Physical Chemistry

Mechanisms of nucleophilic reactions of carbonyl compounds in the gas phase and in a solution

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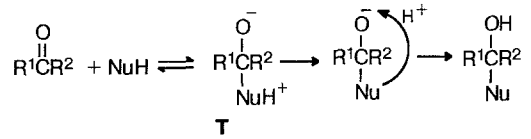
The effect of substituents on nucleophilic addition at the C=O bond, which occurs by the mechanism of intramolecular proton transfer, has been studied by the quantum-chemical MNDO/H method. The effect of nucleophiles and substituents at the carbonyl C atom in the gas phase is opposite to that in solution. Strengthening of the bond between the nucleophile and the carbonyl compound as the result of the transfer of electron density to the carbonyl C atom results in the stabilization of the tetrahedral bipolar adduct. In the formation of an adduct with a strong nucleophile the geometry of the transition state (TS) is closer to that of the reaction product, whereas in the case of a weak nucleophile it is similar to that of the initial reagents. Attack by a weak nucleophile and electron-donating groups at the carbonyl C atom favor the situation in which the reaction system achieves a TS earlier and proton transfer occurs with a low activation barrier.

Key words: nucleophilic reactions of carbonyl compounds, tetrahedral adduct, MNDO/H method, intramolecular proton transfer.

Nucleophilic reactions of carbonyl compounds (CC) are one of the most important types of organic and biochemical reactions.[1] It is generally accepted that nucleophilic attack on the carbonyl C atom results in the formation of a metastable intermediate with a tetrahedral C atom (Ref. 2); in this case, transfer of a proton from the nucleophile NuH to the carbonyl C atom becomes energetically profitable (Refs. 3—5).



T

Therefore, nucleophilic addition readily proceeds in an aqueous medium where proton transfer is possible with no potential barrier.[3] To date extensive experimental data have been accumulated on the mechanisms of reactions of CC occurring in an aqueous medium and on the effect of the nature of nucleophiles and the structures of CC. These data are confirmed by quantum-chemical calculations, which attest to the stabilization of a bipolar tetrahedral adduct **T** in a polar medium.[6]

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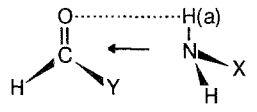
Stabilization of the adduct **T** due to its interaction with polar H_2O molecules is the stronger the higher the positive charge at the carbonyl C atom and the negative charge on the attacking nucleophile. According to calculations, the more polarized the reaction system, the earlier the local minimum of adduct **T** appears on the potential plot as the reagents approach each other. Approaching the reagents at short distances requires much energy consumption, and the height of the activation barrier to the reaction occurring in an aqueous solution has to depend on the R(C—NuH) distance at which adduct **T** is stabilized. If the nucleophile is strong and the C atom is electron-deficient, the local minimum appears on the potential plot at a large R(C—NuH) distance (1.7÷1.8 Å) that determines low activation barrier of the reaction.

Many biochemical processes, for example peptide bond formation, belong to nucleophilic reactions of CC. It is well known that enzymes possess both desolvated sites and sites available for solvent molecules. The desolvation of the active center (AC) of an enzyme during the formation of an enzyme—substrate complex can result in acceleration or inhibition of the reaction.[7,8] The process occurring in the desolvated AC can be considered to be a gas-phase process. The addition of NuH at the C=O bond in the gas phase implies the intramolecular transfer of a proton in the adduct **T**.

In the present paper, nucleophilic addition occurring by the mechanism of the intramolecular transfer of a proton from the nucleophile to the carbonyl O atom is considered, using reactions with amines, generally used for characterizing aldehydes and ketones,[9] as examples.

The quantum-chemical MNDO/H method[10] was used to calculate the geometry, electronic structure, and relative stability of complex **1** for various lengths of the C—N bond. Other geometric parameters were optimized by varying the X or Y substituents at the nucleophile and the carbonyl C atom, respectively. The R(C—N) distance, at which the transfer of a H(a) proton of the N—H(a)...O bond to the carbonyl O atom occurs, has been estimated. The data are summarized in Tables 1 and 2, where the structural characteristics of the complexes are calculated at R(C—N) = 1.5 Å at which the formation of a covalent bond between the N atom of the nucleophile and the carbonyl C atom is possible.



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The most characteristic feature is the change in the O—C—N angle of the nucleophilic attack, which increases in the series X = OH < CH_2OH < NH_2 < CH_3 < H (Table 1). This series holds also for the electron density transferred from the nucleophile to formaldehyde and accordingly for the stabilization of the tetrahedral adduct. For X = H, decreasing the R(C—N) distance from 2.1 to 1.5 Å results in the minimum reagent repulsion energy in the complex. In this case, approching the reagents is accompanied by the maximum transfer of electron density (0.453). As can be seen from Table 1, the complex tends to acquire the tetrahedral configuration corresponding to

Table 1. Parameters* of complex **1** calculated by the MNDO/H method for different substituents at the nucleophile, R(C—N) = 1.5 Å

X	E_r /kcal mole^{-1}	R_t(C—N) /Å	R(O...H(a)) /Å	Angle/deg			$-Q_t$/au
				OCN	OCH	OCNH(C)	
OH	26.6	1.48	1.851	96.2	118.5	113.8	0.378
CH_2OH	23.6	1.44	1.879	97.0	118.4	114.0	0.421
NH_2	23.0	1.42	1.915	97.9	118.3	114.3	0.433
CH_3	20.5	1.35	1.924	99.5	117.9	115.9	0.441
H	16.9	Переноса нет	2.061	101.1	117.5	116.2	0.453

* E_r is the energy of reagent repulsion, R_t(C—N) is the distance at which H(a)+ transfer occurs. Q_t is the charge at the OCH_2 fragment.

Table 2. Parameters* of complex **1** calculated by the MNDO/H method for different substituents at the C atom, R(C—N) = 1.5 Å

Y	E_r /kcal mole^{-1}	R(O...H(a)) /Å	Angle/deg		Q^c/au	$-Q_t$/au
			OCN	CNH(a)		
CH_3**	20.6	1.961	97.6	104.9	0.257	0.391
NH_2	17.1	2.048	100.7	106.1	0.342	0.404
OH	16.5	2.085	102.0	106.7	0.373	0.411
Cl	8.1	2.145	104.4	108.0	0.389	0.423

* See Table 1; Q^c is the charge at the carbonyl C atom. ** $H(a)^+$ transfer at R_t(C—N) = 1.37 Å.

sp^3-hybridization of the C atom in the above series: the O—C—H bond angle decreases and the O—C—N—H(C) dihedral angle increases, approaching their minimum and maximum values in the formaldehyde—ammonia complex.

It should be noted that the electron-donating properties of CC substituents relative to the carbonyl C atom, on the other hand, decreases in the above series. In this case, the high electron-donating ability of the NR^1R^2 and OR groups is explained by the conjugation of the lone electron pairs at the N and O atoms with the C=O bond.[9] Unfortunately, conjugation effects cannot always be correctly described by means of quantum-chemical methods. In the present case, the MNDO/H method, which correctly describes the qualitative effects of CC substituents, overestimates the electron-accepting ability of NH_2- and OH-groups.

As the negative inductive effect of substituent X (CH_2OH, OH) at the nucleophile increases, approching the reagents gradually becomes energetically unfavorable. When a complex with a weak nucleophile is formed, the structure carrying the H(a) proton at the carbonyl O atom becomes very much preferred to that of the bipolar adduct. This is confirmed by data on the O...H(a) interatomic distances (Table 1). A weak nucleophile strengthens the H-bond in N—H(a)...O, in this case, the geometry of the adduct **T** formed is closer to the geometry of the initial reagents, whereas in the case of a strong nucleophile the geometry of the transition state (TS) is closer to that of the reaction product. In the formaldehyde—ammonia system no proton transfer occurs even when the distance between the reagents decreases to R(C—N) = 1.3 Å. Attack by a weak nucleophile (NH_2OH) is associated with the creation of an earlier TS in the system (R(C—N) is similar to the C—N bond distance), therefore, the proton transfer occurs with a low activation barrier. Thus, the situation occurring in the gas phase is opposite to that in solution, where the stronger the bond that can be formed between the nucleophile and the carbonyl C atom the more the equilibrium is shifted towards addition (see above). In the gas phase, stronger bond formation prevents the proton transfer.

Table 2 presents data on ammonia complexes with HYC=O (Y = CH_3, NH_2, OH, Cl). The analysis of Table 2 shows that the effects of substituents at the CC and in the nucleophile on nucleophilic addition at the C=O bond are opposite to their effects on the reaction in solution. Increasing the positive charge at the C atom facilitates the transfer of electron density from the nucleophile to the CC, providing stabilization of adduct **T**, which is confirmed by the increase in the O—C—N angle from 97.6° to 104.4° (Table 2). In this case, the C—NH(a) angle and the R(O...H(a)) distance also increase. These changes in the geometry of the complex are associated with the decreasing electron-donating properties and the increasing electron-accepting properties of the substituents in the series: CH_3 < NH_2 < OH < Cl. Bringing the reagents closer (R(C—N) again varies from 2.1 to 1.3 Å) resulted in proton transfer only for Y = CH_3. Hence, the ability of carbonyl group to participate in addition reactions via the mechanism of intramolecular proton transfer should decrease if the carbonyl C atom is bound with electron-accepting substituents, but their effect is weaker than if they are present in the nucleophile. On the other hand, an electron-accepting group in the nucleophile inhibits the formation of a strong bond with CC and facilitates the transfer of a proton to the carbonyl O atom. The presence of an electron-donating group at the carbonyl C atom and of an electron-accepting group in the nucleophile considerably lowers the activation barrier to proton transfer. Thus, for X = CH_2OH and Y = CH_3, H(a) transfer occurs even at R(C—N) = 1.55 Å (the activation barrier drops to 13 kcal mol^{-1}).

The calculations permit us to propose a possible role for the functional groups of enzyme AC's with known structures in certain reactions involving the carbonyl group. For example, several probable mechanisms of peptide bond hydrolysis in the AC of serine proteases are discussed in literature. One of them implies the preliminary formation of a strong nucleophile as a result of deprotonation of the hydroxyl group of the serine fragment of protease.[11] However, according to calculations, the transfer of a proton in a gas-phase reaction with a strong nucleophile is energetically unfavorable, and this mechanism seems to be improbable.

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