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On the Relative Reactivity of Carbonyl and Iminium Ion Moieties

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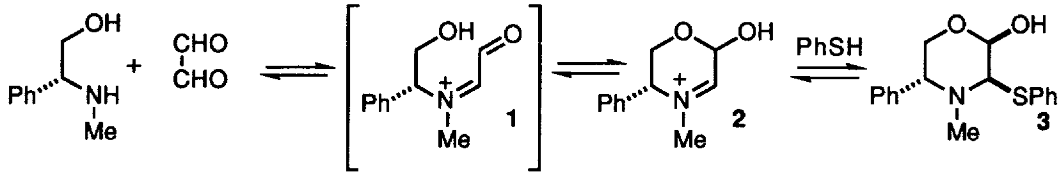
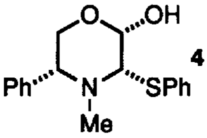
Abstract: AM1 calculations, performed on models exhibiting both moieties, show that, in agreement with experimental work, an aldehyde group is more reactive than an iminium ion towards a hard nucleophile.

Iminium ions have been long recognized as intermediates in a number of well-known synthetic processes[1] and important works concerning ene-iminium and ene-acyliminium cyclizations have recently reenhanced the usefulness of these species.[2] Moreover iminium ions are frequently involved in enzymatic mechanisms,[3] for example in the aldolase reaction,[3a] pyridoxal phosphate-mediated reactions[3b] as well as the binding of retinal to opsin.[3c] Since carbonyl compounds are the usual precursors of iminium ions, it is of interest to know the relative reactivity of these two moieties. We recently described[4] a heterocyclization which addresses this problem: the reaction displays two competitive pathways involving both aldehyde and iminium moieties. Thus the condensation of an aqueous solution of glyoxal with *N*-methyl phenylglycinol, in the presence of thiophenol, led to tetrahydrooxazine **3**. When treated with a Lewis acid, this heterocycle reverts to the cyclic iminium ion **2**. Compound **2** arose from a cyclization of intermediate **1** in which the nucleophilic attack of the hydroxyl group occurs exclusively on the aldehyde function: no 1,3-oxazolidine, resulting from an attack onto the iminium moiety was isolated though this is the expected product when a β-amino alcohol reacts with a monoaldehyde.[5]



As regards both the regioselectivity and the stereoselectivity, this condensation is independent of the medium acidity. No difference was observed when the aqueous medium was buffered either at pH 5 (phtalate buffer), pH 7 (phosphate buffer) or pH 10 (borax buffer). On the other hand, oxazine **3** was produced under kinetic control: carried out in a 50/50 THF-water mixture, the condensation led to a mixture of compounds **3** and **4** in a 75/25 ratio. This corresponds to a thermodynamically controlled reaction since the same ratio was attained when pure oxazine **3** was dissolved in a THF-water mixture. Production of the single stereoisomer **3** in water solution can be ascribed to its insolubility in this medium.

AM1 calculations[6] were performed on compound **5** which corresponds to the aldehyde iminium intermediate **1** and on the related compound **6** in order to examine the effect of getting the two moieties apart.



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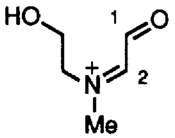

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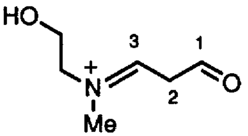

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In fact, the presence of the carbonyl group directly linked to the iminium moiety induces but small differences with respect to atomic charges[7] and LUMO coefficients. These calculations show that in such oxoiminium ions : (i) there is a much higher positive charge on the aldehydic carbon than on the iminium moiety, (ii) the value of the LUMO coefficient is larger on the iminium than in the aldehydic carbon. Following the HSAB theory, these two features are characteristic for the iminium and the aldehydic carbon atoms being respectively soft and hard acids.[8] Actually, during the cyclisation depicted above, the aldehyde is more reactive than the iminium moiety towards the hard hydroxyl nucleophile.

Table 1. AM1 Calculations on Oxo Iminium Models **5** and **6**

α-Oxo iminium ion **5**			β-Oxo iminium ion **6**		
LUMO energy (eV)	Total charge	Coefficient of LUMO on atom	LUMO energy (eV)	Total charge	Coefficient of LUMO on atom
- 6.357	O - 0.132	- 0.329	- 5.765	O - 0.194	0.016
	C_1 0.176	0.265		C_1 0.182	-0.012
	C_2 - 0.009	0.698		C_3 0.100	0.784
	N - 0.019	- 0.538		N - 0.058	- 0.538

In order to take into account the question of five-membered *vs.* six-membered ring formation, calculations were carried out for the intermolecular additions of CH_3OH and CH_3SH, *i.e.* respectively hard and soft nucleophiles, onto the two electrophilic centers of $O{=}CH{-}CH{=}N(CH_3)_2^+$. The SADDLE procedure[6] gave coarse geometries of the transition states which were then optimized by minimizing the norm of the gradients (NLLSQ). Attack of CH_3OH onto the aldehyde moiety is favored, the activation energy difference (including a zero point energy correction) between the two competing processes being equal to 4 kcal.mol^{-1}. On the other hand, the opposite trend was observed with CH_3SH: now attack onto the iminium moiety is the prefered path and the corresponding energy difference amounts to 13.5 kcal.mol^{-1}.

It is worth noting that NMR chemical shifts differences between aldehyde and iminium ion groups were recently ascribed to a smaller electron density in the latter moiety.[9] The fundamental differences between the electrophilicities of an aldehydic and an iminium carbon atom should allow a better understanding of their respective behaviour. In that respect the well-known propensity of an iminium ion to react with a carbon-carbon double or triple bond,[2] *i.e.* soft nucleophiles, is in agreement with the present results.

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