups represented by "Y" in Figure 1.

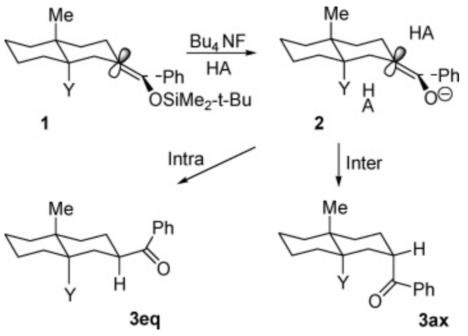


**Figure 1.** Generation and reactivity of the decalyl enolate.

Additionally, we used carboxyl, already having a proton to deliver (i.e., Y = COOH).

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[1] This is Paper 278 of our General Series.

[2] For Paper 277, see: Zimmerman, H. E.; Pushechnikov, A. *Org. Lett.* **2004**, *6*, 3779−3780.

[3] Zimmerman, H. E. *J. Org. Chem.* **1955**, *20*, 549−557.

[4] (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. (c) See also papers cited within ref 4b.

[5] (a) Zimmerman, H. E.; Ignatchenko, A. *J. Am. Chem. Soc.* **1998**, *120*, 12992−12993. (b) Zimmerman, H. E.; Ignatchenko, A. *J. Org. Chem.* **1999**, *64*, 6635−6645. (c) Zimmerman, H. E.; Wang, P. *Org. Lett.* **2002**, *4*, 2593−2595. (d) Zimmerman, H. E.; Wang, P. *J. Org. Chem.* **2002**, *69*, 9216−9226.

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In Figure 1, the *Z* stereoisomer of **1** is depicted, although in the case of Y = formyl, both stereoisomers were available. The stereochemistry is assigned on the basis of X-ray structure determination in the case of the formyl derivative.[7] In this case, there were appreciable NMR differences between the two isomers, each with characteristic trimethylsilyl patterns. In the remaining examples, the NMR spectra were characteristic of the *Z* isomer (see Supporting Information for both X-ray and NMR details).

For generation of the desired enolic species, the corresponding silyl enol ethers were ideal.[8,9] The *tert*-butyldimethylsilyl enol ethers were used with tetrabutylammonium fluoride for generation of the enolates. Solvents employed were THF, acetonitrile, and DMSO as described below. Acetic acid was used as the proton source.

When Y was hydroxymethylene (**1-CH$_2$OH**), carboxaldehyde (**1-CHO**), or methoxymethoxymethylene (**1-MOMOM**), ketonization proceeded by external protonation with the less hindered approach of the proton donor (See Table 1). In our previous studies,[5] we had encountered a dramatic change in stereochemistry as a function of the acidity of the medium. However, in the present study no dependence on acid concentration was encountered for the various Y groups described thus far.

**Table 1.** Protonation Stereoselectivity of Silyl Enol Ethers

| | enol derivatives[a] (Y) | | | | |
|---|---|---|---|---|---|
| diastereomer ratio | COOH[b] | CHO[c] | CH$_2$OH | MOMOM[d] | CH$_2$NH$_2$ |
| (**3-eq/3-ax**) | 98:2 | 5:95 | 2:98 | 2:98 | 86:14 |

[a] All runs in THF with acetic acid concentration = 0.37 M. [b] Also runs in DMSO with excess lithium acetate. [c] Both *Z* and *E* isomers gave the same stereoselectivity. [d] MOMOM = CH$_2$OCH$_2$OMe.

Dramatically, in the case where Y was carboxyl (**1-COOH**), in THF, we encountered a reversal of stereochemistry. Intramolecular protonation had become dominant with formation of diastereomer **3eq** (see Table 1).

In the case where Y was carboxyl, it was of interest to compare carboxyl with carboxylate. For this we made use of a lithium acetate−acetic acid buffer in solvent DMSO with the intent of varying Y from carboxyl to carboxylate (**1-COO$^-$**) in incremental degrees. However, the reaction stereochemistry proved to be unaffected by the buffer and thus whether **Y** was carboxylate or carboxyl (See Table 1). Also, there was no dependence on solvent, THF vs DMSO. Only more hindered protonation resulted with formation of **3eq** (see Table 1).

In the case of aminomethylene (i.e., Y = CH$_2$NH$_2$, **1-CH$_2$NH$_2$**), the ketonization reaction led to diastereomer **3eq**, thus providing a second example of intramolecular protonation and reversal of the usual less hindered protonation. Conversely, protonation with phenol led to the less hindered protonation to afford **3ax**.

Hence, both intramolecular and intermolecular proton transfer were occurring with a dependence on the nature of group Y.

As noted above, there was the matter of silyl enol ether configuration with the *Z* stereoisomers generally being used. However, in the case of Y as carboxaldehyde, both stereoisomers proved to be synthetically accessible. Interestingly, the kinetic protonation of the (*Z*)- and (*E*)-enolates led stereoselectively to the same **3ax** ketonization product.

An important point is that where the equatorial benzoyl protonation products were formed, the corresponding axial diastereomers proved to be stable under reaction conditions, thus precluding the intervention of epimerization.

Another rather interesting observation was the behavior of the two diastereomeric aldehydo ketones, **3eq** and **3ax** (i.e., Y = CHO). LDA reacted nicely with **3ax** (i.e., the isomer with an equatorial hydrogen) but was unreactive with its **3eq** diastereomer. The same observation was made in the case of the carboxylic acid diastereomers, **3ax** and **3eq** (Y = COOH). This result derives from two factors (vide infra).

We turn now to a discussion of the results. A salient point is that two of the five potential proton transfer groups (i.e., the Y groups) successfully transfer the proton intramolecularly in analogy to 2-pyridyl groups.[5] The general behavior of the aminomethylene derivative **1**, with its greater basicity relative to pyridyl, is parallel to that of the pyridyl example studied earlier. There was (ca.) 5-fold more intramolecular proton transfer in the present aminomethylene case compared with pyridyl not only with the 0.37 M acetic acid concentration run listed in Table 1 but also at double this concentration. This observation might be anticipated from the greater basicity of aminomethylene. However, in both cases, the earlier pyridyl example and the present aminomethylene one, as the acetic acid concentration was increased, the role of the intramolecular process was enhanced. In contrast, the remaining enols lacking basic or acidic moieties were insensitive to acid concentration.

The kinetics are the subject of an ongoing study that will be reported. However, the increase in intramolecular protonation with increased acetic acid concentration in this aminomethylene case reveals that more acetic acid molecules are involved in the intramolecular process relative to the intermolecular reaction.

One result is particularly significant. The identity of the stereoselectivity from the (*Z*)- and (*E*)-enolates in the case where both were available (i.e., Y = CHO) signifies that the protonation process at the α-carbon is independent of the geometry of the enolate oxygen. Any coordination or ion-pairing at the oxygen must be irrelevant.

Another interesting finding is the ease of α-proton removal when that proton is equatorial and the benzoyl group is axial, as in diastereomer **3ax-CHO**. This result contrasts with the difficulty of removal of the axial proton in diasteromer **3eq-CHO** (Scheme 1). This effect, noted also for Y = COOH,

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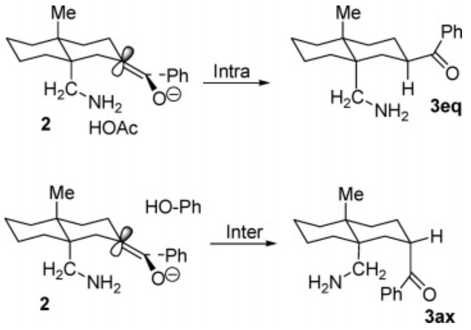
(6) Synthetic and reaction details are collected in Supporting Information.

(7) X-ray data is available from the Cambridge Crystallographic Data Centre.

(8) Nayori, R.; Nishida, I.; Sakata, J. *J. Am. Chem. Soc.* **1983**, *105*, 1598−1608. (c) Kuwajima, I.; Nakamura, E. *Acc. Chem. Res.* **1985**, *18*, 181−187.

(9) The rather long synthesis is described in a separate publication.

**Scheme 1.** Contrast between HOAc and PhOH Protonation



arises from two independent factors. One is purely energetic, namely that with the higher energy axial benzoyl diastereomer, the reactant state energy is higher than that of the equatorial counterpart, thus diminishing the activation energy for enolization. The second factor results from microscopic reversibility. Thus, the lower energy transition state is the one between the enol and **3ax-CHO** rather than between the enol and **3eq-CHO**, as evidenced from the protonation preference leading to **3ax-CHO**.

Particularly critical is the observation that ketonization with phenol of the aminomethylene enol led to intermolecular protonation stereochemistry, this being the reverse of the intramolecular course encountered with acetic acid. This confirms the requirement that intramolecular proton transfer needs a proton donor that is sufficiently acidic to bond with the Y moiety in the enol. In this case phenol is weakly acidic and not capable of protonating the aminomethylene nitrogen. A similar effect was encountered in our earlier work[5] where weakly acidic donors unable to protonate the pyridyl groups led to ketonization governed by mere steric effects.

In the case of ketonization of **1-COOH** in DMSO over a wide range of buffer basicities, the invariance of the stereochemistry requires that even with primarily carboxylate present, the protonated species, carboxyl, transfers the proton.

In summary, we find three factors that lead to alternative stereochemical results. It is seen that intramolecular proton transfer occurs when the group Y is (i) basic, as in the carboxylate and aminomethylene cases, or (ii) acidic, as in the carboxyl case, but not (iii) with oxygen moieties that are too weakly basic and can merely hydrogen bond with the donor and are too weakly acidic to protonate the α-carbon. This is the case for the carboxaldehyde, hydroxymethylene, and methoxymethoxymethylene examples.

In terms of basicity, the carboxylate example is close to that of the 2-pyridyl donor of our previous study[5] and, on protonation, can deliver a proton intramolecularly.

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**Supporting Information Available:** Experimental procedures and X-ray and NMR details (CIF). This material is available free of charge via the Internet at http://pubs.acs.org.

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