Determination of Reactivities by MO Theory (XI).
Nucleophilic Substitution Reactions of N-Acetylpyrrolidone

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ABSTRACT. The orbital mixing analysis was applied to the acid-catalyzed nucleophilic substitution reaction of N-acetylpyrrolidone. It was found that the reactivity of protonated carbonyl carbon is greatly enhanced due to increase in positive charge (for charge controlled reaction) and also increase in LUMO AO coefficient (for orbital controlled reaction) of the carbonyl carbon atom.

INTRODUCTION

During the last two decades MO theory has been used increasingly to describe and elucidate organic reaction mechanisms. For analysis of the origin of molecular interactions, two basic approaches are now in use employing perturbation-molecular orbital formalism. One is to partition the mutual perturbation energies of the reacting systems into various contributing interaction modes such as coulomb, exchange repulsion, induction and charge-transfer energies. The other is to analyze mixing of orbitals of interacting systems. The concept of orbital mixing has been useful in elucidating different chemical phenomena. For example Libit and...
Hoffmann, and Whangbo et al., employed the orbital mixing concept in the analysis of substituent and conformational effects. The idea of orbital mixing has been recently applied usefully to the analysis of chemical reactions by Lowe, Zimmerman, Fujimoto and Hoffmann, Imamura and Hirano, and Fukui and Coworkers.

The purpose of this paper is to apply the orbital mixing analysis to nucleophilic substitution reaction of N-acetyl pyrrolidone and to gain some insight into characteristics of the acid catalyzed reactions of the compound.

**THEORY**

Let us consider that a molecule A is subjected to the effect of an outer field due to an approaching molecule B. The characteristic set of orbitals of these two molecules will interact as a result of this mutual perturbations.

$$\Psi_1' = \Psi_1 + \sum_{J} C_{IJ} \Psi_J$$

(1)

Here the coefficient $C_{IJ}$ of the second term measures how much orbital $J$ mixes into orbital $I$. Obviously the subscript $J$ can be factored into subsets of orbitals on A and B, representing intra- and inter-molecular orbital mixings.

$$\Psi_1' = \Psi_1 + \sum_{I} C_{IJ} \Psi_J + \sum_{M} C_{M} \Psi_M$$

(2)

Now let the energies of MO's $\Psi_J$ and $\Psi_M$ be $E_I$ and $E_M$ respectively, the one-electron Hamiltonian of the total system be $H$, and the change of the one-electron Hamiltonian of molecule A due to the perturbation by the molecule B be $H'$. By adopting one-electron formalism, the application of perturbation theory becomes particularly simple and we can directly speak of the mixing of orbitals neglecting the attendant interaction of electrons.

Application of the pertubational formalism leads to the following expressions for the mixing coefficients to second order.

$$C_{II} = 1 - \sum_{M} S_{IM} (H_{IM} - E_I S_{IM})$$

$$- \frac{1}{2} \sum_{M} (H_{IM} - E_I S_{IM})^2$$

(3)

$$C_{IJ} = \sum_{M} \frac{(H_{IM} - E_I S_{IM}) (H_{IM} - E_I S_{IM})}{(E_I - E_M)}$$

(4)

$$C_{MI} = \sum_{M} \frac{H_{IM} - E_I S_{IM}}{E_I - E_M}$$

(5)

where

$$H_{IM} = \int \Psi_I H \Psi_M d\tau$$

(6a)

$$S_{IM} = \int \Psi_I \Psi_M d\tau$$

(6b)

and

$$H'_{IJ} = \int \Psi_I H' \Psi_J d\tau$$

(6c)

The coefficient $C_{II}$ is the second-order self-correction term arising from a renormalization of the perturbed wave function $\Psi_I'$. This term is in general qualitatively unimportant. Imamura and Hirano called the first term of (4) “static orbital mixing” and the second term “dynamic orbital mixing”. The intermolecular orbital mixing, Eq (5), is a first-order “dynamic orbital mixing”.

If we concern ourselves with two orthonormal sets of orbitals with nonzero overlap between orbitals in different set, the mixing coefficients...
can be simplified as follows.

\[ C_{II} = 1 - \frac{1}{2} \sum_{r} \left( \frac{H_{II}}{E_I - E_M} \right)^2 \]  
\[ C_{IJ} = \sum_{r} \left( \frac{H_{IJ}}{E_I - E_J} + \frac{H_{JM}}{E_I - E_M} \right) \]  
\[ C_{MI} = \sum_{r} \frac{H_{IM}}{E_I - E_M} \]

Further simplification was achieved by considering only the frontier orbitals concerned.\(^{10,11}\) Eq. (1) now becomes\(^*\)

\[ \psi_I = \psi_I^0 + C^S_{IJ} \psi_J + C^D_{IJ} \psi_J + C^D_{MI} \psi_M \]  
where

\[ C^S_{IJ} = \frac{H_{IJ}^*}{E_I - E_J} \]  
\[ C^D_{IJ} = \frac{H_{IM} H_{JM}}{(E_I - E_J)(E_I - E_M)} \]  
and

\[ C^D_{MI} = \frac{H_{IM}}{E_I - E_M} \]

and levels \( I, J \) and \( M \) are the frontier orbitals, i.e., highest occupied (HO)MO or lowest unoccupied (LU)MO. There are two ways of intra-molecular orbital mixing (e.g., \( J \) into \( I \)).

(a) One is by static orbital mixing which takes place through perturbing electric field of a point charge (\( Ze \)) at distance \( r \) from an electron. Thus the perturbed Hamiltonian is given by

\[ H_I^* = -\frac{Ze^2}{r} \]

Substituting this into (6c) and integrating with simplifying assumptions the static orbital mixing coefficient was shown to have a form\(^{10}\) (10).

\[ C^S_{IJ} = -Z \left( \frac{a_J a_I}{E_I - E_J} \right) \gamma \]

where \( a_I \) and \( a_J \) are the atomic orbital coefficients of atom \( r \) which is nearest to the point charge and \( \gamma \) is a positive quantity representing the electrostatic interaction energy. (b) The second is through dynamic orbital mixing in which the two interacting orbitals of a molecule, e.g., \( I \) and \( J \) of \( A \), overlap with an orbital of a second molecule, e.g., \( M \) of \( B \) (Fig. 1).

Fig. 1. Schematic representation of intra-molecular orbital mixing: (a) static and (b) dynamic orbital mixings.

These two modes of intra-molecular orbital mixing have been shown to be responsible for the catalytic activity of a point charge and a catalyst orbital\(^{10}\). Using Eqs. (10) and (8b), Imamura and Hirano\(^{48}\) were able to arrive at the following general rules of orbital mixing.

(a) Static orbital mixing: Eq (10) shows that the sign and magnitude of mixing of the orbital \( J \) into \( I \) are determined by the product \( a_J a_I \) and the difference \( E_I - E_J \) for a given point charge since \( E_I - E_J \) is only dependent on the distance \( r \) (Eq. 9) and an AO of the nearest atom to the unit point charge. The sign of \( C^S_{IJ} \) is given as in the following Table 1.

Table 1. Signs of orbital mixing coefficients.

<table>
<thead>
<tr>
<th></th>
<th>( a_I, a_J )</th>
<th>( E_I - E_J )</th>
<th>( C^S_{IJ} )</th>
</tr>
</thead>
<tbody>
<tr>
<td>(+)</td>
<td>(+)</td>
<td>(+)</td>
<td>(+)</td>
</tr>
<tr>
<td>(+)</td>
<td>(-)</td>
<td>(\pm)</td>
<td>(-)</td>
</tr>
<tr>
<td>(-)</td>
<td>(+)</td>
<td>(-)</td>
<td>(+)</td>
</tr>
<tr>
<td>(-)</td>
<td>(-)</td>
<td>(+)</td>
<td>(-)</td>
</tr>
</tbody>
</table>

The magnitude of the mixing \( |C^S_{IJ}| \) is
approximately proportional to the absolute value of the product of the AO coefficients, \(a_i a_j\), and inversely proportional to the absolute value of the difference of the two energy levels, \(|E_i - E_j|\).

(b) Dynamic orbital mixing: Similarly judged using \(C^4\) (Eq. 8b). The intermolecular orbital mixing, \(C^I\) (Eq. 8c), is not important in the proton catalysis and therefore will not be considered here.

**CALCULATIONS**

CNDO/2 MO's were calculated for both the trans-trans and cis-trans forms of N-acetylpyrrolidone and for their protonated forms. The extent to which N-acetylpyrrolidone \(\pi\)-MO's participate in \(\pi\)-MO's of the protonated forms has been calculated by the scalar products between particular MO's of the protonated forms and each of the MO's of N-acetylpyrrolidone using PDP 11 at the Inha University computing center. Planar conformations have been assumed in the calculation. The numbering scheme for non-hydrogen atoms is given below for the trans-trans form.

```
  C    3
1    C
2
3    C
  4
```

**RESULTS AND DISCUSSION**

N-Acetylpyrrolidone is reported to undergo both acyl and ring cleavages at comparable rates in alkaline hydrolysis whereas the ring cleavage proceeds faster in acid hydrolysis. The question of whether the acyl group or the ring will be cleaved is of great interest in synthetic work. Let us now see how this question can reasonably be answered theoretically considering MO's of N-acetylpyrrolidone and its protonated form.

Atomic charges and \(\pi\)-bond populations for the two planar forms of N-acetylpyrrolidone are reproduced for relevant part in Fig. 2. Among ten \(\pi\)-MOs for the N-acetylpyrrolidone obtained by CNDO/2 calculation, we were able to identify five \(\pi\)-MOs which had large \(p_2\) AO coefficients at the five atoms (N\(1\), C\(2\), O\(6\), C\(7\) and O\(8\)) forming a pseudo-pentadienyl system. These \(\pi\)-MOs are shown in Fig. 3 together with the nodal property of the pentadienyl. Similarity of the nodal characteristics of our pseudo-pentadienyl systems with that of the true pentadienyl is very striking. The two pseudo-pentadienyl systems for the trans-trans and cis-trans show little difference in energy and have the same nodal properties. In both cases, first three \(\pi\)-orbitals, \(\pi_1\), \(\pi_2\), and \(\pi_3\), are occupied and the rest two unoccupied. The most important orbital in dictating the rate of an orbital controlled nucleophilic substitution reaction is the LUMO, and in this case it is the fourth \(\pi\)-orbital, \(\pi_4\). This MO was the lowest unoccupied among all MOs i.e., for \(\sigma\) and \(\pi\), and also it was the lowest unoccupied among pseudo-pentadienyl \(\pi\)MOs. The largest AO coefficient of the LUMO is that of C\(1\) for both pseudo-pentadienyl systems, indicating that the acyl cleavage will be preferred in an orbital controlled process. However the orbital controlled process will not be very efficient due to very small,
almost negligible, AO coefficient of the N atom

giving very small anti-bonding character to the
C–N, bond. On the other hand, Fig. 2 shows

that the ring cleavage is preferred in a charge
controlled process since positive charge is greater
at the ring carbonyl carbon, C₂. Again this
preference will not be an overwhelming one,
since π-bond order of the N₁–C₂ bond which
must be broken at the initial stage of the nucleo-
philic attack is larger, and hence it is more
difficult to break, than that of N₁–C₂ bond which
must be broken in the acyl cleavage. It may
be possible that the ring cleavage is slightly
faster since the nucleophiles in the neutral and
alkaline hydrolysis are hydroxyl anion and water
molecules, hard bases, and the reaction will
be charge controlled. But it is more likely that
in a neutral or alkaline hydrolysis no one mode
of cleavage prevails over another and the two

processes proceed at comparable rates.

The situation becomes very different and the
preference in the mode of cleavage becomes
more definite for the protonated form. Table 2
shows the formal atomic charges of the two
 carbonyl carbon atoms and the AO coefficients
of LUMOs for various protonated forms of
the pseudo-pentadienyl systems. In the previous
report, we have shown that the protonation should
occur on oxygen atoms, the ring carbonyl oxygen
being a little preferred. For the protonated
forms, the formal positive charge is larger at
the protonated carbonyl carbon atom: thus for
the ring carbonyl oxygen protonated, TTR and
CTR, C₂ has the larger positive charge whereas
for the acyl oxygen protonated, TTA and CTA,
C₇ is more positive. This means that ring cleav-
age will occur for TTR and CTR while acyl
cleavage prevails for TTA and CTA in the

Fig. 3. Nodal properties of pentadienyl-π-system and CNDO/2 π-πMOs of pseudo-pentadienyl systems of
trans-trans and cis-trans N-acetylpyrrolidones. (AO coefficients and energies are shown for N-acetylpyrrolidone-
π-systems)

Table 2. The formal atomic charges (positive) of carbonyl carbons and the AO coefficients of LUMO(\( \pi \)) for the various protonated and unprotonated forms of N-acetylpyrrolidone (shown for the pseudo-pentadienyl only).

<table>
<thead>
<tr>
<th>Formal atomic charges(+):</th>
<th>AO coeff. of LUMO (( \pi ))</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>( C_2 )</td>
</tr>
<tr>
<td>TTR1</td>
<td>0.406</td>
</tr>
<tr>
<td>TTR2</td>
<td>0.408</td>
</tr>
<tr>
<td>TTR3</td>
<td>0.401</td>
</tr>
<tr>
<td>TTR4</td>
<td>0.458</td>
</tr>
<tr>
<td>TTA1</td>
<td>0.399</td>
</tr>
<tr>
<td>TTA2</td>
<td>0.363</td>
</tr>
<tr>
<td>TTA3</td>
<td>0.350</td>
</tr>
<tr>
<td>TTA4</td>
<td>0.343</td>
</tr>
<tr>
<td>CTR1</td>
<td>0.403</td>
</tr>
<tr>
<td>CTR2</td>
<td>0.398</td>
</tr>
<tr>
<td>CTR3</td>
<td>0.390</td>
</tr>
<tr>
<td>CTR4</td>
<td>0.429</td>
</tr>
<tr>
<td>CTA1</td>
<td>0.349</td>
</tr>
<tr>
<td>CTA2</td>
<td>0.343</td>
</tr>
<tr>
<td>CTA3</td>
<td>0.346</td>
</tr>
<tr>
<td>CTA4</td>
<td>0.349</td>
</tr>
<tr>
<td>TTN</td>
<td>0.319</td>
</tr>
<tr>
<td>CTN</td>
<td>0.324</td>
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<tr>
<td>TTB1</td>
<td>0.389</td>
</tr>
<tr>
<td>TTB2</td>
<td>0.469</td>
</tr>
<tr>
<td>TT</td>
<td>0.355</td>
</tr>
<tr>
<td>CT</td>
<td>0.354</td>
</tr>
</tbody>
</table>

TT = trans-trans, CT = cis-trans, TTR = trans-trans-ring carbonyl oxygen protonated, CTA = cis-trans-acyl oxygen protonated etc. TTN = trans-trans-nitrogen protonated etc. TTB1 = trans-trans-proton-bridged form (pentagonal), TTB2 = trans-trans-proton-bridged form (hexagonal). The other numbers 1, 2, 3 and 4 indicate angles of rotation, \( \phi \) (clockwise) of O—H around C—O bonds started from the molecular plane and angles of \( \angle \)COH, \( \theta \), in the molecular plane. For 1: \( \theta = 120^\circ, \phi = 0^\circ \), 2: \( \theta = 120^\circ, \phi = 90^\circ \), 3: \( \theta = 120^\circ, \phi = 180^\circ \), 4: \( \theta = 180^\circ, \phi = 0^\circ \).

Acid catalyzed hydrolysis since the nucleophile, \( H_2O \), is a hard base and the reaction will be charge-controlled. This trend in the preference of cleavage mode will be the same in an orbital-controlled acid catalyzed nucleophilic substitution reaction, since the AO coefficient of the protonated carbonyl carbon in the LUMO is the largest. Thus irrespective of the hardness (or softness) of the nucleophile the ring carbonyl oxygen protonation leads to the ring cleavage and the acyl oxygen protonation leads to the acyl cleavage. Therefore we conclude that the ring cleavage is preferred in the acid catalyzed hydrolysis of N-acetylpyrrolidone, since the ring carbonyl oxygen is shown to be protonated preferentially. This agrees well with the experimental findings reported.

It is interesting to note that if the protonation occurs on the nitrogen (N1) atom, no clear prediction is possible since formal charges of N do not differ much and both of the C—N bonds are bonding in the LUMO. For the bridged proton forms TTB1 and TTB2, the nucleophilic reactivity will remain the same as for the unprotonated...
nated form in an orbital controlled reaction while it will reverse in a charge-controlled reaction by protonation.

**STATIC ORBITAL MIXING**

In Table 3 we have shown the perturbed LUMO's (of the protonated form) in terms of the \( \pi \)-orbitals of unprotonated N-acetylpyrrolidones. As expected from the large energy differences (Eq. 10) contributions of lower energy levels, \( \pi_1 \) and \( \pi_2 \), were very small and therefore they were neglected and attention has been solely focussed on the mixing of two orbitals \( \pi_3 \) and \( \pi_4 \) into the LUMO(\( \pi_6 \)). These two \( \pi_3 \) and \( \pi_4 \) are nearest neighbors for \( \pi_6 \) and the HO and next to the lowest unoccupied (NLU) orbitals respectively. According to the rule, Table 1, the contributions of orbitals \( \pi_3 \) and \( \pi_4 \) to \( \pi_6 \) will be positive, i.e., \( C_{36} > 0 \) and \( C_{46} > 0 \) for the ring carbonyl oxygen (\( O_6 \)) protonation, since the energy differences are \( (E_4 - E_6) > 0 \) and \( (E_4 - E_5) > 0 \), and signs of the product of AO coefficients for \( O_6 \) are \( a_{63}a_{64} > 0 \) and \( a_{63}a_{64} < 0 \). On the other hand the mixing coefficients are both negative i.e., \( C_{36} < 0 \) and \( C_{46} < 0 \) for the acyl oxygen (\( O_5 \)) protonation judging similarly from Table 1. Thus the static orbital mixing rule predicts that both HO and NLU orbitals will give positive contributions in the ring carbonyl oxygen protonation while they will give negative contributions in the acyl oxygen protonation. As a result of both orbital mixing the absolute value of the AO coefficient increases significantly at \( C_2 \) in the ring carbonyl oxygen protonation and at \( C_6 \) in the acyl oxygen protonation respectively.

These predictions are exactly borne out in the result of our calculation (Table 3). Since the magnitude of mixing, i.e., \( |C_{j6}| \), is dictated by \( |E_4 - E_6| \) and \( |a_{j3}a_{j4}| \), we would expect the contribution of NLU (\( \pi_6 \)) orbital to be greater than that of HO (\( \pi_2 \)), as \( |E_4 - E_5| > |E_1 - E_3| \) and \( |a_{63}| < |a_{64}| \). Thus the contribution of the NLU (\( \pi_6 \)) orbital is always much larger than that of HO (\( \pi_2 \)) orbital as can be seen from Table 3.

The static orbital mixing rule does not apply for the N-protonated forms. This may well be due to the approximations introduced in derivations and also due to extremely small, near zero, values of AO coefficient of the N atom in the LUMO, \( a_{6n} \equiv 0 \).

For the bridged protonation the rule is applicable but the mixing coefficients are extremely small and therefore the perturbed LUMO remain nearly the same as that of the unperturbed.

**DYNAMIC ORBITAL MIXING**

If we assume that a Lewis acid is present near an oxygen atom, \( O_6 \) or \( O_3 \), the electrostatic effect will be small but the Lewis acid will provide empty d orbitals that can overlap with both the

| Table 3. Mixing coefficients of \( \pi_6 \) (HO), \( C_{36} \), and of \( \pi_4 \) (NLU), \( C_{46} \), into \( \pi_6 \) (LU) of the protonated N-acetylpyrrolidones. |
|-------------------|--------|-------|-------|
| Protonated forms  | \( C_{36} \) | \( C_{46} \) | \( C_{54} \) |
| TTR1             | 0.766  | 0.178 | 0.452 |
| TTR2             | 0.608  | 0.342 | 0.422 |
| TTR3             | 0.731  | 0.201 | 0.497 |
| TTR4             | 0.748  | 0.159 | 0.481 |
| TTTA1            | 0.812  | -0.188| -0.201|
| TTTA3            | 0.927  | -0.163| -0.172|
| CTR1             | 0.850  | 0.159 | 0.294 |
| CTR2             | 0.795  | 0.189 | 0.402 |
| CTN              | 0.795  | -0.162| -0.299|
| CTA3             | 0.796  | -0.163| -0.288|
| TTN              | 0.014  | -0.415| 0.393 |
| CTN              | 0.341  | -0.332| 0.423 |
| TTB1             | 0.885  | 0.012 | 0.094 |
| TTB2             | 0.887  | 0.016 | 0.103 |

* e.g. The perturbed LUMO can be represented as either, (for TTR1)

\[
\Phi_{LU'} = 0.766 \Phi_{LU} + 0.178 \Phi_{HO} + 0.452 \Phi_{NLU} \quad \text{or} \quad \Phi_{LU'} = 0.766 \Phi_{LU} + 0.178 \Phi_{S} + 0.452 \Phi_{S}
\]
LU and HO or NLU, and the dynamic orbital mixing will take place. Since the energy of the vacant d orbitals will be relatively large, the orbital overlap can become appreciable in many cases. This type of situation is met in the Meerwein—Ponndorf reaction, in which aldehydes are reduced to alcohols by the catalysis of aluminum isopropoxide. The transition state of this reaction is usually considered to be a cyclic complex by the coordination of the carboxyl oxygen with aluminum, followed by the transfer of the hydride ion (a soft base). In this case Al provides vacant d orbitals which can overlap with πMOs (HO, LU and NLU) of the carboxyl group of aldehydes. However, the contribution of HO to LUMO in the dynamic orbital mixing calculated from Eq (8b) was exactly the same as we would have expected if the Al had been replaced by a proton and the static orbital mixing is considered, i.e., the carboxyl carbon was activated (the absolute value of the AO coefficient increased) as a result of coordination with Al (a Lewis acid) with the carboxyl oxygen. This means that the Al atom being an acid acts like a proton, or vice versa. The difference between the two cases is that in the Lewis acid catalysis the reaction is normally orbital controlled (as in the case of hydride ion transfer) and the absolute magnitude of the AO coefficient of the carboxyl carbon has the predominant effect in determining the reactivity, while in the proton catalysis the reaction is likely to be charge-controlled and the magnitude of formal atomic charge (positive) of the protonated carboxyl carbon dictates the reactivity.

We therefore conclude that in the acid catalysis of carboxyl compounds all the acid, whether it is a Lewis type or a proton, acts the same way in activating the carboxyl carbon. Both the static and dynamic orbital mixings increase the positive charge and the absolute value of the AO coefficient of the carboxyl carbon whose oxygen is coordinated with the acid. Thus the reactivities of both charge-controlled (by a hard base) and orbital controlled (by a soft base) SN reaction increase by the coordination of oxygen with acid.

**ACKNOWLEDGMENT**

We wish to thank the Eusok Foundation for the support of this work.

**REFERENCES**

(1968).
19. Imamura and Hirano did not report the charge distributions for Al-alkoxide-formaldehyde complex. However the second-order polarization of the occupied π- orbitals by mixing in of unoccupied π- orbitals, i.e., by dynamic orbital mixing, is expected to increase positive charge of the carbonyl carbon atom when an acid is coordinated with the carbonyl oxygen.