A Localized Molecular Orbital Calculation of Chemically Interacting Systems. Interaction between Amines and Carbonyls

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(Received October 11, 1977)

The bond interchange in the course of the addition of amine to carbonyl has been studied by means of a localized molecular orbital method with a clear chemical-bond concept, and the mechanism of the addition has been elucidated theoretically. It is ascertained by the present calculation that the charge transfer interaction from the highest occupied molecular orbital of amine to the lowest unoccupied molecular orbital of carbonyl is of importance to form a new nitrogen-carbon bond. Furthermore, the stereospecificity of the nucleophilic addition to a double or triple bond has been studied. When an intermediate is created by the addition of a nucleophile to the unsaturated bond, it is suggested that the intermediate is reactive for the electrophilic attack on the side *trans* to the new bond formed by the first attack. This is reasoned in terms of the mode of orbital interaction.

Addition of amine to carbonyl is one of the simplest nucleophilic reactions.1) Recently, the course of the addition was studied experimentally by analyzing the molecular structure of adducts of amine to ketone with presumably different strength of the interaction.2) The path of the approach of amine to carbonyl revealed in the work is expected to provide us with valuable information for a theoretical study of chemical reactions. In general, the path of the chemical reaction is governed by various energy factors in a molecular orbital (MO) viewpoint.3) A partitioning analysis of the interaction energy suggested that the exchange and charge transfer (CT) interactions are generally of importance in the interaction between two reagents, while the Coulomb interaction plays a dominant role in an early stage of ionic reactions.4) Even in ionic cases, however, the CT interaction is the origin of the formation of new chemical bonds.5)

In discussing the orientation and stereoselection in chemical reactions, the CT interaction from the highest occupied (HO) MO of electron donors to the lowest unoccupied (LU) MO of electron acceptors is usually of a particular importance.5) The HOMO and LUMO of many molecules, however, are delocalized over p atomic orbitals (AO's) of component heavy atoms and hydrogen 1s AO's. The s AO's of first and second row atoms are found for the most part in low-lying MO's. When a configuration interaction expansion of the wavefunction of the interacting system is carried out in terms of various kinds of the electron configurations, there is non-negligible contribution of the charge transferred and locally excited configurations from low-lying MO's, in addition to the major charge transferred configurations from the HOMO to the LUMO. Therefore, the formation of new bonds and the loosening of old bonds, together with the rehybridization at the reaction centers, may be interpreted by means of orbital interactions between the isolated molecules including the HOMO-LUMO interactions.

In general, the MO's of a sizable molecule are delocalized over the constituent AO's and the bonding property of a given atom pair is discussed by means of the electron density contour,6) the overlap population7) and the bond energy.8) On the other hand, the method of the Edmiston-Ruedenberg localized MO (LMO)9) presents us an alternative way of visualizing the chemical bonds in a chemically graspable manner. It may be worthwhile to show that the application of the LMO method to chemically interacting systems is really helpful in disclosing the mechanism of bond interchange and rehybridization in the course of the reaction. These are interesting problems in organic chemistry.

In the present paper, we first apply the LMO method to the chemically interacting system composed of amine and carbonyl in order to obtain a theoretical way of representing the bond interchange and rehybridization in the course of the addition reaction. Next, the mechanism of the addition is clarified by the mode of the orbital interaction mentioned above. Furthermore, the general aspect of the nucleophilic addition to unsaturated bonds is explained schematically in terms of the shape of MO's of the isolated reactants.

Calculation of Assumed Reaction Models

Method of Calculation. In this study, a system composed of an ammonia and a formaldehyde is selected as a reaction model in the calculation of the LMO's. The canonical MO's (CMO's) of the isolated molecules and the reacting system which are transformed into the LMO's9) are obtained by the INDO MO method.8)

Figure 1 illustrates the geometry of assumed reaction models. In the present calculation, three variables (R, r, and θ) are changed. The geometry of ammonia10) is kept frozen throughout the calculation, whereas that of formaldehyde11) is deformed. The parameter, R, means the intermolecular distance between the nitrogen atom (N) of ammonia and the carbon atom (C) of formaldehyde. "r" is the distance of the C=oxygen (O) bond of formaldehyde, and "θ" is defined as the angle between the C=O bond and the methylene plane of formaldehyde. A preliminary calculation on this system gives a result which is in a fairly good agreement with the experimental reaction path.2) In consideration of the preliminary result and the experimental reaction path, the angle between the N···C line and the C=O is fixed to be 107° in the present calculation. The N···C distance, R, is restricted to the range, 3.0—2.0 Å. At $R=3.0$ and 2.5 Å, the geometry of formaldehyde is not deformed ($r=1.21$ Å and $\theta=0°$),11) whereas at $R=2.2$

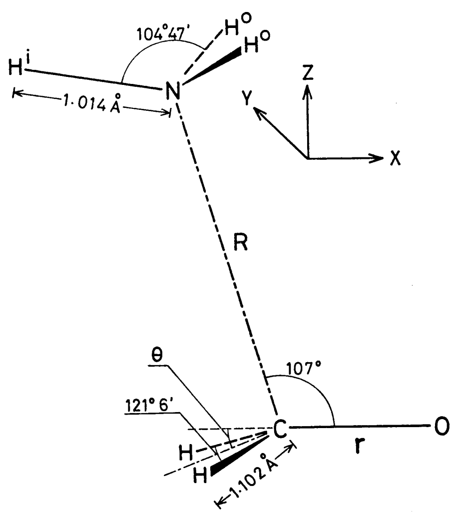


Fig. 1. The assumed reaction model employed for the calculation of the LMO.

and 2.0 Å it is deformed to give the minimum total energy of the interacting system at each value of R ($r=1.25$ Å, $\theta=10°$ at $R=2.2$ Å and $r=1.27$ Å, $\theta=15°$ at $R=2.0$ Å). On these models, the LMO's of the reacting system are calculated.

The energy of each LMO (B_i) is calculated to study the formation and disappearance of the bond.[12] The energy, B_i, is represented by the sum of the electron energy ($E_i^{\rm el}$) of the LMO and the nuclear repulsion energy.

$$B_i = E_i^{\rm el} + E_i^{\rm n}. \qquad (1)$$

The nuclear repulsion energy is partitioned and assigned to the bonds according to the procedure introduced by Parks and Parr.[13] $E_i^{\rm n}$ in Eq. 1 is the partitioned nuclear repulsion energy assigned to the bond i.

Furthermore, the LMO is expanded in terms of the CMO's of ammonia and formaldehyde in order to see the origin of the bond formation, the bond cleavage and the rehybridization in the course of the reaction.[5b]

$$\psi_{\rm LMO} = \sum_{i=1}^{7} C_i a_i + \sum_{j=1}^{10} D_j b_j. \qquad (2)$$

$\psi_{\rm LMO}$ is one of the LMO's of the reacting system. The CMO of ammonia is defined a_i, while that of formaldehyde is named b_j. The suffix attached to the right bottom of "a" and "b" stands for the numbering order counted from the lowest occupied MO.

Results. In Fig. 2, the CMO's of ammonia and formaldehyde are schematically depicted. In Fig. 3, the shapes of the LMO's of these are also schematically pictured. They are three N–H (hydrogen) bond orbitals and an N lone pair orbital in ammonia, and two C–H bond orbitals, two O lone pair orbitals and two C–O bent bond orbitals in formaldehyde. The upper C–O bent bond orbital is hereafter called the CO bond 1, and the lower one is called the CO bond 2. For each value of R, the energies of LMO's are calculated. The result is given in Table 1. In Table 1, it is shown that the N lone pair orbital is stabilized. This corresponds to the formation of the N···C bond. On the other hand, the two C–O bent bond orbitals are destabilized, indicating the weakening of the bonds. Interestingly, the CO bond 2 is loosened more easily than the CO bond 1, and the latter is even stabilized at $R=2.0$ Å. A more detailed discussion on this point will be given later. It is found from Table 1 that the remaining bond orbitals do not change much in comparison with the three bond orbitals mentioned above.

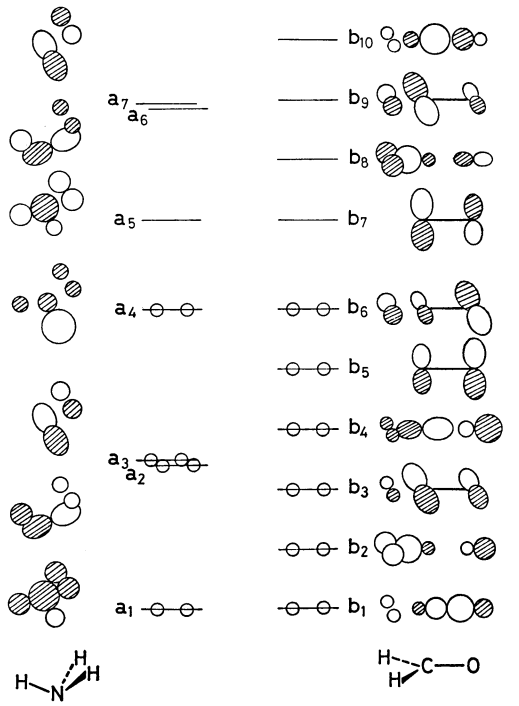


Fig. 2. The shape of the CMO's of the isolated ammonia and formaldehyde.

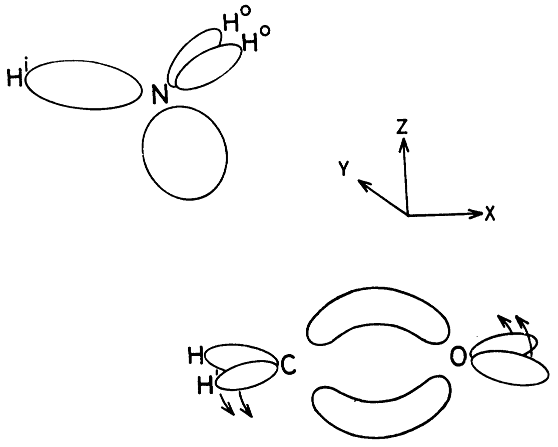
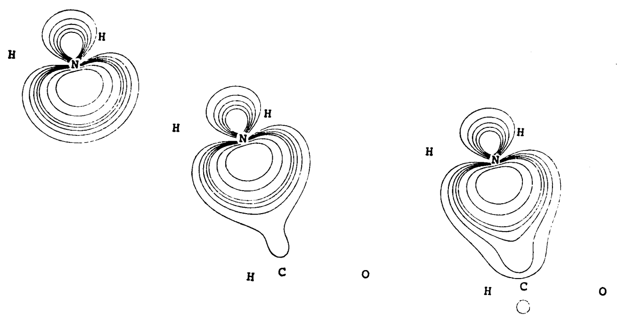


Fig. 3. The shape of the LMO's of the isolated ammonia and formaldehyde.

Let us examine the change in the LMO's for the N lone pair and the two C–O bonds. These bonds are considered to participate significantly in the addition reaction. In Fig. 4, the LMO corresponding to the N lone pair is pictured. It is shown that the N lone pair orbital begins to deform so that it would include the component of the carbon AO's. The s-nature of the N lone pair orbital of the isolated ammonia is calculated to be 35.5%, and that at $R=2.0$ Å is found

Table 1. The calculated energy of the bond orbitals in the addition of ammonia to formaldehyde
The NH bond is the N–H^1 bond of ammonia which is in the N–C–O plane.
The NH^o bonds are not in the N–C–O plane.

$\frac{R}{\text{Å}}$		CO bond 1	CO bond 2	CH bond	CH bond	O lone pair	O lone pair	N lone pair	NH^o bond	NH^o bond	NH^1 bond
	E_i^{el}	−212.25	−212.25	−168.27	−168.27	−211.73	−211.73	−148.85	−151.44	−151.44	−151.44
8	E_i^n	79.78	79.78	100.28	100.28	62.02	62.02	42.60	65.65	65.65	65.65
	B_i	−132.47	−132.47	−67.99	−67.99	−149.71	−149.71	−106.25	−85.79	−85.79	−85.79
	E_i^{el}	−245.42	−245.30	−204.20	−204.20	−242.73	−242.73	−202.13	−201.79	−201.79	−201.01
3.0	E_i^n	113.47	113.47	136.41	136.41	93.09	93.09	95.62	115.51	115.51	114.70
	B_i	−131.95	−131.83	−67.79	−67.79	−149.64	−149.64	−106.51	−86.28	−86.28	−86.31
	E_i^{el}	−250.71	−250.65	−210.32	−210.32	−246.89	−246.89	−212.15	−210.30	−210.30	−209.21
2.5	E_i^n	119.09	119.09	142.82	142.82	97.59	97.59	104.85	123.57	123.57	122.42
	B_i	−131.62	−131.56	−67.50	−67.50	−149.30	−149.30	−107.30	−86.73	−86.73	−86.79
	E_i^{el}	−252.53	−250.22	−213.19	−213.19	−247.70	−247.70	−220.47	−216.73	−216.73	−215.34
2.2	E_i^n	121.28	121.28	145.56	145.56	98.85	98.85	111.31	129.12	129.12	127.65
	B_i	−131.25	−128.94	−67.63	−67.63	−148.85	−148.85	−109.16	−87.61	−87.61	−87.69
	E_i^{el}	−260.68	−244.38	−215.66	−215.66	−248.37	−248.37	−228.26	−222.22	−222.22	−220.57
2.0	E_i^n	123.69	123.69	148.37	148.37	100.34	100.34	116.53	133.54	133.54	131.81
	B_i	−136.99	−120.69	−67.29	−67.29	−148.03	−148.03	−111.73	−88.68	−88.68	−88.76



(a) (b) (c)

Fig. 4. The lone pair orbital of ammonia (N lone pair). The contour lines show the electron density. Each line indicates 0.1, 0.2, 0.3, 0.5, 0.7, 1.0 and 1.5 e/Å^3 from out side.
(a); The lone pair orbital of the isolated ammonia. (b); The lone pair orbital at R=2.2 Å. (c); The lone pair orbital at R=2.0 Å.

to be 35.3%. It is suggested, therefore, that ammonia gets into the interaction with formaldehyde, without changing its hybridized state significantly. The N lone pair orbital at R=2.5 Å corresponding to the N···C bond in the reacting system is expanded in terms of the CMO's of the two reactants.

$$\phi_{\text{N lone pair}} = 0.933a_4 - 0.343a_1 + 0.110b_7 + 0.020b_8 + \cdots \quad (3)$$

In Eq. 3, the coefficients larger than 0.02 (absolute value) are displayed. From Eq. 3, it is found that in addition to the dominant interaction between the HOMO (a_4) of ammonia and the LUMO (b_7) of formaldehyde, there are certain contributions of the low-lying and high-lying sigma MO's (a_1 and b_8). The former sigma MO, a_1, contributes to build up a hybridized orbital of ammonia (sp^3), and the latter, b_8, contributes to the change of the hybridization of the carbon of formaldehyde (sp^2→sp^3). The CT interaction from the HOMO (a_4) to the LUMO (b_7) is primarily important in the formation of the new N···C bond, and then the low-lying and high-lying MO's contribute to the rehybridization of the reacting centers.

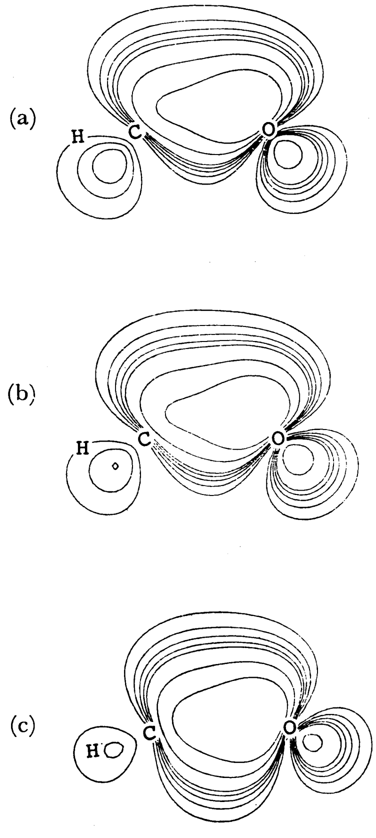


Fig. 5. One of the bent bond orbitals of formaldehyde (CO bond 1). The contour line means the same as is used for the lone pair orbital.
(a); One of the bent bond orbitals of the isolated formaldehyde. (b); The bent bond orbital at R=2.2 Å. (c); The bent bond orbital at R=2.0 Å.

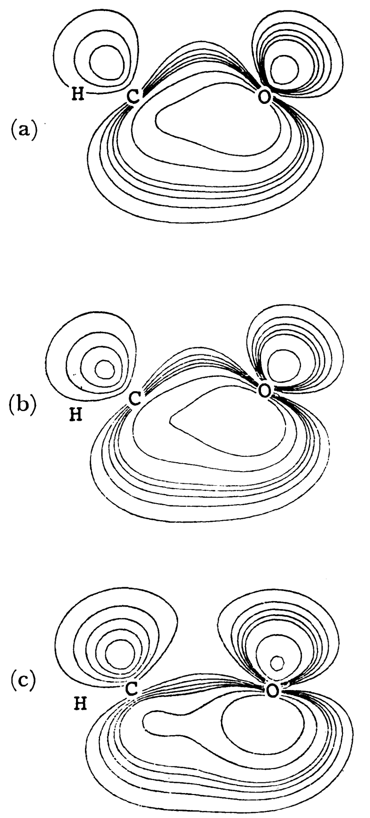


Fig. 6. The other bent bond orbital of formaldehyde (CO bond 2). The contour line means the same as is used for the lone pair orbital.
(a); The other bent bond orbital of the isolated formaldehyde. (b); The bent bond orbital at R=2.2 Å. (c); The bent bond orbital at R=2.0 Å.

In Figs. 5 and 6, the two bent bond orbitals of the C=O double bond are drawn. Let us compare Fig. 5 with Fig. 6. This comparison, together with the energy change of the bond orbitals in Table 1, shows that the CO bond 1 is converted into the CO sigma bond, whereas the CO bond 2 is transformed into the O lone pair. This result seems to be interesting in regard to the stereospecific phenomena observed in the nucleophilic additions as will be shown in the next section.

The result obtained here is explicable in terms of the orbital interaction in the following manner. In Fig. 7, the mode of the orbital interaction of the HOMO of ammonia with the π (b_5) and π^* (b_7) orbitals of formaldehyde is schematically illustrated. The interaction of the a_4 with the π and π^* leads to two occupied MO's (ϕ_1 and ϕ_2) and one unoccupied MO (ϕ_3) of the composite system. Among the three MO's, ϕ_1, ϕ_2 and ϕ_3, the mixing of the π and π^* through the a_4 is the largest in the ϕ_2.[14] If our attention is focused on the sign of the component MO's the ϕ_2 is represented[15] as

$$\phi_2 = a_4 - \pi + \pi^*.$$

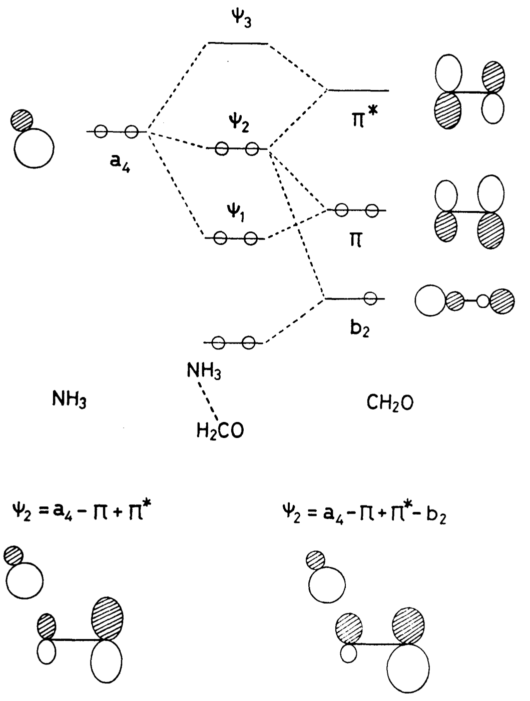


Fig. 7. The schematic representation of the electron polarization by the orbital mixing of the b_2, π, and π^* through the a_4.

The mixing of the π and π^* through the a_4 contributes to the polarization of the electrons in the direction from the carbon atom to the oxygen atom, although this mixing does not give the difference of the polarization between the upper and lower sides of the molecular plane of formaldehyde. However, the b_2 mixes into the ϕ_2 through the interaction with the a_4, and then the ϕ_2 is rewriten[15] as

$$\phi_2 = a_4 - \pi + \pi^* - b_2.$$

Consequently, the polarization of the C=O bond is more effective in the lower side of the molecular plane of formaldehyde than the upper side. From the above result, it is considered that in the addition of ammonia to formaldehyde one of the C=O bent bond orbitals (CO bond 1) is converted into the C–O sigma bond and the other (CO bond 2) is transformed into the O lone pair. That is, the O lone pair stays as far away from the N···C bond as possible.

In the present calculation, the LMO's representing the C–H bonds of formaldehyde are shown to be pushed down by the approach of ammonia as is indicated by the arrow in Fig. 3, whereas the O lone pair orbitals are lifted, when the nuclear framework is kept unchanged. Such rehybridizations on the carbon atom and oxygen atom are obviously in favor of the change of the CO bond 2 to the O lone pair spreading over the region opposite to the initial attack at the carbon atom. The rehybridization of the carbon is explicable in terms of the orbital mixing of the b_2, b_5, and b_7 through the interaction with the a_4. This orbital mixing is shown in Eq. 4.

$$\phi_{\mathrm{CH\ bond}} = 0.238b_1 + 0.624b_2 + 0.586b_3 - 0.226b_4 + 0.018b_5 - 0.395b_6 - 0.039b_7 + \cdots. \quad (4)$$

In Eq. 4, the expansion coefficients are obtained at R=2.0 Å and the values larger than 0.015 (absolute value) are displayed. The rehybridization on the oxygen is also explicable in the way similar to that on the carbon. In Eq. 5, the expansion coefficients which are obtained at $R=2.0$ Å are shown and those smaller than 0.015 (absolute value) are neglected.

$$\psi_{\text{O lone pair}} = 0.345b_1 - 0.316b_2 + 0.395b_3 - 0.491b_4 + 0.198b_5 + 0.586b_6 - 0.016b_7 + \cdots. \quad (5)$$

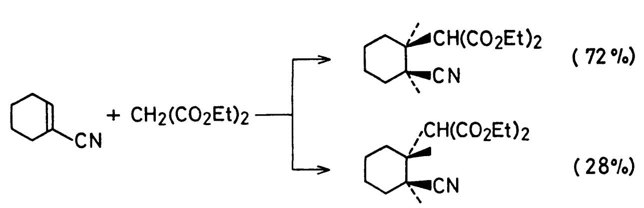
In Eqs. 4 and 5, the coefficient of the a_4 is very small, but when the CMO's of the interacting system are expanded by the use of those of the isolated molecules, the mixing of the b_2, b_5, and b_7 is shown to be due to the interaction with the a_4. It should be noted that the LMO's representing the N–H bonds are not changed markedly in the present calculation.

Let us summarize the results obtained so far. When the C=O double bond of the formaldehyde is represented by two bent bond orbitals, the attack of ammonia to the C=O bond is shown to bring about the breaking of the bent bond orbital on the side opposite to the attack. The bond orbital is shown to be converted into the O lone pair orbital having large amplitudes on the side opposite to the initial attack at the carbon atom. Furthermore, the C–H bonds and the O lone pairs are shown to rotate to assist the transformation of the bent bond orbital into the O lone pair. In the present calculation, the system composed of ammonia and formaldehyde is selected as a reaction model. It is reasonable to consider that a compound with a double bond or triple bond (A=B or A≡B) has π, π^*, and σ MO's which are delocalized over A and B. Consequently, the result obtained by the present calculation on such a simple system seems to be generalized for the nucleophilic additions to the unsaturated compounds. The electron pair dislodged from the double bond or triple bond will stay as far away from the electron pair of the nucleophile as possible. Then, the addition to an unsaturated bond initiated by a nucleophile is expected to be trans if the intermediate reacts with an electrophile without the change of its conformation. In the next section, this expectation will be compared with the experimental data reported so far.

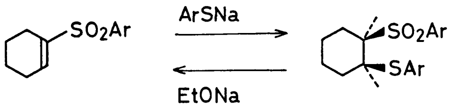
Comparison with Experimental Results

In the previous section, the change of the chemical bonds in the course of the addition of ammonia to formaldehyde was investigated by the use of the LMO method. The intermediate produced by the initial attack of the nucleophile to a double bond or triple bond is predicted to be more reactive for the *trans*-approach of the electrophile than the *cis*-approach. In this section, the validity of the prediction is checked by investigating the stereochemistry of the products of the nucleophilic additions reported so far.

First, let us investigate the nucleophilic additions to double bonds. The additions are known to be stereospecific.[16,17] In the reaction of 1-cyanocyclohexene with malonic ester, 72% of product is the *cis* and only 28% the *trans* isomer, and probably no equilibration of the products takes place.[16] Evidently, this result is attributable to the preference of *trans* addition.

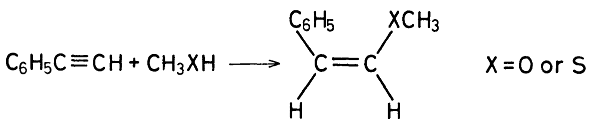


Similarly, the addition of *p*-toluenethiol to 1-(*p*-tolylsulfonyl) cyclohexene gives a *cis* product.[17]



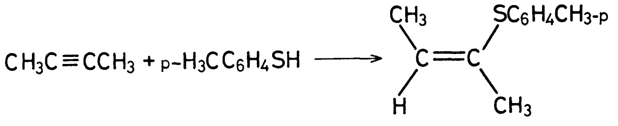
(Ar = p-$CH_3C_6H_4$-)

The stereochemistry of the nucleophilic addition to acetylene is known as *trans*.[18,19] The addition of sodium methoxide in methanol to phenylacetylene gives *cis*-β-methoxystyrene,[18] and a similar addition of sodium methanethiolate gives *cis*-β-(methylthio)stylene.[19]



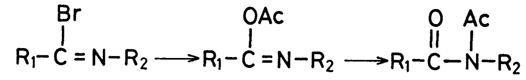
$$C_6H_5C{\equiv}CH + CH_3XH \longrightarrow (C_6H_5)(H)C{=}C(XCH_3)(H) \qquad X = O \text{ or } S$$

The product obtained from sodium *p*-toluenethiolate and 2-butyne, 2-(*p*-tolylthio)-2-butene, is also assigned the *trans* structure on the basis of infrared evidence[19] and this reaction appears to involve the *trans* addition.



$$CH_3C{\equiv}CCH_3 + p\text{-}H_3CC_6H_4SH \longrightarrow (CH_3)(H)C{=}C(SC_6H_4CH_3\text{-}p)(CH_3)$$

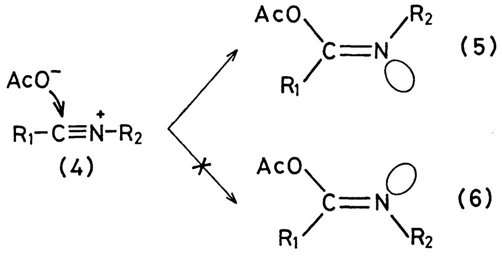
Hegarty and McCormack have suggested from the experimental result that the nucleophilic attack on alkylidyneammonium ion by acetate ion is stereospecific, giving rise to just a single imine isomer.[20]



$$R_1{-}\overset{Br}{C}{=}N{-}R_2 \longrightarrow R_1{-}\overset{OAc}{C}{=}N{-}R_2 \longrightarrow R_1{-}\overset{O}{\overset{\|}{C}}{-}\overset{Ac}{N}{-}R_2$$

(1) (2) (3)

The treatment of *N*-(α-bromoalkylidene) amine (**1**) in 1 : 1 acetone–water in the presence of sodium acetate gives the *O*-acyl compound (**2**), which is uncontaminated by the isomer (**3**). The isoimide structure is rare in organic chemistry and is generally limited to cyclic materials in which the rearrangement to the imide is inhibited.[21] They attributed the stability of the *O*-acyl structure to its existence in the configuration (**5**) in which the nucleophilic lone pair electrons on the neighboring nitrogen and the acyl group would be *trans*. It has been demonstrated that the starting bromide (**1**) reacts *via* rate-determining alkylideneammonium ion (**4**) formation in aqueous acetone.[22] They have concluded that the nucleophilic attack by acetate ion on (**4**) must, therefore, be stereospecific as is shown in the following scheme.[20]



Their suggestion is in agreement with the prediction in the present work.

Conclusion

In this work, the LMO method is applied to the addition of ammonia to formaldehyde. The bond interchange in the course of the reaction is investigated and some comparative studies between the present results and the experimental data reported so far are made. Then, the conclusion obtained here is as follows.

In the addition of ammonia to formaldehyde, the LMO method is convenient to represent the bond interchange in the course of the reaction. In this addition reaction, the electron pair contributed by ammonia and that dislodged from the double bond of formaldehyde tend to stay as far away from each other as possible. It is suggested that this trend is general in nucleophilic additions to an unsaturated bond. Therefore, the intermediate created by the attack of a nucleophile to the unsaturated bond is more reactive at the *trans* position to the new bond than at the *cis* position.

The authors would like to express their gratitude to the Data Processing Center, Kyoto University, for its generous permission to use the FACOM 230-75 computer. The MO calculation was carried out under financial support of the Ministry of Education of Japan (Grant-in-Aid 139012).

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15) When the CMO's of the interacting system at $R=2.5$ Å are expanded in terms of the CMO's of ammonia and formaldehyde, the expansion coefficients of the ϕ_2 are obtained as follows.

$$\phi_2 = 0.922a_4 - 0.343b_5 - 0.108b_2 + 0.106b_7 + \cdots$$

The coefficients larger than 0.10 (absolute value) are displayed in the above equation.

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