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Carbonyl Coordination Chemistry from a New Angle: A Computational Study of α-Carbon Acidity Based on Electrophile Coordination Geometry

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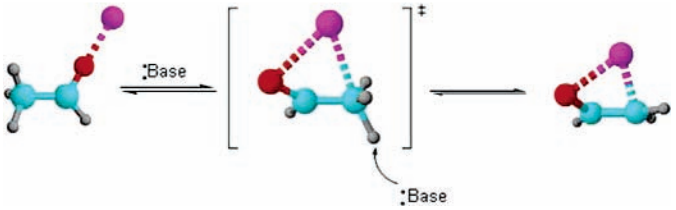
ABSTRACT



The dependence of acidity on Li$^{\oplus}$ coordination geometry to α-carbon acids is investigated by generating potential energy surfaces of Li$^{\oplus}$ complexation with acetaldehyde and its respective enolate. The global minimum for the enolate complex shows significant Li$^{\oplus}$–π-system coordination to both oxygen and the α-carbon. The gas-phase acidity analysis reveals significantly more α-carbon coordination, which presumably enhances the lability of the cleaving proton in the transition state of deprotonation.

Perhaps some of the most intriguing transformations within enzymology involve carbonyl chemistry. A typical α-hydrogen of a carbon acid has a pK_a far above those of the conjugate acids of arginine, lysine, or histidine. Yet, enolases, racemases, aldolases, and various other enzyme classes readily form enolates at physiological pH. Several theories as to how this process occurs have been proposed.[1] Although solvation of an enzyme active site can vary significantly from the surrounding environment in terms of pH, hence facilitating pK_a shifts,[2] there must also be further electrostatic stabilization of the carbonyl to lower the pK_a and the kinetic barrier for deprotonation.[3]

Transition-metal coordination has been invoked as one possible explanation for these unusual acidity enhancements. Kimura[4] and our group[5] have shown that shifts of nearly 12 pK_a units are observed for α-hydrogens upon transition-metal coordination to carbonyls. However, these findings do not account for enzymes in which no metals are present at the active site of enolate formation. For these enzymes, some other electrophilic stabilization must occur. Formation of short, strong hydrogen bonds has been postulated to kinetically activate the deprotonation event.[3,6] This theory, however, has drawn considerable criticism.[7] Irrespective of the method of electrophilic activation, little work has been performed to understand the best geometry for such an activation.

In previous studies, we have shown that placement of a hydrogen bond directed toward the π-system of a carbonyl

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moiety can reduce the pK_a's of α-hydrogens by over 2 pK_a units more than similar coordination to the carbonyl oxygen lone pair.[8] This enhanced pK_a shift arises by destabilizing the hydrogen bonds oriented at the carbonyl while enhancing the stability of its enolate. Because the negative charge in an enolate is delocalized through the π-system, we concluded that coordination through the π-system would grant a greater degree of stability. Recently, several enzymes have been identified which support this conclusion. Crystal structures and computer models reveal π-directed hydrogen bonding in their substrate binding.[9] The goal of the study described here was to reveal with computational quantum chemistry the best geometry for electrophilic activation of α-hydrogen acidity.

In an effort to fully understand the optimal coordination geometry for an electrophile to enhance α-hydrogen acidity, we generated potential energy surface maps of a lithium ion coordinated to acetaldehyde and its corresponding enolate. The lithium ion was used as a generic electrophile, to mimic a hydrogen bond donor or a transition metal. Ab initio calculations at the MP2 level using the 6-31G* basis set were conducted using the ACES II program package.[10] Surface scans were run as opposed to single-point energies because the goal was to predict the best placement of the electrophile to increase the acidity of a carbon acid. Such a geometry may not be a global energy minimum for either individual complex.

Each surface was created by optimizing all geometric parameters of the system save two. The Li−O−C bond angle (x-axis) and the Li−O−C−C dihedral angle (y-axis) were each varied in five-degree increments. Each single-point energy thus calculated was then subtracted from the calculated enthalpy of uncomplexed acetaldehyde or its enolate, respectively, to give the resultant contours that represent the energy of lithium coordination (Figures 1A and 2A). It is evident that for acetaldehyde the energy minimum occurs at the accepted linear coordination geometry (Figure 1B).

Interestingly, the minimum for the enolate is quite different, having a global minimum at a Li−O−C bond angle of 85° and a Li−O−C−C dihedral angle of 45° (Figure 2B). The out-of-plane dihedral angle suggests a significant amount of π-system coordination.

Rudimentary resonance analysis reveals that the two centers of negative charge in an enolate reside at the oxygen and the α-carbon. Hence, it is reasonable to assume this energy minimum arises due to coordination of the lithium ion to both the oxygen and the α-carbon through the delocalized π-electrons.

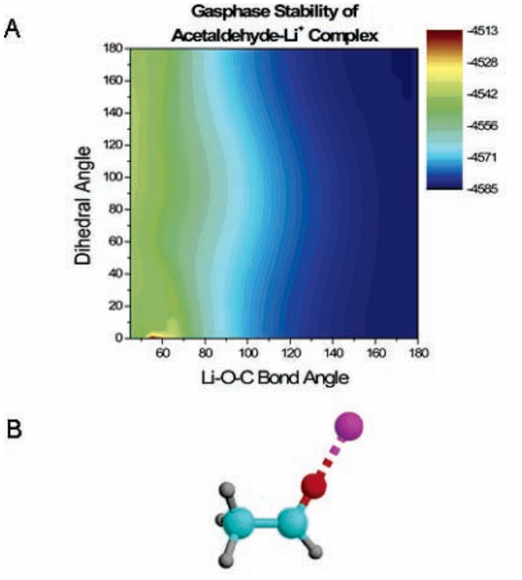

Figure 1. (A) Li$^\oplus$ dihedral angle vs Li−O−C bond angle enthalpy (kcal/mol) contour plot for the Li$^\oplus$−acetaldehyde complex generated at the MP2 level with a 6-31G* basis set, and (B) a graphical representation of the minimum energy structure.

From these analyses, the gas-phase acidity can be determined, as well as can the best geometry for enhancing the acidity of acetaldehyde by lithium coordination. The contour plot shown in Figure 3 is the difference of the enthalpies of lithium coordination to acetaldehyde and its corresponding enolate (see Figures 1A and 2A).

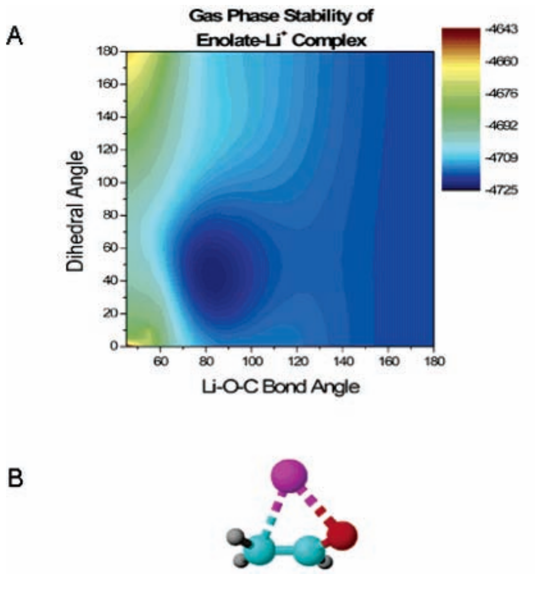

Figure 2. (A) Li$^\oplus$ dihedral angle vs Li−O−C bond angle enthalpy (kcal/mol) contour plot for the Li$^\oplus$−ethylenolate complex generated at the MP2 level with a 6-31G* basis set. The global minimum structure (B) is shown with a dihedral angle of 45° and a Li−O−C bond angle of 85°.

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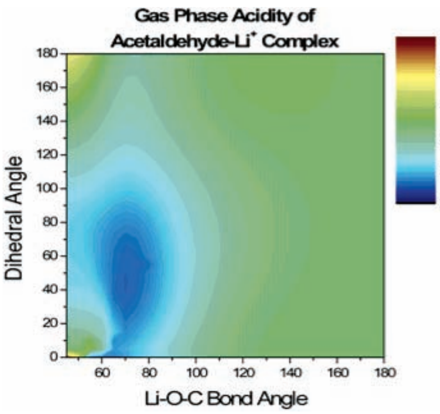

Figure 3. Contour plot of the gas-phase acidity (kcal/mol) of the acetaldehyde−Li$^{\oplus}$ complex derived as the difference of the above acetaldehyde and enolate surfaces.

The contour in Figure 3 represents the energy gained or lost at each single-point geometry upon enolate formation. Whereas the lowest-energy conformation derived by inspection of the enolate surface resides at a bond angle of 85°, the gas-phase acidity analysis reveals a new minimum occurring at 70° while the dihedral angle remains 45° (Figure 4). The lithium now resides nearly perfectly antiperiplanar to the α-hydrogen that will be deprotonated to create the enolate. Hence, backside electrophilic coordination to the orbital of the cleaving C−H bond as well as π-system coordination to the carbonyl create a more labile proton. Such a geometry does not exist as a global energy minimum for either individual complex.

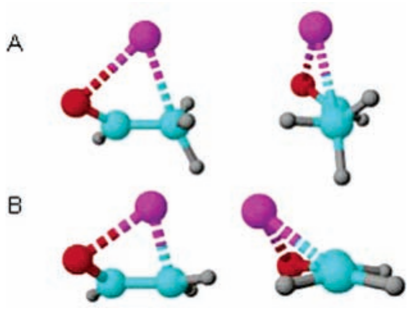

Figure 4. (A) Front and side views of the optimum geometry for lithium coordination to enhance the acidity of acetaldehyde. (B) Analogous views of the enolate complex.

The calculated configuration for the best enhancing acidity can be contrasted with the normally accepted geometry for enhancing acidity—coordination to the carbonyl lone pair. The acidity enhancement of the minimum depicted in Figure 3 vs lone pair coordination is the energy difference of the two single-point enthalpies of the respective geometries. This difference amounts to 20.6 kcal/mol. At 0 K, this value results in a 15.2 unit greater shift in pK_a with π-directed coordination of a Li cation as opposed to coordination to the lone pair. Previous work conducted by Squires suggests an attenuation of the absolute stabilization in a study similar to ours of 30−40% upon solvation.[11] Regardless of the actual value of attenuation, this enhancement provides a clear understanding of the optimal geometry of coordination for maximum augmentation of acidity.

In summary, carbon acid activation can be most effectively facilitated via a coordination event to the emerging delocalized π-electron density. The effect of this coordination appears to be 2-fold. First, a destabilizing interaction through backside C−H coordination increases the lability of the proton, and second, the coordination stabilizes the resulting charge upon enolate formation. Although this study reflects thermodynamics, its conclusions can be extended to kinetics. By weakening the C−H bond via backside coordination, the activation barrier for deprotonation should be decreased. This study explains the π-system coordination found for enzymes and our earlier synthetic models and makes a clear prediction as to the optimal orientation for electrophiles to enhance reactions that commence through α-hydrogen deprotonation.

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Supporting Information Available: Sample Z-matrixes and energy output arrays for both the neutral and the enolate systems. This information is available free of charge via the Internet at http://pubs.acs.org.

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