Pathways of the reaction of nucleophilic addition of ammonia to formaldehyde in the gas phase and in the complex with formic acid: *ab initio* calculations

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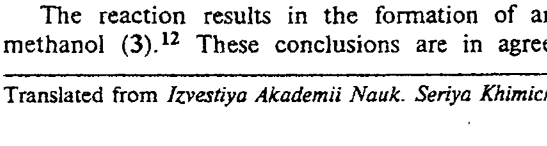
The gradient pathways of the reaction of nucleophilic addition of ammonia to formaldehyde were calculated for free molecules and in the $NH_3\cdots H_2CO\cdots HC(O)OH$ complex by the *ab initio* RHF/6-31G**, MP2(fc)/6-31G**, and MP2(full)/6-311++G** methods. Both reactions proceed concertedly. In the first case, the reaction successively passes through two transitional states with an energy barrier exceeding 35 kcal mol^{-1}. In the case of the complex with formic acid, the reaction follows a conventional pathway, although its activation barrier calculated by the RHF/6-31G** and MP2(fc)/6-31G** methods decreases to 12.6 and 3.8 kcal mol^{-1}, respectively.

Key words: ammonia, formaldehyde, formic acid, nucleophilic addition; reaction pathway, *ab initio* calculations.

The addition of various nucleophiles to the C atom of the carbonyl group is one of basic reactions in chemistry and biochemistry.[1–3] Studies of the interactions controlling mutual orientation of reacting molecules, their trajectories on the reaction pathway, and energetic characteristics of the reaction are of paramount importance for a target control of these processes.[3–5] Calculations of the reaction pathways of nucleophilic addition on the corresponding potential energy surfaces (PES) provide information that cannot be obtained using other methods indispensable for establishing a detailed mechanism for all transformations proceeding in the system.[3,6–10] The addition of ammonia to formaldehyde is the most convenient and well studied model reaction of nucleophilic addition to the C atom of the carbonyl group.[3,11–14] According to the first *ab initio* calculations,[11] in the initial stage of the reaction the NH_3 and H_2CO molecules form a weak prereaction complex **1**, in which the N···C distance (r) is equal to 2.6 Å.



1 **2** **3** (1)

Further, the system passes through a four-center transition state **2** overcoming an energy barrier of 40 kcal mol^{-1} (or higher).

The reaction results in the formation of aminomethanol (**3**).[12] These conclusions are in agreement with the data of calculations performed by the HF/3-21G method.[13] However, the HF-calculations using the extended 6-31G* basis set taking into account the correlation energy according to the MP2/6-31G* scheme showed that there is a strong repulsive potential in the initial portion of the pathway of reaction (1) at $r \geq 2.5$ Å.[13] Only comparatively recent[14] *ab initio* calculations by the MP2/6-311G(2d) method confirmed the initial formation of the weakly bonded pre-reaction complex **1** with $r = 3.00$ Å.

According to the *ab initio* calculations,[11–13] the activation barrier to reaction (1) proceeding in the gas phase is very high. At the same time, similar reactions in the liquid phase are known to proceed at considerably lower activation barriers due to specific solvation.[13] The effect of specific solvation on the mechanism and energy barrier of the nucleophilic addition of ammonia to formaldehyde has been studied for the model $NH_3+H_2CO+nH_2O$ systems containing one or two water molecules ($n = 1$ or 2, respectively).[13] It has been shown[13] that in this case the activation barrier to the reaction decreases by more than an order of magnitude. However, no continuous pathway of reaction (1) from initial compound **1** to product **3** was calculated for either the PES of the NH_3+H_2CO system or the PES of the NH_3+H_2CO+catalyst system up to the present, which made it impossible to draw an unambiguous conclusion on the reaction mechanism.[10] In this work, the continuous gradient pathways[10] of addition of NH_3 to H_2CO in the gas phase (reaction (2)) and in the catalysis with formic acid (reaction (3)) were calculated by the *ab initio*[15]

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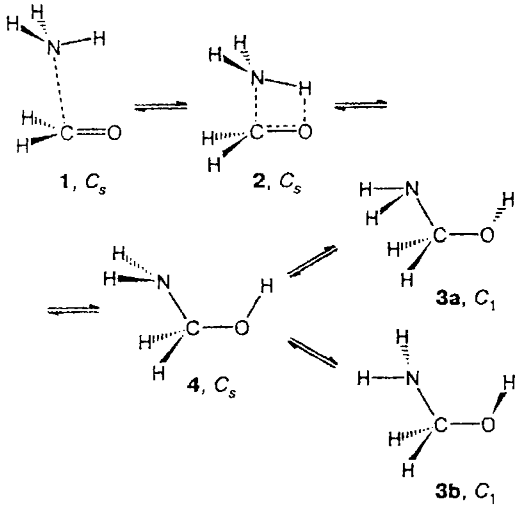
RHF/6-31G**, MP2(fc)/6-31G**, and MP2(full)/6-311++G** methods.



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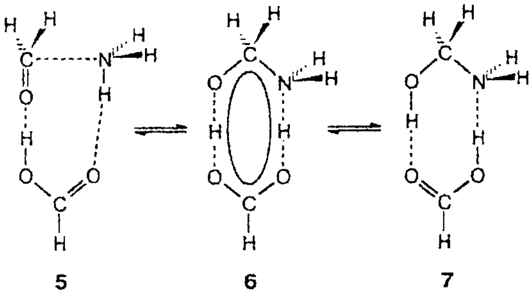


(3)

It was shown that the nucleophilic addition of ammonia to formaldehyde in the gas phase follows pathway (2) rather than pathway (1): first, the pre-reaction complex **1** is formed; then, the system successively passes through two transition states **2** and **4** with close energies, and as a result, two enantiomeric products **3a,b** are formed. The energy barrier to reaction (2) predicted by calculations is ~34 kcal $\mathrm{mol^{-1}}$. The nucleophilic addition of ammonia to formaldehyde (reaction (3)) in the complex with formic acid proceeds at a considerably lower energy barrier (~4 kcal $\mathrm{mol^{-1}}$).

The mechanisms of reactions (2) and (3) differ fundamentally. Both reactions proceed concertedly; however, the enantiomeric channel is excluded in reaction (3), and all processes of the proton transfer proceed asynchronously. In the initial portion of the reaction pathway (to transition state **6**), the C—N bond is formed; after passing transition state **6**, the proton transfer from the OH group of formic acid to the O atom of formaldehyde occurs first, and then one of the protons of ammonia goes to the other O atom of formic acid in the last portion of the pathway.

Calculation Procedure

Ab initio calculations were carried out by the restricted Hartree—Fock (HF) method[15] with full geometry optimization in the 6-31G(d,p) basis set including polarization functions on the atoms (a synonym of the 6-31G** basis set)[15] and in the 6-311++G(d,p) basis set including polarization and diffuse functions on the atoms (a synonym of the 6-311++G** basis set). Further calculations were performed with full geometry optimization taking into account the electron correlation energy at the second-order Møller-Plesset level of perturbation theory (MP2) using the frozen core version, MP2(fc), and the full core version taking into account all molecular orbitals, MP2(full). The calculations were performed using the GAUSSIAN-94[16] and GAMESS[17] programs on the RISC-6000 and DEC Alpha-station-500 workstations.

Optimization of the geometry of the structures corresponding to the saddle points (λ = 1, hereinafter λ is the number of negative eigenvalues of the Hesse matrix at a given critical point[10]) and to the energy minima (λ = 0) on the PES was carried out up to the gradient value of 10^{-5} Hartree/Bohr. The force constant matrices for the NH_3, H_2CO, HC(O)OH, and $NH_3\cdots H_2CO$ systems were calculated analytically by the SCF and MP2 methods; those for complexes $HC(O)OH\cdots NH_3\cdots H_2CO$ were calculated analytically at the SCF level and numerically at the MP2(fc)/6-31G** level.

The gradient pathway of the reaction on the PES was found by the method of steepest descent along both directions (positive and negative) of normalized transition vector from the saddle point (transition state) to the neighboring critical points (a saddle point or a minimum).[10] The initial direction of the gradient line was specified by minor displacement (1/10 of the value of the transition vector) along the direction of the transition vector of the corresponding structure.

The superposition error[18] in the calculations of the stabilization energy of complexes relative to the individual molecules was not taken into account since multimolecular reaction pathways were mostly studied rather than the dissociation limits, for which the inclusion of this error is believed to be important. At the same time, if complexation results in reasonably large changes in the geometry (as in the case under consideration), taking into account the superposition correction is a moot question.[19]

Graphic images of the molecular structures were obtained using the PC MODEL program[13] (the PLUTO mode)[20] for which Cartesian atomic coordinates taken at the final step of optimization of the geometry of corresponding structures served as input parameters.

The gradient lines (orthogonal trajectories) for the analytical function approximating the PES of the $NH_3\cdots H_2CO$ system in the reaction region were calculated using the program written by E. A. Lepin.[21]

Results and Discussion

The structure of NH_3, H_2CO, and HC(O)OH molecules in the gas phase. To test the adequacy of the methods used for predicting the properties of the molecules under study, physical characteristics of the NH_3, H_2CO, and HC(O)OH molecules were calculated by three different methods (RHF/6-31G**, MP2(fc)6-31G**, and MP2(full)/6-311++G**). As was

Table 1. Total energies (E_{tot}/au)[a], dipole moments (μ/D), zero point energies (*ZPE*/au), and first six vibrational frequencies (ν_i/cm^{-1}) calculated by the RHF/6-31G** (*A*), MP2(fc)/6-31G** (*B*), and MP2(full)/6-311++G** (*C*) methods and those obtained experimentally (*D*) for the NH_3, H_2CO, and HC(O)OH molecules

Structure (symmetry)	Method	$-E_{tot}$	*ZPE*	μ	ν_1	ν_2	ν_3	ν_4	ν_5	ν_6
NH_3	*A*	56.19554	0.03681	1.84	1141	1810	1810	3708	3845	3845
(C_{3v})	*B*	56.38322	0.03546	1.79	1123	1726	1726	3559	3716	3716
	C	56.43468	0.03486	1.73	1072	1667	1667	3531	3682	3682
	D [b]			1.48	950	1628	1628	3337	3443	3443
H_2CO	*A*	113.86974	0.02898	2.66	1336	1377	1668	2026	3120	3195
(C_{2v})	*B*	114.18350	0.02739	2.23	1218	1296	1586	1791	3025	3103
	C	114.27923	0.02698	2.39	1208	1279	1560	1774	2980	3051
	D [b]			2.34	1180	1257	1507	1748	2780	2847
HC(O)OH	*A*	188.77056	0.03708	1.63	692	712	1193	1272	1433	1545
(C_s)	*B*	189.26050	0.03453	1.31	625	710	1072	1152	1333	1443
	C	189.41893	0.03419	1.34	634	670	1063	1146	1314	1430
	D [b]			1.41	508	552	990	1000	1178	1772

[a] 1 au = 627.5095 kcal mol^{-1}.

[b] Experimental data were taken from Refs. 25 and 26.

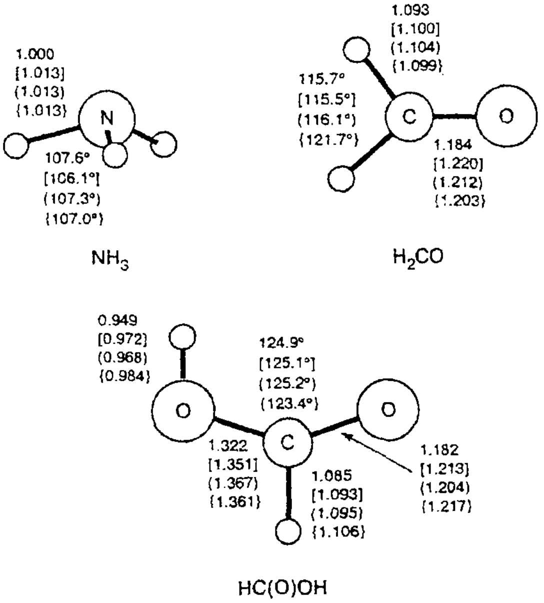
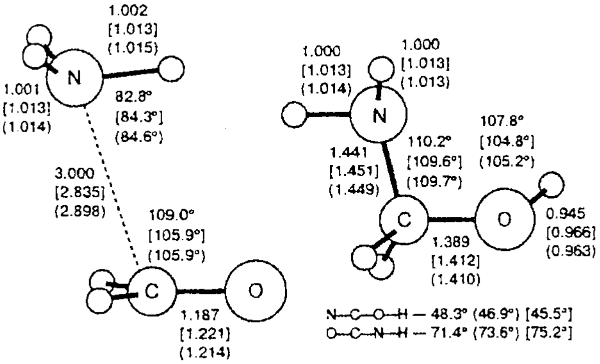


Fig. 1. Geometric characteristics of the NH_3, H_2CO, and HC(O)OH molecules calculated by the RHF/6-31G**, MP2(fc)/6-31G** (figures in brackets), and MP2(full)/6-311++G** (figures in parentheses) methods and their experimental values for ammonia,[22] formaldehyde,[23] and formic acid[24] in the gas phase (figures in braces). Bond lengths (in Å) and bond angles are shown.

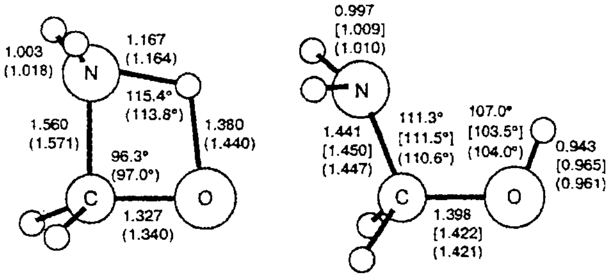
shown by *ab initio* calculations, the structures of the ammonia, formaldehyde, and formic acid molecules correspond to the energy minima on the PES. Their geometric and energetic characteristics obtained by different methods as well as the experimental values are presented in Fig. 1 and in Table 1. As can be seen in Fig. 1, the geometric parameters of the NH_3, H_2CO, and HC(O)OH molecules predicted by the MP2(fc)/6-31G** and MP2(full)/6-311++G** methods are in the best agreement with each other and with the data obtained from the gas-phase measurements. The dipole moments of the formaldehyde and formic acid molecules calculated using the same methods (see Table 1) are also in good agreement with each other and with experimental values. The dipole moment of ammonia calculated using any of these methods appreciably differs from the experimental value. The vibrational frequencies calculated in the harmonic approximation are overestimated, on the average, by 10% in the SCF/6-31G** and by 5% in the MP2(fc)/6-31G** and MP2(full)/6-311++G** calculations as compared to the data of the gas-phase experiments.[15] Thus, it can be concluded that the Hartree—Fock calculations give a reasonably good qualitative account of the systems under study, whereas the calculations taking into account the energy of electron correlation give a quantitative description and that the values obtained by the MP2(fc)/6-31G** and MP2(full)/6-311++G** methods differ insignificantly.

Gradient pathway of the reaction of nucleophilic addition of the NH_3 molecule to formaldehyde in the gas phase. According to *ab initio* calculations, structures **1** and **3** correspond to the energy minima (λ = 0) while structures **2** and **4** correspond to the saddle points (λ = 1) on the PES of the $NH_3 \cdots H_2CO$ system. The geometric and energetic characteristics of structures **1**—**4** are presented in Figs. 2 and 3 and in Table 2. The parameters of pre-reaction complex **1** and transition structure **2** calculated in the present work are in fairly good agreement with the previously obtained data.[13,14] The stabilization energy of complex **1** relative to the individual fragments predicted by the RHF/6-31G**, MP2(fc)/6-31G**, and MP2(full)/6-311++G** methods is equal to 3.4, 4.1, and 3.6 kcal mol^{-1}, respectively, and is due to the donor-acceptor interaction between the lone electron pair of the N atom and the vacant π-MO of formaldehyde.[3] It is of interest to note that while the expansion of the basis set and taking into account of the energy of electron correlation slightly affect the calculated value of the stabilization energy of complex **1**, they nevertheless substantially change the geometric parameters of the structures (see Figs. 2 and 3). The addition reaction **1** $\rightleftharpoons$ **2** $\rightleftharpoons$ **4** $\rightleftharpoons$ **3a,b** proceeds concertedly *via* a four-center transition state **2** with an activation barrier of 46.9, 35.2, and 34.1 kcal mol^{-1} (according to the RHF/6-31G**, MP2(fc)/6-31G**, and MP2(full)/6-311++G** calculations, respectively). Taking into account the electron correlation decreases the energy barrier by more than 10 kcal mol^{-1}. The conformation of aminomethanol **3** as the end product of reaction (2) predicted in this work differs from that obtained previously.[14] This distinction is explained by the fact that only the most stable rotamer has been found in the calculations[9] whereas the continuous reaction pathway was not studied. The PES of the $NH_3 \cdots H_2CO$ system calculated in the reaction region is schematically presented in Fig. 4. The system moves from minimum **1** along the gradient line to the saddle point (transition state) **2**. Then, the system descends along the same line from point **2** to the neighboring saddle point **4**. Such a pathway is confirmed by the continuous smooth decrease in total energy of the system, retention of the C_s point group of symmetry (the mirror plane passing through the N, C, and O atoms is retained) and correlation of the eigenvectors of the Hessian along the gradient line connecting points **2** and **4**.[10] Along this gradient line, the transition vector of point **2** is smoothly transformed into the eigenvector of the least positive eigenvalue of the Hessian at point **4**, while the eigenvector of the least eigenvalue of structure **2** is transformed into the transition vector of structure **4**. At point **4**, the direction of the movement of the system over the PES is changed by the perpendicular direction, and the system passes to another gradient line corresponding to internal rotation about the C—O bond with an activation barrier of 2.0, 2.2, and 1.7 kcal mol^{-1} (according to the RHF/6-31G**, MP2(fc)/6-31G**, and MP2(full)/6-311++G** calculations, respectively). Following two branches of this line, the system arrives at minima **3a** and **3b**. It is important to emphasize that the internal rotation of the OH group about the C—O bond is correlated with the rotation of the NH_2 group about the C—N bond (cooperative internal rotation).



1, C_s ($\lambda = 0$) **3**, C_1 ($\lambda = 0$)

Fig. 2. Geometric characteristics of structures **1** and **3** corresponding to the energy minima on the PES of the $NH_3 \cdots H_2CO$ system calculated by the RHF/6-31G**, MP2(fc)/6-31G** (figures in brackets), and MP2(full)/6-311++G** (figures in parentheses) methods. Bond lengths (in Å) and bond angles are shown.



2, C_s ($\lambda = 1$) **4**, C_s ($\lambda = 1$)

Fig. 3. Geometric characteristics of structures of transition states **2** and **4** corresponding to the saddle points on the PES of the $NH_3 \cdots H_2CO$ system calculated by the RHF/6-31G**, MP2(fc)/6-31G** (figures in brackets), and MP2(full)/6-311++G** (figures in parentheses) methods. Bond lengths (in Å) and bond angles are shown.

Thus, calculations show that the topology of the PES of the NH_3+H_2CO system in the region of the nucleophilic addition reaction **1** $\rightleftharpoons$ **2** $\rightleftharpoons$ **4** $\rightleftharpoons$ **3a,b**

Table 2. Total energies (E_{tot}/au), relative energies (ΔE/kcal mol^{-1}), the number of negative eigenvalues of the Hessian (λ), zero point energies (*ZPE*/au), relative energies taking into account *ZPE* (ΔE_{ZPE}/kcal mol^{-1}), and the imaginary or minimum frequencies (($i\nu/\nu_1$)/cm^{-1}) calculated by the RHF/6-31G** (*A*), MP2(fc)/6-31G** (*B*), and MP2(full)/6-311G** (*C*) methods for structures **1**—**4** of the $NH_3 \cdots H_2CO$ system

Structure (symmetry)	Method	$-E_{tot}$	ΔE	λ	*ZPE*	ΔE_{ZPE}	$i\nu/\nu_1$
1 (C_s)	*A*	170.07067	0	0	0.06805	0	49.3
	B	170.57328	0	0	0.06521	0	38.7
	C	170.71960	0	0	0.06396	0	33.3
2 (C_s)	*A*	169.99585	46.9	1	0.06964	47.9	*i*1812.1
	B	170.51713	35.2	1	0.06496	34.7	*i*1460.6
	C	170.66524	34.1	1	0.06496	34.7	*i*1460.6
3 (C_1)	*A*	170.08437	−8.6	0	0.07524	−4.1	279.7
	B	170.58714	−8.7	0	0.07173	−4.6	282.8
	C	170.73553	−10.0	0	0.07001	−5.6	262.5
4 (C_s)	*A*	170.08120	−5.9	1	0.0724	−2.7	*i*292.9
	B	170.58365	−6.5	1	0.07076	−3.0	*i*305.5
	C	170.73279	−8.3	1	0.06994	−4.5	*i*294.4

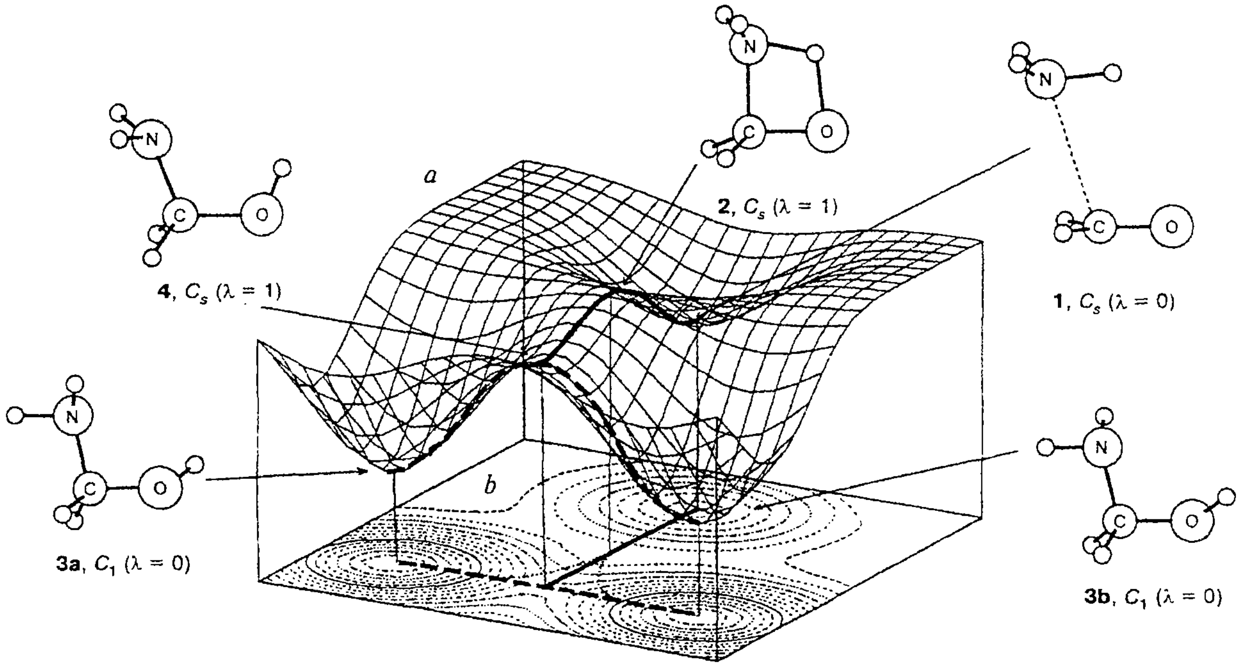


Fig. 4. Three-dimensional scheme (*a*) of the PES of the $NH_3 \cdots H_2CO$ system and its two-dimensional map (*b*) in the region of reaction of nucleophilic addition of NH_3 to H_2CO (reaction (2)). Bold solid line is the gradient line connecting minimum **1** and the saddle point **4** and passing through the saddle point **2**; bold dashed line is the gradient line connecting the energy minima **3a** and **3b** and corresponding to internal rotation about the C—O bond in aminomethanol. The gradient pathway of nucleophilic addition of ammonia to formaldehyde consists of these two gradient lines.

is rather intricate. At the same time, a study of the behavior of "all" gradient lines in the region of the reaction rather than those constituted the gradient pathway of the reaction is necessary for a clear and adequate understanding of the pathway and, hence, the reaction mechanism.[10] It is obvious that investigation of the behavior of all gradient lines in the $(3N - 5)$-dimensional $(N = 8)$ space is impossible. To overcome this difficulty, in this work the PES of the $NH_3 \cdots H_2CO$ system in the region of the reaction was approximated by an analytical function $V(r, \varphi)$ (r is the distance between the N and C atoms and φ is the angle of rotation of the OH group about the C—O bond) whose topology was qualitatively identical with that of the PES of the system under consideration and for which the behavior of all gradient lines (Fig. 5) was investigated. As can be seen in Fig. 5, all gradient lines issue out of or terminate at stationary points (gradient $\nabla E = 0$) or go to infinity.[10,21] The gradient lines at regular points $(\nabla E \neq 0)$ cannot either disappear or appear. Minima **3a** and **3b** are connected by only one gradient line passing through the saddle point **4** and corresponding to the pathway of cooperative internal rotation of the OH group about the C—O bond in structure **3**. The only gradient line issuing out of minimum **1** and passing through saddle point **2** passes through the neighboring saddle point **4**, where it intersects the pathway of internal rotation in perpendicular direction, and goes uphill along the PES bypassing minima **3a** and **3b**.

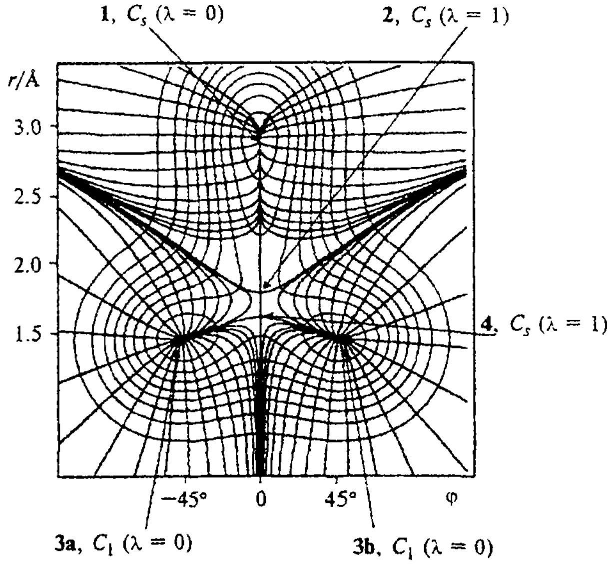
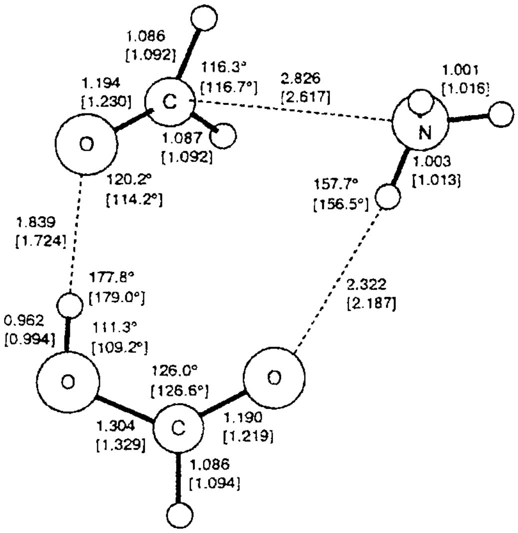


Fig. 5. Two-dimensional map of analytical function $V(r, \varphi)$ approximating the PES of the $NH_3 \cdots H_2CO$ system in the region of reaction of nucleophilic addition of NH_3 to H_2CO (see Fig. 4) and its orthogonal trajectories (gradient lines). Thin closed lines are the level lines; thin lines orthogonal to the level lines are the gradient lines. The gradient reaction pathway consists of two gradient lines, **1** $\rightleftharpoons$ **2** $\rightleftharpoons$ **4** and **3a** $\rightleftharpoons$ **4** $\rightleftharpoons$ **3b**, the latter corresponds to internal rotation of the OH group about the C—O bond; $\varphi = 0°$ corresponds to the staggered conformation of **4**.

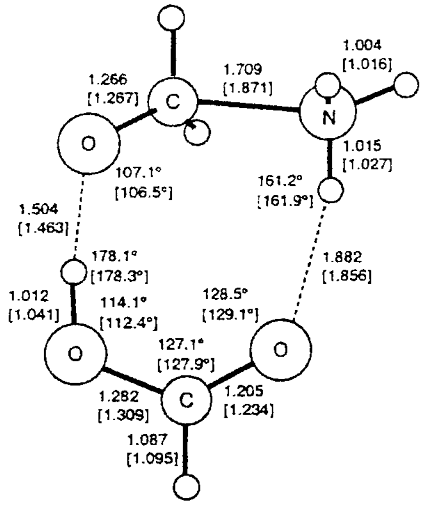
Thus, the gradient pathway of the reaction of nucleophilic addition of NH_3 to H_2CO consists of two different gradient lines. One of them successively passes through two saddle points, **2** and **4**, while the other passes through one saddle point **4** moving in the perpendicular direction with respect to the first line and corresponds to the cooperative internal rotation in molecule **3**.



5, C_1 ($\lambda = 0$)

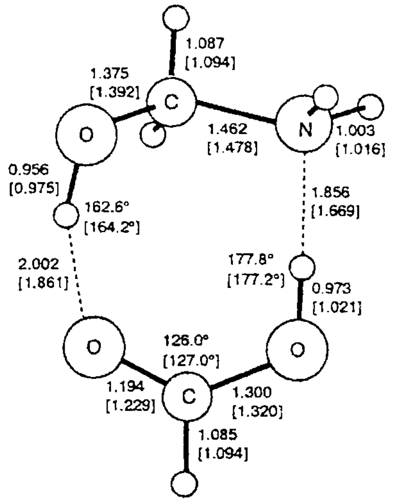
Fig. 6. Geometric characteristics of complex **5** corresponding to the energy minimum on the PES of the $NH_3\cdots H_2CO\cdots HC(O)OH$ system calculated by the RHF/6-31G** and MP2(fc)/6-31G** (figures in brackets) methods. Bond lengths (in Å) and bond angles are shown.

Gradient pathway of the reaction of nucleophilic addition of NH_3 to formaldehyde in complex $HC(O)OH\cdots NH_3\cdots H_2CO$. As was shown by *ab initio* calculations of the gas-phase reaction (2), the results obtained by the RHF/6-31G**, MP2(fc)/6-31G**, and MP2(full)/6-311++G** methods exhibit qualitative agreement, while the MP2(fc)/6-31G** and MP2(full)/6-311++G** methods give nearly quantitatively coinciding results. Therefore, to save computing time, further calculations of the structures corresponding to the stationary points on the PES of the $HC(O)OH\cdots NH_3\cdots H_2CO$ system were performed using the RHF/6-31G** and MP2(fc)/6-31G** methods, while those for the continuous reaction pathway were performed using the RHF/6-31G** method. According to the RHF/6-31G** and MP2(fc)/6-31G** calculations, structures **5** and **7** correspond to the energy minima ($\lambda = 0$) while structure **6** corresponds to the saddle point ($\lambda = 1$) on the PES. The calculated geometric and energetic characteristics of structures **5**—**7** are presented in Figs. 6—8 and in Table 3. Trimolecular complex **5** is stabilized due to the formation of two H-bonds and a rather strong donor-acceptor $C\cdots N$ interaction. According to the RHF/6-31G** and MP2(fc)/6-31G** calculations, the stabilization energy of complex **5** relative to the individual molecules is equal to 13.2 and 18.5 kcal mol^{-1}, respectively. As can be seen from a comparison of these two values, taking into account the electron correlation appreciably increases the stabilization energy of complex **5**. The lengths of the $OH\cdots O$ and $O\cdots HN$ bonds predicted by calculations are within the limits of the known experimental values of the lengths of similar bonds in organic[2,5] and biological structures.[27] It



6, C_1 ($\lambda = 1$)

Fig. 7. Geometric characteristics of complex **6** corresponding to the saddle point on the PES of the $NH_3\cdots H_2CO\cdots HC(O)OH$ system calculated by the RHF/6-31G** and MP2(fc)/6-31G** (figures in brackets) methods. Bond lengths (in Å) and bond angles are shown.



7, C_1 ($\lambda = 0$)

Fig. 8. Geometric characteristics of bimolecular complex **7** corresponding to the energy minimum on the PES of the $NH_3\cdots H_2CO\cdots HC(O)OH$ system calculated by the RHF/6-31G** and MP2(fc)/6-31G** (figures in brackets) methods. Bond lengths (in Å) and bond angles are shown.

Table 3. Total energies (E_{tot}/au), relative energies (ΔE/kcal mol^{-1}), the number of negative eigenvalues of the Hessian (λ), zero point energies (ZPE/au), relative energies taking into account ZPE (ΔE_{ZPE}/kcal mol^{-1}), and the imaginary or minimum frequencies (($i\nu/\nu_1$)/cm^{-1}) calculated by the RHF/6-31G** (*A*) and MP2(fc)/6-31G** (*B*) methods for structures **5**—**7** of the $HC(O)OH\cdots NH_3\cdots H_2CO$ system

Structure (symmetry)	Method	$-E_{tot}$	ΔE	λ	ZPE	ΔE_{ZPE}	$i\nu/\nu_1$
5 (C_1)	*A*	358.85908	0	0	0.10864	0	31.3
	B	359.85647	0	0	0.10394	0	44.5
6 (C_1)	*A*	358.83898	12.6	1	0.11268	15.1	*i*220.1
	B	359.85066	3.8	1	0.10601	5.1	*i*259.7
7 (C_1)	*A*	358.87710	−11.3	0	0.11588	−6.7	56.1
	B	359.87840	−13.6	0	0.10961	−10.0	62.7

is noteworthy that the O—H bond of formic acid is directed toward the lone electron pair of the O atom of formaldehyde located on the hybrid sp^2 orbital.[28] This results in a tilt of the C—O bond of the formaldehyde molecule, its deviation out of the plane in which the formic acid molecule lies and, hence, in a complete asymmetrization of the system. The distance between the C atoms of formaldehyde and the N atoms of ammonia in structure **5** is nearly 0.2 Å shorter than those in complex **1**. In complex **5**, the C—O bond of formaldehyde and the O—H bond of formic acid are slightly lengthened as compared to analogous bond lengths in the individual molecules. Reaction (3) proceeds concertedly *via* transition state **6**, whose structure is similar to the initial structure **5** and results in the formation of bimolecular complex **7**, H-bonded molecules of formic acid, and aminomethanol. According to the

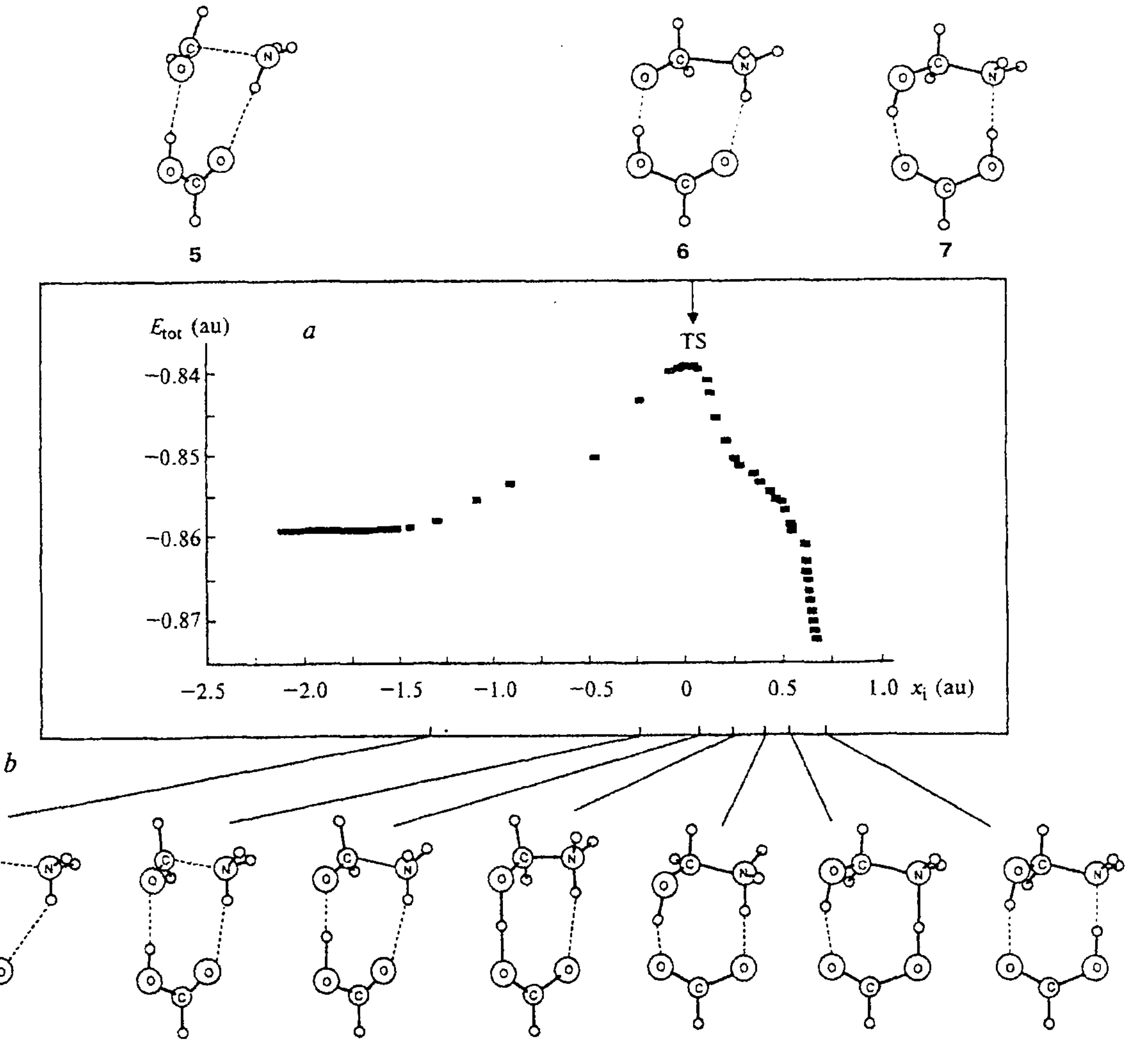


Fig. 9. The energy profile (E_{tot} is total energy, and x_i is the integrated displacement) along the pathway of reaction (3) on the PES of the $NH_3\cdots H_2CO\cdots HC(O)OH$ system (*a*) and the evolution of the trimolecular complex **5** along this pathway (*b*) calculated by the RHF/6-31G** method (TS is transition state). Structures **5** and **7** correspond to the energy minima while structure **6** corresponds to the saddle point; the position of transition structure **6** in the series of evolving structures is shown by an arrow.

RHF/6-31G** and MP2(fc)/6-31G** calculations, the energy barrier to reaction (3) is equal to 12.6 and 3.8 kcal mol^{-1}, respectively. Thus, the introduction of catalyst considerably decreases the barrier to reaction (3) as compared to that to reaction (2). To investigate the stereochemistry and the sequence of all intracomplex transfers, we calculated the evolution of complex 5 along the pathway of reaction (3) (Fig. 9). In the initial portion of the reaction pathway (up to transition state **6**), the molecules of formaldehyde and ammonia approach each other. After passing transition state **6**, the proton of formic acid participating in the formation of the OH···O bond moves first to the O atom of formaldehyde and then, in the final portion of the pathway, the H atom of ammonia, participating in the formation of the NH···O bond, migrates to the O atom of formic acid. Thus, despite the fact that reaction (3) proceeds concertedly, the displacements of heavy atoms and proton transfers along the hydrogen bridges occur asynchronously and successively. According to the RHF/6-31G** and MP2(fc)/6-31G** calculations, the energy of the H-bond of complex 7 is equal to 13.9 and 19.3 kcal mol^{-1}, respectively, which is somewhat higher than the total stabilization energy of complex 5.

The nature of catalytic action of formic acid. The complexation of ammonia and formaldehyde with formic acid acting as a catalyst due to the formation of strong H-bonds makes the "interacting molecules" come close together, orients in a proper direction, and "activates" them (*cf.* Figs. 2 and 6). Therefore, from the stereochemical viewpoint, formic acid almost ideally "arranges" the pre-reaction complex 5: the OH···O and O···HN hydrogen bonds with the O—H—O and O—H—N angles equal to 177.8° [179.0°] and 157.7° [156.5°], respectively, differ little from the stereochemically most favorable linear H-bonds,[2–5,28–30] and the O—C—N angle is equal to 110.0° [106.6°], *i.e.*, is fairly close to the exact value of tetrahedral angle.[2–5] The energy barrier to reaction (3) is decreased as compared to that to reaction (2) due to the acid-base catalysis by formic acid and the change of the mechanism of reaction (3) as compared to that of reaction (2). The C—O bond of formaldehyde is lengthened as compared to the analogous bond not only in a free molecule (see Fig. 1), but also in complex **1** (see Fig. 2). Unlike reaction (2), in the course of which an extremely strained four-membered cycle is formed in transition state **3**, in the course of reaction (3) the protons move along the most favorable pathways (hydrogen bridges), whose stereochemistry in structure **5** is the closest to the ideal stereochemistry,[4,5,28,29] while the N atom of ammonia approaches the C atom following the stereochemically most favorable Burgi's pathway.[4,5] The final state **7** is more stabilized than the initial pre-reaction complex **5**. It is likely that the catalytic action of formic acid, considered as the simplest model of enzyme system, differs from that of conventional catalysts: it changes not only the kinetics of the process decreasing the energy barrier, but also its thermodynamics, since the "enzyme-substrate complex" is a unified supramolecular system and the initial state of "enzyme" (formic acid) in this system is not equivalent to its final state.

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