

SEMI-EMPIRICAL MO STUDY OF REACTION MECHANISM OF CARBINOLAMINES FORMATION BY MINDO/3 METHOD

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Abstract—Reaction pass of noncatalytic formation of carbinolamines from amines (NH_3 , MeNH_2 , Me_2NH , NH_2NH_2 , NH_2OH , NH_2CHO) and formaldehyde by means of MINDO/3 semi-empirical MO method has been studied. The reaction is ascertained to proceed in two stages and at first, gives an energetically unfavourable, as compared to the starting agents, adduct $\text{>NH}-\overset{|}{\underset{|}{\text{C}}}-\text{O}$, whose stability depends strongly on the effect of substituent at the N atom. The second step is isomerization $\text{>NH}-\overset{|}{\underset{|}{\text{C}}}-\text{O} \rightarrow \text{>N}-\overset{|}{\underset{|}{\text{C}}}-\text{OH}$ occurring by way of intramolecular proton transfer. The issue of rate-determining reaction stage is discussed.

The kinetics studies^{1,2} on the reaction of amine addition to carbonyl compounds have revealed that in the absence of catalyst the first step affords a thermodynamically unfavourable, as compared to the starting reagents, intermediate. The product stability is dependent on the effects of polar substituents in the initial amine and is enhanced with increasing amine basicity.² This product is believed to be a zwitterion of the general formula $\text{>NH}-\overset{+}{\underset{|}{\text{C}}}-\text{O}^-$. However, according to the quantum chemical calculations,³ the total energy of zwitterion of this structure is equal to the sum of total energies of the starting reactants. Thus, either the above investigators^{1,2} wrongly interpret the structure of the intermediate, or the results of calculations are incorrect.³

To investigate the mechanism of the reaction we modelled the entire pathway from the starting reagents to carbinol amine using the MINDO/3 method.⁴

The influence of environmental factors, such as catalyst or solvent molecule was neglected. To assess the effects of substituents at the N atom of amine on its reactivity, the reaction pathways were calculated for various amines. The carbonyl compound was the same in all cases—formaldehyde, which allowed us to ascribe all the differences among the reactions to variation in amine structure.

Activation barriers for the first step of the reaction involving the N–C bond formation were found by estimating the pathways by which amine molecules move to the CO group.

The distance between the attacking nucleophilic N atom and the C of the CO group $R_{\text{N-C}}$ was chosen as reaction coordinate. At each reaction coordinate step, all other geometrical parameters (bond lengths, valence and torsion angles) characterizing mutual relationships between reagents and atom within them were optimized.

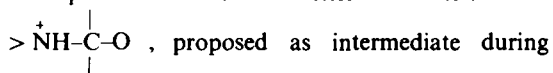
As an illustration of geometrical changes observed

in reagents all along the pathway of the stepwise reaction mechanism, Fig. 1 presents the molecules of methylamine and formaldehyde at various phases of chemical conversions. As can be seen from Fig. 1, at the beginning of interaction when the reagents are located far from one another, the C of the CO group retains planar configuration and the direction of nucleophilic attack being almost perpendicular to the plane of the CO group. With mutual attraction of atoms, the C in electrophile undergoes a gradual transition from planarity in the carbonyl compound to tetrahedral configuration in the zwitterion.

Different values were chosen for the reaction coordinate step. In regions close to the transition state and in that of the reaction end product they did not exceed 0.05 Å.

Figure 2 represents plots of complete energy changes during the reaction system as a function of reaction coordinate value $R_{\text{N-C}}$. As can be seen from Fig. 2, the attraction of reagents can be achieved when the system overcomes the potential barrier. This is followed by formation of a tetrahedral adduct with the general formula: $(R_1, R_2)\text{NH}-\text{CH}_2-\text{O}$. The geometry of adduct for methylamine and formaldehyde is depicted in Fig. 1c.

In the plots of the dependence of complete energies on $R_{\text{N-C}}$, zwitterions correspond to potential minima. During adduct formation the most dramatic structural changes affect the N, C and O atoms and interactions thereof. A new bond N–C is obtained. The double C=O bond undergoes elongation. Atom C changes from the planar to tetrahedral configuration. The structure of the tetrahedral adduct corresponds to the zwitterion intermediate



proposed as intermediate during noncatalytic addition of amine to aldehyde in the case of their stepwise interaction.¹ In compliance with these authors¹ the adduct will be referred to as

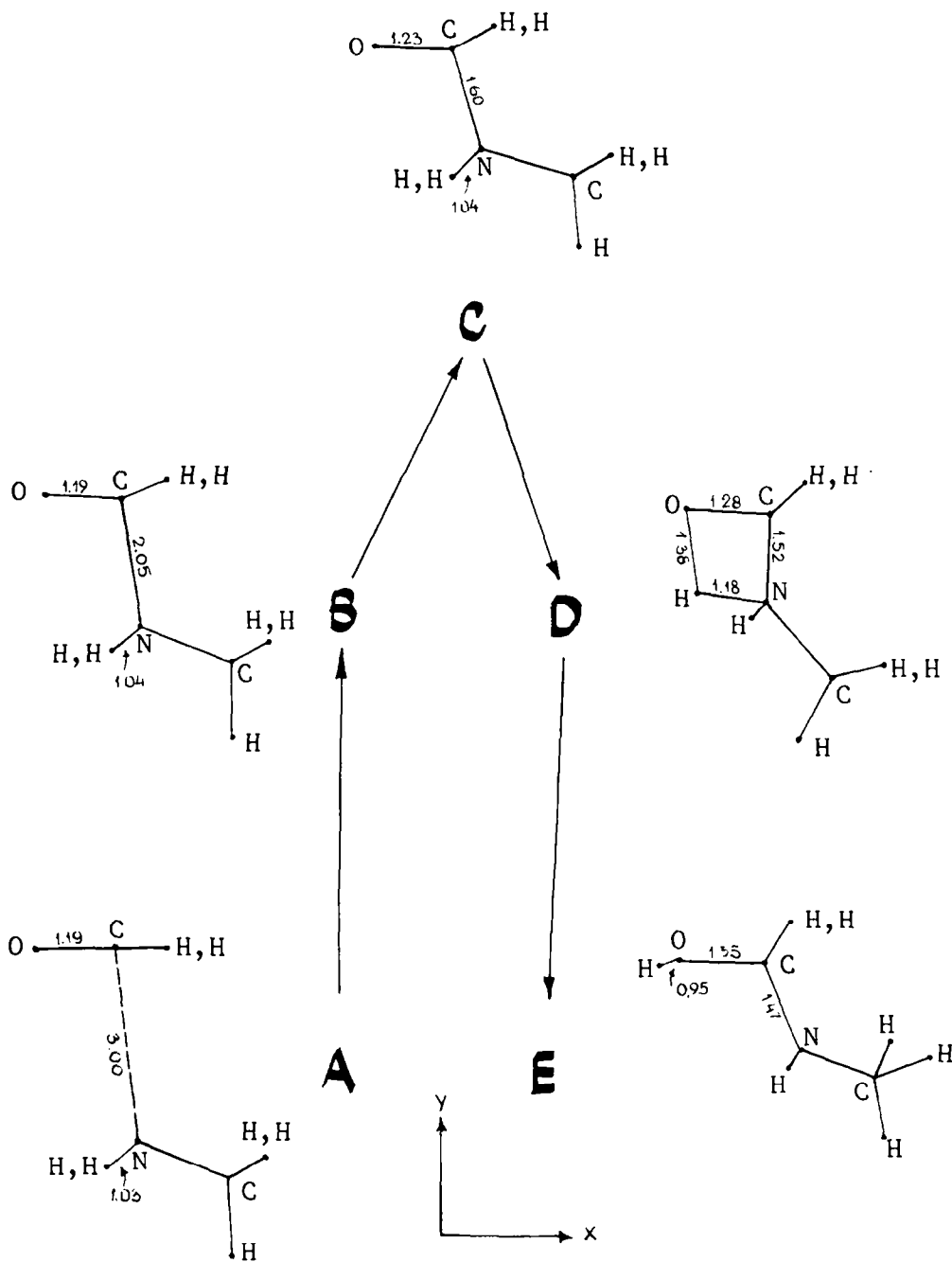


Fig. 1.

zwitterion and designated T^\pm in the course of subsequent discussion. It must be pointed out, however, that the greatest positive charge is concentrated on the C, but not on the N atom. The structural data for T^\pm are summarized in Table I. Bond populations were calculated after the method of Wiberg.⁵ It is interesting to note that the common feature of all T^\pm is that the population of their C-N bond approximately amounts to the half value of the single C-N bond.

The activation barriers for T^\pm formation and decomposition to the starting reagents, as well as the energies of zwitterion formation from the starting compounds are presented in Table 2. These data

indicate that the formation of T^\pm is energetically not profitable for all the amines in question.

The activation barriers and energies of T^\pm formation show a strong dependence on the structure of the starting amines. The curves in Fig. 2 demonstrate that the less stable is T^\pm , as compared to the starting reagents, the closer is the location of the extreme points corresponding to T^\pm and the transition state of the reaction. Along with such close spacing of these points, the potential barrier for the reverse transition of T^\pm to the parent reagents practically disappears. This is evident from the curves in Fig. 2 showing a gradual degradation of the potential minimum corresponding to T^\pm upon transition from

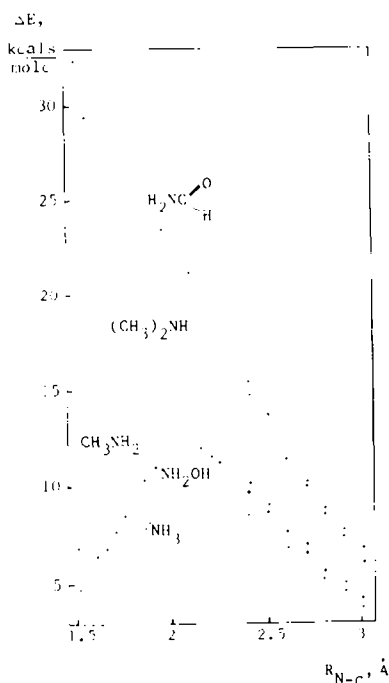


Fig. 2.

ammonia to formamide. Formamide fails to form a zwitterion, the corresponding curve being devoid of the potential minimum. The R_{N-C} values characterizing the transition state of the reaction along with activation barriers for T^\pm formation and decomposition to the initial substances are summarized in Table 2.

In Fig. 3 the energies for zwitterion formation from the starting amines and formaldehydes are comparable with the pK_a values of the corresponding amines. The effect of the substituent at the nucleophilic centre apparently different affects the capacity of nucleophile to attract proton and carbonyl species. This is in contradiction with the conclusions reached² claiming that T^\pm stability is enhanced with growing basicity of the amine.

It should be stressed that hydrazine and hydroxylamine exhibit elevated stability when compared to alkylamines. It is possible that the differences in T^\pm stability are mainly responsible for the fact that some nucleophiles obey the Brønsted's law, whereas others show excessive reactivity.

As can be seen from the results of calculations presented here, the stability of T^\pm is not sufficiently high for all amines, so that the reaction would involve their formation by the stepwise mechanism. Hence, it can be concluded that in all the cases when formation

Table 1. The structure of zwitterions T^\pm

Parent amine	Charges on atoms (a.u.)			N-C		C-O	
	N	C	O	Length (Å)	Population (a.u.)	Length (Å)	Population
NH ₃	0.0954	0.6209	-0.6149	1.58	0.5162	1.2316	1.4976
CH ₃ NH ₂	0.0842	0.6241	-0.6109	1.60	0.5045	1.2266	1.5061
(CH ₃) ₂ NH	0.0211	0.6332	-0.5729	1.74	0.3794	1.2174	1.5905
NH ₂ NH ₂	0.1487	0.5939	-0.6150	1.58	0.5416	1.2412	1.4641
HONH ₂	0.3452	0.5670	-0.5922	1.56	0.5144	1.2346	1.4610

Table 2. Activation barriers of $\text{>NH} + \text{CH}_2\text{O}$ reaction and energies of T^\pm and T^0 formation from parent reagent

Amine	Bond length N-C in transition complex (Å)	Activation barrier of direct reaction (kcal/mol)	Activation barrier of reverse reaction (kcal/mol)	Energy of T^\pm formation from parent compounds (kcal/mol)	Energy of T^0 formation from parent compounds (kcal/mol)
NH ₃	2.12	9.7	6.6	3.1	-17.0
(CH ₃)NH ₂	2.05	12.6	3.3	9.5	-14.4
(CH ₃) ₂ NH	1.88	19.6	0.2	19.4	-6.9
HONH ₂	2.10	12.0	5.7	6.3	-17.5
H ₂ NNH ₂	*	*	*	8.2	-20.1

* not calculated

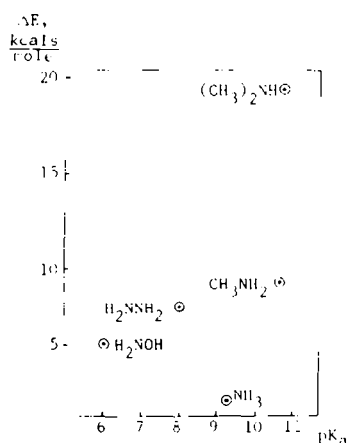
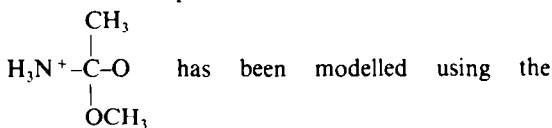


Fig. 3.

of T^\pm is made difficult or impossible, the stepwise mechanism for carbinolamine formation is not realized. Thus, the formation of zwitterion T^\pm may represent a rate determining stage of the reaction pathway at which differences in amine structure are capable even of preventing the formation of carbinolamines. In these cases, probably the reaction does not proceed without catalysis which would direct the reagents along the pathway without formation of T^\pm .

This suggestion is supported by the experimental findings that amides react with formaldehyde only under acid catalysis conditions.⁶ The conclusion that the formation of T^\pm is the rate-determining step appears all the more plausible, if we take into account that zwitterion $T^\pm \rightarrow$ carbinol amine T^0 isomerization is always energetically profitable. The data for T^\pm and T^0 energy comparison are given in Table 2. As to the activation barrier for $T^\pm \rightarrow T^0$ isomerization, an intramolecular proton transfer in the zwitterion



has been modelled using the

CNDO/BW method.⁷ It has been found that the activation barrier for this process can be brought down dramatically due to the electrostatic interaction with a molecule carrying a heteroatom. If proton transfer, however, follows the "switch" mechanism, the barrier of activation actually drops to zero.

In this study, though, proton transfer was fulfilled

in the simplified scheme: the proton following a straight line from atom N to atom O.

We have modelled $T^\pm \rightarrow T^0$ isomerization to occur by way of intramolecular proton transfer for two zwitterions: $\text{H}_3\text{NCH}_2\text{O}^-$ and $\text{CH}_3\text{NH}_2\text{CH}_2\text{O}^-$. The effects of extrinsic factors were neglected.

The $R_{\text{H-O}}$ distance between the transferred proton and O atom was chosen as reaction coordinate, the remaining geometrical parameters being optimized at each reaction coordinate step.

Figure 4 represents the plot of net energy changes of the molecule against the reaction coordinate value $R_{\text{H-O}}$. The zero energy is taken equal to the sum of total energies of the corresponding amine and aldehyde removed infinitely apart from one another.

The main feature of the plots given in Fig. 4 is the slow growth of the curves before they reach the extreme points corresponding to the transition state of the reaction. As soon as they are reached, the energy of the reaction mixture in both cases shows a precipitous drop to the values corresponding to the end-products of the reaction, carbinolamines. This type of curve is caused by the structure of the reaction

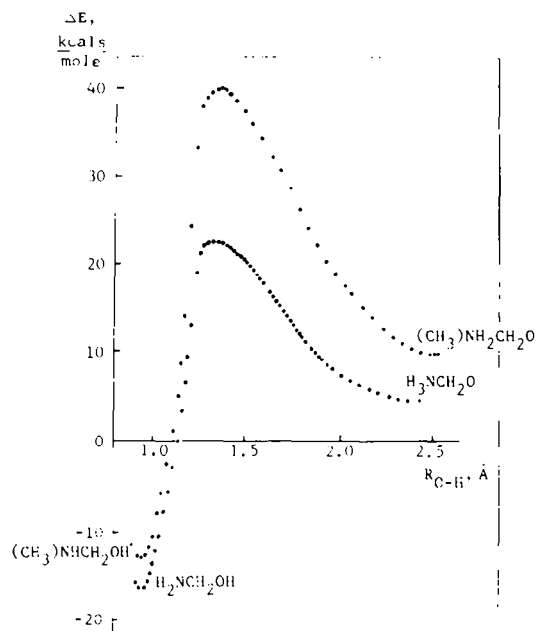


Fig. 4.

Table 3. Energetic components of activation barrier for isomerization $T^\pm \rightarrow T^0$

Amine	Differences in energy of interatomic interaction between transition complex and T^\pm (eV)				Total contribution (eV)	Activation barrier (eV)
	N-H	N-C	O-H	C-O		
NH ₃	3.730	-3.547	-4.148	4.184	0.219	0.845
(CH ₃)NH ₂	4.199	-3.280	-4.251	4.354	1.022	1.301

system characterized by the N and O atoms in the zwitterion being spaced far apart. Therefore, the energy required for breaking the N-H bond upon removal of proton from N to O at the initial stages of the reaction cannot be offset by the attraction to the O atom. This results in both cases in a high activation barrier for the intramolecular proton transfer to give 19.5 kcal/mol for $\text{NH}_3\text{CH}_2\text{O}$ and 30.0 kcal/mol for $(\text{CH}_3)\text{NH}_2\text{CH}_2\text{O}$.

The N and O atoms being spaced far apart, this is a common feature shared by all zwitterions regardless of the type of substituent at the N atom. However, as indicated by the above findings, the presence of various substituents at the N atom appreciably affects the value of activation barrier during $\text{T}^{\pm} \rightarrow \text{T}^0$ isomerization. Is it possible that variation in the stability of N-H bond in the zwitterions under discussion is mainly responsible for the observed differences?

The stronger is the N-H bond, the greater is the energy contribution upon its breakage to the activation barrier of the isomerization process $\text{T}^{\pm} \rightarrow \text{T}^0$. The measure of stability of the N-H bond is the proton affinity of anions formed upon cleavage of these bonds. We have calculated the appropriate proton affinity values to give 14.19 eV for $\text{NH}_2\text{CH}_2\text{O}^-$ and 13.88 eV for $(\text{CH}_3)\text{NHCH}_2\text{O}^-$. It is apparent that the stability of N-H bonds is inversely related to activation barriers. Hence, conclusion can be reached that the observed differences in activation barriers of $\text{T}^{\pm} \rightarrow \text{T}^0$ isomerization are not principally due to the stability of N-H bonds in zwitterions.

Intramolecular proton transfer between N and O atoms affects most strongly the following interatomic interactions: N-H bond is broken, C-O is weakened and converted to single bond, O-H bond is formed, N-C is made single from half-bond. As a measure of energy of these bonds the sums of two-centre interactions between the corresponding atoms have been used which were obtained after the scheme for breaking down the total molecular energies into components.⁸ The energy differences between these interatomic interactions for the transition state of the reaction and T^{\pm} are given in Table 3 for ammonia and methylamine. The tabulated results show that in both cases the four interacting pairs of atoms involved are characterized by comparable energy contributions to the activation barrier. Differences in the sums of these alterations for the two molecules reflect differences in the activation barriers. Changes in all examined bonds occur simultaneously which can be

easily demonstrated by comparing the geometries of the starting species T^{\pm} , transition state reaction and its product T^0 . Figure 1 depicts molecule

$\text{CH}_3\overset{\uparrow}{\text{N}}\text{H}_2\text{CH}_2\text{O}$ at the appropriate phases on conversion. Consequently, the process of $\text{T}^{\pm} \rightarrow \text{T}^0$ isomerization involves simultaneous alteration of the four bonds. Differences in activation barriers are largely due to the sum of energy effects elicited by alterations of these bonds.

CONCLUSIONS

The formation of carbinolamine T^0 from amine and aldehyde appears energetically profitable and proceeds in the absence of catalyst in two stages. The first

step yields the adduct $\text{NH}-\overset{\uparrow}{\text{C}}-\text{O}$ which is energetically unfavourable, as compared to the starting products. Its stability depends on the effect of substituent at the N atom. In the case of formamide, T^{\pm} is not formed. The heteroatomic substituents NH_2 and OH stabilize T^{\pm} more effectively than CH_3 . The common feature of all hence zwitterions T^{\pm} is the increased length of N-C bond and its twice as low electron population and stability when compared to the standard single bond N-C.

The second step of the reaction involving $\text{T}^{\pm} \rightarrow \text{T}^0$ isomerization is energetically favourable in all cases.

Zwitterion $\text{T}^{\pm} \rightarrow$ carbinolamine T^0 isomerization proceeding via a four-centre cyclic intermediate is the process of concerted alterations of four chemical bonds involved in this cycle. Differences in activation barriers during $\text{T}^{\pm} \rightarrow \text{T}^0$ isomerization are mainly determined by the sum of energy effects caused by changes affecting these bonds.

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