Mechanism of the reaction of neutral and anionic N-nucleophiles with α-halocarbonyl compounds

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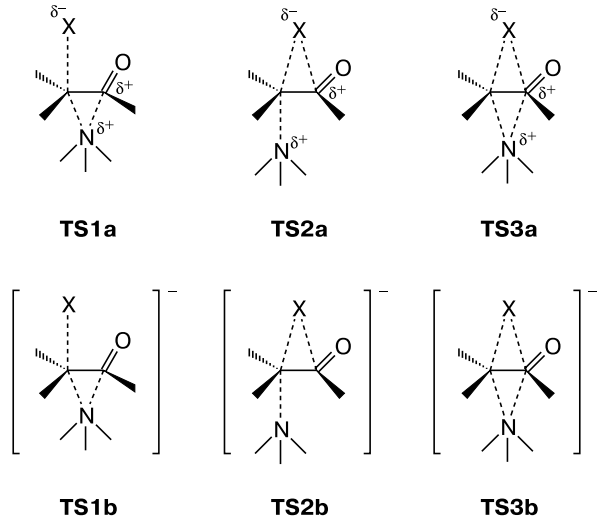
N-Acylalkylation of neutral and anionic N-nucleophiles with α-halocarbonyl compounds was investigated by quantum chemical methods in terms of the density functional theory and by experimental methods for 2,3-dihydroimidazo[2,1-*b*]quinazolin-1(10)*H*-5-one, its N-anion, and simpler model structures. High reactivity of these reagents is determined primarily by stabilization of transition states (TS) by bridge bonds involving halogen or nitrogen atoms rather than by conjugation, as has been commonly accepted. Bridged TS are formed by both the substitution mechanism S_N2 and the addition—elimination mechanism. α-Haloalkyl-substituted zwitterions, which are potential intermediates of stepwise *N*-acylalkylation of neutral N-nucleophiles, do not exist in the isolated state, but they are rather efficiently stabilized upon solvation. These zwitterions, as well as analogous O-anions generated from anionic N-nucleophiles, can serve as intermediates of *N*-acylalkylation, as was demonstrated by localization of the corresponding TS.

Key words: acylalkylation, transition states, bridge bonds, α-halocarbonyl compounds, 2,3-dihydroimidazo[2,1-*b*]quinazolin-1(10)*H*-5-one, N-anion of 2,3-dihydroimidazo[2,1-*b*]quinazolin-1(10)*H*-5-one, tetrahedral intermediates, addition—elimination mechanism.

When studying *N*-acylalkylation of 2,3-dihydroimidazo[2,1-*b*]quinazolin-1(10)*H*-5-one (**1**) with bielectrophilic α-haloketones (α-acylalkyl halides (AH)) **2**, we noticed that there is uncertainty in the interpretation of the mechanism of these synthetically important transformations.[1a,b] For example, the character and the number of reaction steps, the role of the second electrophilic center of AH (the CO group) in *N*-acylalkylation, and the factors responsible for higher reactivity of AH compared to that of usual alkyl halides remain unclear.

Taking into account the second reaction order,[2—4] the *N*-acylalkylation, like the acylalkylation as a whole, is most commonly considered as the nucleophilic substitution by the S_N2 mechanism (see, for example, Refs 5—8). In this case, high activity of AH is generally explained by stabilization of the transition state (TS) of the reaction by the CO group, stabilization being provided not directly by the electron-withdrawing character of this group (*cf.* Ref. 9) but by its conjugation with the p-electron pair of the attacked carbon atom of AH.[10—14] It was also suggested that this effect could lead to the transformation of the reagent in TS into the enolate form.[15] In addition, stabilization of TS was sometimes accounted for by such factors as the promotion of the indirect interaction between the frontier orbitals of the substrate and the reagent by the carbonyl group,[16] high electron affinity of the reagent (see Ref. 17),* and, finally, the formation of additional nonclassical bonds between the nucleophile or (and)



* In the present study, the terms "reagent" and "substrate" are used in the sense opposite to that used in S_N2 reactions based on the classification of the reaction under consideration as acylalkylation.

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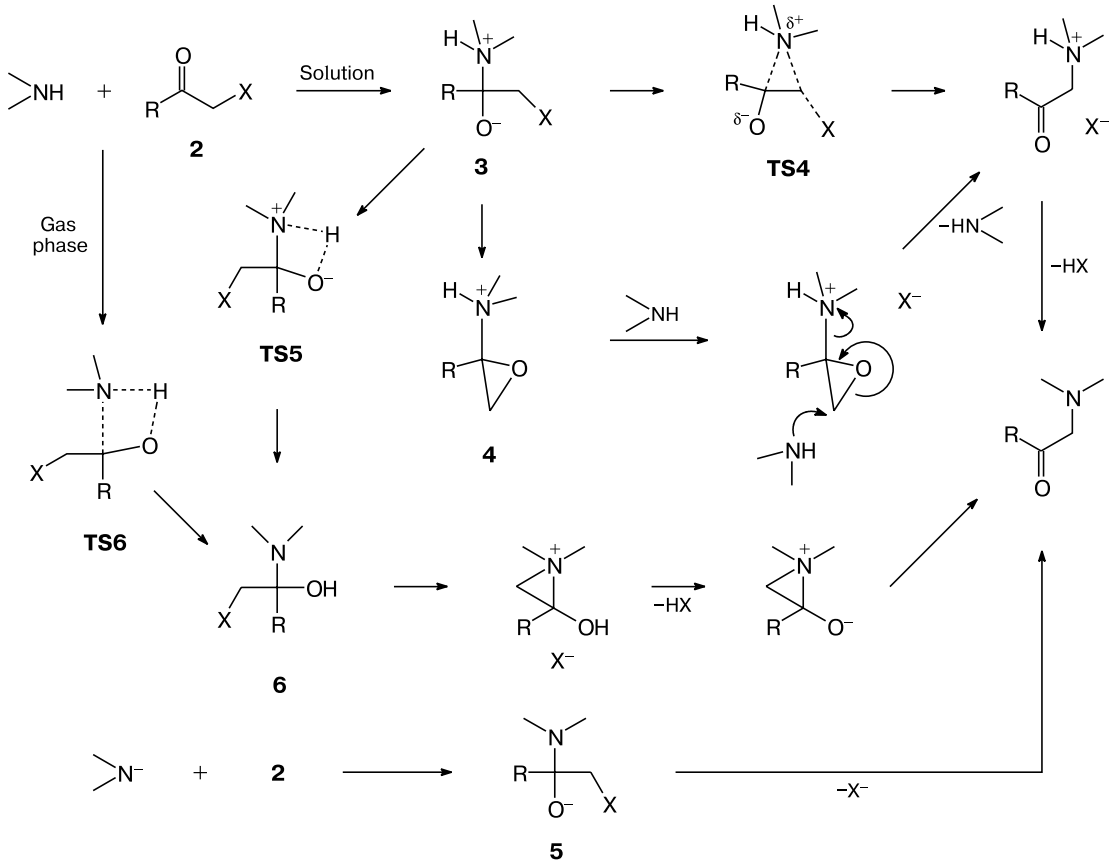
Scheme 1



R = Ar, Alk, Alk_2N; X = Hal

the halogen atom and the CO group,[6,7,15,18,19] which impart the bridged character to TS. The last-mentioned factor can be illustrated by bridged structures **TS1a**—**TS3a** and **TS1b**—**TS3b** for neutral and anionic N-nucleophiles, respectively.

Besides, the possible stepwise mechanism was proposed for the acylalkylation involving the addition of the nucleophile at the CO group of AH to form zwitterionic tetrahedral intermediate **3*** as the first step followed by the transformation of the latter into the final product either in one step *via* the intramolecular substitution of the halogen atom concerted with the carbon—nucleophile bond cleavage[1,5,21–24] or *via* cyclization to amino oxirane **4** followed by its nucleophilic cleavage.[22,23] Hereinafter, we will refer to this nonconcerted reaction pathway as S_NAE, *i.e.*, the nucleophilic substitution *via* the addition and elimination. Direct experimental evidence in support of the possible formation of zwitterions **3** is lacking. However, the stepwise mechanism has recently been confirmed by kinetic experiments with pyridine, benzylamine, and their derivatives.[22–24] In this case, **TS4** corresponding to the intramolecular substitution of the halogen atom was suggested as the major transition state for the transformation of zwitterion **3** into *N*-acylalkylation products. Like S_N2-type transition state **TS1a**, **TS4** has the N-centered bridge bond (Scheme 1). However, the existence of structures **TS4** was not confirmed by their quantum chemical localization.

The S_NAE mechanism of acylalkylation is indirectly confirmed by the fact that the CO group of AH is competitive as the center of the nucleophilic attack, which is convincingly demonstrated for such nucleophiles as hydroxylamine,[1a] thiosemicarbazide,[1b] and a series of O- and C-anions (see, for example, Refs 1 and 25—31) by the preparative isolation of the transformation products of tetrahedral intermediates, which are not associated with acylalkylation, in good yields. Since these data refer also to anionic substrates, it is reasonable to suggest that the *N*-acylalkylation of anionic nucleophiles can also proceed through the initial nucleophilic addition at the CO group of AH with the only difference that O-anions **5**

* Analogous tetrahedral intermediates were assumed[20] for the reactions of N-nucleophiles with carbonyl compounds as a whole.

rather than zwitterions serve as tetrahedral intermediates (see Scheme 1).

Therefore, the S_NAE mechanism is characterized by the initial capture of the N-nucleophile by the CO group as the second electrophilic center of the reagent to form zwitterionic or O-anionic tetrahedral intermediates. Since this transformation is not accompanied by the bond cleavage, it would be expected that, in the case of the favorable thermodynamics, the lowest activation barrier should correspond to this transformation, and the S_NAE mechanism would be most probable for highly nucleophilic substrates.

Although zwitterions **3** have not been characterized, it can be predicted that they are absolutely unstable in the isolated state. Semiempirical and *ab initio* (RHF/4-31G(3-21G)) calculations showed[32a,b,33] that the simplest zwitterion of carbonyl compounds, $H_3N^+—CH_2—O^-$, does not correspond to a minimum on the potential energy surface in the absence of solvation and it does not exist as an isolated species because the repulsion between the reagent and the substrate dominates, resulting in the barrierless cleavage of the zwitterion to form NH_3 and CH_2O. At the same time, the calculations demonstrated that oligohydrates of the $H_3N^+—CH_2—O^-$ zwitterion tend to be stabilized, and this tendency increases with increasing number of solvation water molecules.[32a,33] The possibility of the existence of zwitterions under the conditions of solvation is confirmed also by experimental data. For example, it was demonstrated that 4-dimethylaminobutyraldehyde and its derivatives exist in solution in equilibrium with rather stable cyclic zwitterionic pyrrolidine-type species stabilized due to the absence of prototropically active hydrogen and the intramolecular character of their formation. Zwitterions, which are rather stable under the conditions of solvation, can be generated also in bimolecular reactions of carbonyl compounds with tertiary N-nucleophiles.[34—37] At the same time, zwitterions of primary or secondary N-nucleophiles are extremely unstable because they undergo very rapid isomerization to give *N*-hydroxyalkyl derivatives (α-aminocarbinols).[20] For example, the formation of the zwitterion of piperazine in the reaction of the latter with pyridyl-4-aldehyde proceeds with the rate constant of $\sim 10^7$ L mol^{-1} s^{-1}, whereas the prototropic isomerization of this zwitterion into the corresponding α-aminocarbinol in the spontaneous reaction (transition state **TS5**) has the rate constant of $\sim 10^6$ s^{-1}.[38] The isomerization of the zwitterion proceeds even faster under acid or base catalysis.[38] In a rather strong proton-donating medium, such processes can, evidently, proceed as the direct protonation of the zwitterion at the oxygen atom[39] characterized by rather high basicity.[34,39] Therefore, the above-considered data show that the *N*-hydroxyalkylation in solution proceeds through zwitterions intermediates. This is the difference from the analogous gas-phase reaction, which is concerted and proceeds through 1,3-prototropic **TS6** (see Scheme 1) due to instability of the unsolvated zwitterions.[32a,33] Consequently, it can be concluded that, under the conditions of *N*-acylalkylation, the substrate would undergo *N*-hydroxyalkylation to a greater or lesser extent to give the corresponding hydroxyalkyl derivative **6**. Apparently, the latter is yet another potential intermediate of *N*-acylalkylation, because it should give *N*-acylalkyl derivatives *via* the cyclization to highly reactive aziridinium cations[40] followed by their cleavage (see Scheme 1).

Evidently, regardless of the mechanism of *N*-acylalkylation, the same structural factors from those mentioned above can make a contribution to stabilization of primary TS and the increase in the reactivity of AH. As for the nitrogen bridge bonds considered as one of such factors, the formation of the latter is, apparently, unlikely in the case of neutral TS generated from molecular N-nucleophiles, because the nitrogen atom in such N-nucleophiles bears only one lone electron pair with the narrowly directed sp^3 or sp^2 orbital and, consequently, it is rather difficult to form two rather strong N—CHal and N—CO bonds. In S_N2-type TS, the formation of an additional N—CO bond is, to a certain extent, hindered also by the total positive charge of the N-nucleophile facilitating its repulsion from the positively charged carbon atom of the CO group. In addition, doubly bridged transition states **TS3a** are somewhat destabilized by the nonlinear configuration of the N—C—Hal reaction unit, which is unfavorable for the overlapping between the p orbital of the attacked carbon atom and the orbitals of the nitrogen and halogen atoms.

On the contrary, the nitrogen bridge (such as in **TS1b**) can, in principle, be formed in anionic TS of *N*-acylalkylation, which are generated from N-anions, because the nucleophilic nitrogen atom in such species generally contains two lone electron pairs.

The transition states of *N*-acylalkylation can be stabilized also by halogen bridge bonds, in particular, in the case of neutral TS, because the hindrance analogous to those described above for nitrogen atoms is absent for halogen atoms. In addition, these TS contain the electron-deficient center (the CO group), which is typical of classical halogen-bridged structure, such as halonium cations,[41—43] the 1-chloroallyl cation,[44,45] and dimers of aluminum halides Al_2X_6 (X = Hal).

Evidently, the validity of these considerations and the actual factors responsible for stabilization of TS of *N*-acylalkylation could be estimated by quantum chemical calculations. However, these investigations have not been performed so far. Only TS of degenerate chloro- and fluoroacylalkylation of X^- ions with haloaldehydes XCH_2CHO (X = Cl (**2a**) or F (**2b**)) were studied (MINDO and RHF/4-31G calculations).[10,12,13,46] It should be noted that bridge bonds were not found in the latter transition states, but it was demonstrated that

these TS are characterized by the virtually right X—C—C angles and the perpendicular orientation of the C—X bonds with respect to the plane of the aldehyde group accompanied by a slight shortening of the C—C bond and an elongation of the C=O bond compared to those in free compounds **2a,b**. These data were interpreted as evidence for the presence of the stabilizing conjugation between the p electrons of the attacked carbon atom and the adjacent CO group in TS, and the increase in the rate of nucleophilic substitution was accounted for by the latter fact. However, this conclusion seems unwarranted because the orthogonal arrangement of the C—X bonds and the CHO group, as well as the direction of motion of X^- ions in the case of formation of TS, can be a consequence of the well-known steric requirements determining the optimal trajectory of nucleophiles in the vicinity of the carbonyl group.[47,48]

In the present study, we investigated *N*-acylmethylation of quinazolinone **1** and its N-anion, as well as of ammonia and amide ions, as representatives of neutral and anionic N-nucleophiles predominantly by quantum chemical methods. The results of our study show that the reaction can proceed both in the concerted (S_N2) and nonconcerted (S_NAE) modes, and the probability of the latter mechanism increases with increasing nucleophilicity of the substrate. These results confirm also (at least, as applied to the *N*-acylalkylation) that it is unreasonable to attribute high reactivity of AH to stabilization of TS *via* the conjugation.[8,10—14]

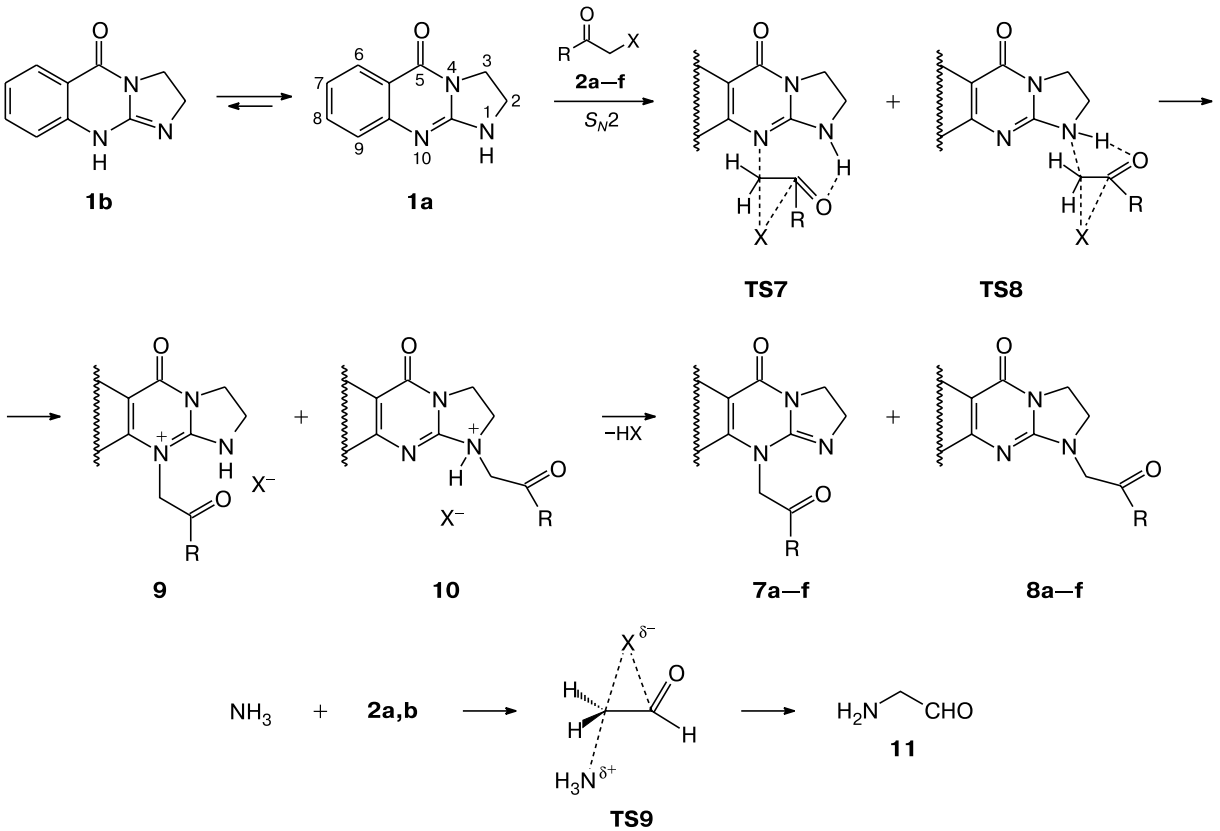
Results and Discussion

***N*-Acylmethylation of quinazolinone 1 and its N-anion with α-haloketones.** To study the acylmethylation by experimental methods, we chose haloketones **2c—f** as typical and most widely used acylalkylating agents (Scheme 2).

Due to very low solubility and the presence of the deactivating electron-withdrawing CO group, quinazolinone **1** almost does not react with phenacyl bromide **2c** in acetonitrile or nitromethane at room temperature but reacts with **2c** under reflux to give a mixture of isomeric N(10)- and N(1)-phenacyl derivatives **7c** and **8c**, with the former predominating (see Scheme 2). Individual compound **7c** can be readily prepared by recrystallization of this mixture; pure isomer **8c**, by a procedure described below.

Both isomers were identified taking into account a much stronger deshielding of the protons of the exocyclic

Scheme 2



R = H, X = Cl (**a**); R = H, X = F (**b**); R = Ph, X = Br (**c**); R = 4-ClC_6H_4, X = Br (**d**); R = 2,6-Bu^t_2-4-OHC_6H_2, X = Br (**e**); R = Bu^t, X = Br (**f**)

Table 1. Melting points and ^{1}H NMR spectra of *N*-acylmethylquinazolinones **7c—f** and **8c**

Compound	M.p./°C (solvent)	^{1}H NMR ($CDCl_3$), δ (*J*/Hz)							
		H(2)	H(3)	H(6)	H(7)	H(8)	H(9)	NCH_2R	Other protons
		2 H		1 H				2 H	
7c	218—222 (EtOH)	3.86—3.94 (m)	4.14—4.21 (m)	8.12 (dd, J^o = 7.8, J^m = 1.6)	7.10 (td, J^o = 7.6, J^m = 0.9)	7.45 (t, *J* = 7.8)	6.64 (d, *J* = 8.3)	5.55 (s)	7.50—7.58 (m, 2 H, *m*-H arom.); 7.63—7.66 (m, 1 H, *p*-H arom.); 8.04—8.08 (m, 2 H, *o*-H arom.)
7d··HBr	312—315 (with decomp.) (EtOH)	3.84—3.92 (m)	4.10—4.20 (m)	8.10 (d, *J* = 7.8)	7.09 (t, *J* = 7.3)	7.40—7.47 (m)	6.60 (d, *J* = 8.4)	5.48 (s)	7.48 (d, 2 H, *m*-H arom., *J* = 8.5); 7.97 (d, 2 H, *o*-H arom., *J* = 8.5)
7e··HBr	306—308 ($MeNO_2$)	3.90 (m)	4.18 (m)	8.11 (dd, J^o = 7.8, J^m = 1.6)	7.09 (t, *J* = 7.5)	7.45 (td, J^o = 7.8, J^m = 1.7)	6.69 (d, *J* = 8.4)	5.51 (s)	1.47 (s, 18 H, Bu^t); 4.78 (s, 1 H, OH); 7.92 (s, 2 H, *o*-H arom.)
7f··HBr	273—275 (with decomp.) ($MeNO_2$)	4.16 (t, *J* = 9.2)	4.45 (t, *J* = 9.2)	8.31 (dd, J^o = 7.9, J^m = 1.5)	7.50 (t, *J* = 7.5)	7.78 (td, J^o = 7.9, J^m = 1.5)	6.98 (d, *J* = 8.5)	6.43 (br.s)	1.43 (s, 9 H, Bu^t); 12.05 (br.s, 1 H, N^+H)
8c	193—197 (AcOEt)	3.85 (t, *J* = 8.3)	4.28 (t, *J* = 8.4)	8.14 (d, *J* = 7.9)	7.17 (t, *J* = 7.6)	7.64 (t, *J* = 7.4)	7.31 (d, *J* = 8.2)	4.98 (s)	7.48—7.58 (m, 3 H, *m*-H arom., *p*-H arom.); 8.03 (d, 2 H, *o*-H arom., *J* = 7.8)

N(10)—CH_2 group in *N*-substituted dihydroimidazoquinazolinones[49a] compared to the analogous group at position 1. The difference in the chemical shifts of the above-mentioned groups in compounds **7c** and **8c** (Table 1, ~0.6 ppm) is approximately equal to that observed for isomeric *N*-methyl, *N*-benzyl, and *N*-β-phenoxyethyl derivatives of imidazoquinazolinone **1**.[49a] It should be noted that the N(10)-isomers of some of these structures were synthesized not only by the *N*-alkylation but also by the independent synthesis from the corresponding *N*-substituted isatoic anhydrides.[49a,b]

The regioselectivity of *N*-phenacylation of compound **1** is similar to that observed in the *N*-alkylation of this compound with monoelectrophilic alkylating reagents under analogous conditions.[49a] The percentage of derivative **7c** in a mixture with substitution product **8c** is ~70% (^{1}H NMR spectroscopic data). This fact, taking into account the results reported earlier,[49a] is indicative of the predominant involvement of the major 1*H* tautomer of substrate **1a** in the substitution, whereas the 10*H* tautomer of **1b** plays a minor role.

The *N*-acylalkylation of compound **1** with phenacyl bromides **2d,e** and with α-bromopinacolone (**2f**) proceeds analogously. The above-described transformations are of particular preparative interest because 10-acylmethylimidazoquinazolinones of type **7**, unlike other N(10)-R-2,3-dihydroimidazo[2,1-*b*]quinazolin-5-ones, cannot be synthesized by cyclocondensation of the corresponding *N*-substituted isatoic anhydrides with 2-methylthio-4,5-dihydroimidazole.[50]

The *N*-phenacylation of quinazolinone **1** with bromide **2c** in the presence of bases (KOH or NaH), like the base-catalyzed *N*-alkylation of compound **1** with monoelectrophilic alkylating reagents,[49a,b] is characterized by the opposite regioselectivity, which is associated with the fact that, under these conditions, the reaction with the involvement of the N-anion of substrate **1c** proceeds by the ionic mechanism. The reaction affords only 1-substituted isomer **8c** (38% yield) corresponding to the attack on the most nucleophilic center of the N-anion.[49a] The low yield of compound **8c** is, apparently, attributed to the competitive decomposition of the reagent under the action of alkali giving rise to colored by-products, which were not observed in the reaction under neutral conditions.

Quantum chemical investigations of N-acylalkylation

***N*-Acylalkylation by the S_N2 mechanism.** In addition to the major 1*H* tautomer of imidazoquinazolinone **1a**, we chose ammonia, which is the simplest representative of neutral N-nucleophiles, as the model substrate, and the simplest *N*-formylmethylating reagents, *viz.*, haloacetaldehydes **2a,b**, as AH. The *N*-formylmethylation reactions under study are presented in Scheme 2. In particular, the corresponding transition states **TS7**—**TS9** and the salt-like and basic forms of the resulting *N*-formylmethyl derivatives **7**—**11** are shown.

The results of calculations of the geometric and energy characteristics, some bond orders, dipole moments, and imaginary vibrational frequencies of the reagents, TS, and *N*-formylmethylation products (DFT, B3LYP/6-31G**) are summarized in Tables 2 and 3. The data on the bond orders show that neutral S_N2-type transition states **TS7**—**TS9** (Figs 1 and 2), as suggested above, contain no N-centered bridge bonds, because the nucleophilic nitrogen atom is bound to the methylene group (the bond order is 0.37—0.47), and the N—CO bond is absent. Moreover, as evidenced from the overlap populations of the corresponding AOs, the interaction between the nitrogen atom and the carbon atom of the CO group is antibonding. The antibonding character of this interaction is confirmed also by an increase in the N—CH_2—CO angles in the reaction unit by 7—17° relative to the right angle characteristic of undistorted trigonal-bipyramidal S_N2-type TS.

Unlike the nitrogen atom, the chlorine and fluorine atoms in **TS7**—**TS9** are bound not only to the methylene group but also to the carbonyl group and, consequently, form halogen bridges, resulting in a substantial decrease in the X—CH_2—CO angles from 90° (to 60—79°) (see Table 2). The order of the additional X—CO bond varies from 0.19 to 0.45, which is indicative of its energy importance. The strongest X—CO bond is present in fluorine-containing TS, where it can have an even higher order than the CH_2—F bond (see Table 2). It should be noted that, according to the Mulliken analysis, the orders of these bonds in TS of ammonia **TS9** (X = Cl or F) are 0.39, 0.35 (CH_2—X) and 0.19, 0.39 (CO—X),

Table 2. Geometric characteristics (bond lengths (*d*) and bond angles (ω)) and bond orders for the reagents, intermediates, and TS of acylmethylation of 1*H*-quinazolinone **1a**, ammonia, and their N-anions with haloaldehydes **2a,b** (B3LYP/6-31G** calculations)

Reagents and TS	X	*d*/Å		ω/deg			Bond order		
		C—N[a]	CH_2—X	N—CH_2—X	N—CH_2—CO	X—CH_2—CO	N—CH_2 (N—CO)	C—X	OC—X
2a	Cl	—	1.80	—	—	—	—	0.97	—
2b	Cl	—	1.38	—	—	—	—	0.92	—
12·4H_2O	Cl	1.58	1.83	91.4	36.8	113.5	0.73	0.93	—
13·20H_2O[b]	Cl	1.59	1.78	93.3	36.8	110.0	—	—	—
15	Cl	1.44	1.82	146	34.9	111.1	(1.05)	0.96	—
16	Cl	1.50	1.81	146.5	35.9	111.2	(0.85)	0.99	—
17	Cl	1.48	1.81	146.3	35.3	111.4	(0.88)	0.99	—
19	—	1.52	—	—	31.4	—	(0.77)	—	—
20	Cl	1.57	1.86	152.7	40.5	112.9	(0.81)	0.89	—
21	Cl	2.72	1.85	163.8	67.0	107.3	(0.07)	0.90	—
22	Cl	2.37	1.87	167.2	61.8	108.5	(0.15)	0.88	—
TS7	Cl	1.96	2.37	178.4	100.0	78.5	0.37	0.43	0.20
TS7	F	1.96	1.85	169.6	103.8	66.2	0.36	0.38	0.38
TS8	Cl	1.81	2.50	169.5	97.9	75.0	0.47	0.33	0.23
TS8	F	1.88	1.94	167.0	107.1	60.4	0.40	0.32	0.45
TS9	Cl	1.88	2.43	172.7	97.0	78.8	0.42	0.39 (0.35)[c]	0.19 (0.14)[c]
TS9	F	1.89	1.90	160.9	98.2	65.2	0.39	0.35	0.39
TS10	Cl	1.58	1.83	95.2	36.0	113.4	(0.74)	0.92[d]	—
TS11	Cl	1.71	1.81	150.8	42.4	109.9	(0.56)	0.98[d]	—
TS12a	Cl	1.70	1.82	97.7	36.3	113.5	(0.60)	0.94[d]	—
TS12b	Cl	1.85	1.82	147.8	40.2	107.6	(0.52)	0.98[d]	—
TS12c	Cl	1.75	1.82	98.0	37.1	112.3	(0.58)	0.94[d]	—
TS13	Cl	1.71	2.64	141.9	56.6	89.9	0.54 (0.75)	0.26	—
TS14	Cl	1.51	1.83	100.0	34.0	113.5	(0.88)	0.92	—
TS15	Cl	1.49	2.62	141.4[e]	33.3	92.9	(0.87)	0.27	—
TS16	—	2.14	—	—	118.0	—	0.26 (0.58)	—	—
TS17	Cl	2.20	2.15	172.8	63.5	109.8	0.21 (0.43)	0.60	—
TS18	Cl	2.12	2.28	175.4	91.6	90.1	0.31	0.51	0.07
TS19	Cl	2.13	2.26	176.0	85.2	93.6	0.29 (0.06)	0.52	—

[a] For TS, the distance between the attacked carbon atom and the attacking nitrogen atom of the nucleophile.
[b] The PM3 calculations.
[c] The bond orders calculated at the CCSD(T)/6-311G**//B3LYP/6-31G** level of theory are given in parentheses.
[d] The N—H, O—H, and C—O bond orders in the reaction unit are 0.54, 0.37, 1.21 (**TS10**); 0.53, 0.33, 1.34 (**TS11**); 0.52, 0.35, 1.23 (**TS12a**); 0.43, 0.41, 1.26 (**TS12b**); 0.47, 0.38, 1.24 (**TS12c**).
[e] For the O—CH_2—Cl angle.

Table 3. Total energies (E_{tot}), the dipole moments (μ_{calc}) of the reagents, intermediates, and TS of *N*-acylmethylation, the energy barriers for the gas-phase reaction ($\Delta E^{\neq}$), and the imaginary vibrational frequencies of TS (ν_i)

Reagents, products, and TS	X	$-E_{tot}$[a]/a.u.	$\Delta E^{\neq}$ /kcal mol^{-1}	μ_{calc}/D	ν_i/cm^{-1}
NH_3	—	56.488220	—	1.8	—
1a[49a]	—	625.477586	—	3.7	—
1c[49a]	—	624.919106	—	2.3	—
2a	Cl	613.227262	—	1.1	—
2b	F	252.887503	—	1.1	—
11	—	208.9901314	—	3.0	—
12 · $4H_2O$	Cl	975.241327	—	3.0	—
13 · $20H_2O$[b]	Cl	349.078082	—	3.5	—
15	Cl	669.728150	—	1.1	—
16	Cl	1238.697608	—	1.9	—
17	Cl	1238.720423	—	1.8	—
19	—	209.295187	—	6.0	—
20	Cl	669.129127	—	3.1	—
21	Cl	1238.170869	—	1.1	—
22	Cl	1238.172220	—	2.5	—
TS7	Cl	1238.678400	16.6	7.0	440.6
TS7	F	878.316741	30.3	4.0	547.0
TS8	Cl	1238.654994	31.3	9.5	380.7
TS8	F	878.289428	47.5	8.0	489.1
TS9	Cl	669.678839	23.0	9.9	405.6
TS9	F	309.313324	39.2	7.7	530.2
TS10	Cl	669.671276	27.7	3.4	1336.0
TS11	Cl	1238.691266	8.5	3.5	839.0
TS12a	Cl	1238.645545	37.2	1.7	1570.7
TS12b	Cl	1238.641749	39.6	3.1	1859.7
TS12c	Cl	1238.647202	36.2	1.6	1773.3
TS13	Cl	669.667937	37.8	10.1	430.8
TS14	Cl	975.211337	18.8[c]	3.0	1500.2
TS15	Cl	975.192612	30.6	5.6	439.0
TS16	—	265.779155	2.7	6.9	422.2
TS17	Cl	669.116992	7.6	1.7	400.4
TS18	Cl	1238.155523	9.6 (−15.4)[d]	6.3	413.9
TS19	Cl	1238.161015	7.0 (−16.2)[d]	7.1	417.9

[a] With the ZPE correction.
[b] Calculations by the PM3 method; the energy is not corrected for ZPE.
[c] Relative to the structure of **12** · $4H_2O$ presented in this table rather than relative to the higher-energy structure formed in the reaction.
[d] The activation energy for the prereaction reagent—substrate complex is given; the energy of this complex relative to the reagents is given in parentheses.

respectively. The formation of halogen bridges in TS is confirmed also by MP2/6-31G** and CCSD(T)/6-311G**//B3LYP/6-31G** calculations for **TS9** (X = Cl), which gave the similar bond orders (0.40 and 0.35 for CH_2—Cl; 0.15 and 0.14 for CO—Cl, respectively).

The formation of bridges causes a substantial decrease in the dipole moments of TS (μ_{calc}) and the charges on the halogen atoms due to donation of the electron density to the CO group, as can be seen from a comparison of μ_{calc} for **TS7** and **TS8** (see Table 3) and their formyl-free analogs studied earlier.[49a] The charges on the chlorine atoms in **TS7** and **TS8** (X = Cl) calculated by the B3LYP/6-31G** method are −0.45 and −0.52, respectively, whereas these charges in the above-mentioned analogs are substantially higher (−0.73 and −0.67, respectively).

Undoubtedly, the additional CO—X bond is the key factor of stabilization of neutral TS of S_N2-*N*-acylalkylation responsible for an increase in the reactivity of AH in the S_N2 reactions with nitrogen nucleophiles.

In addition, the CO...HN hydrogen bonds between the nucleophile and electrophile can also make a contribution to stabilization of TS in the case of

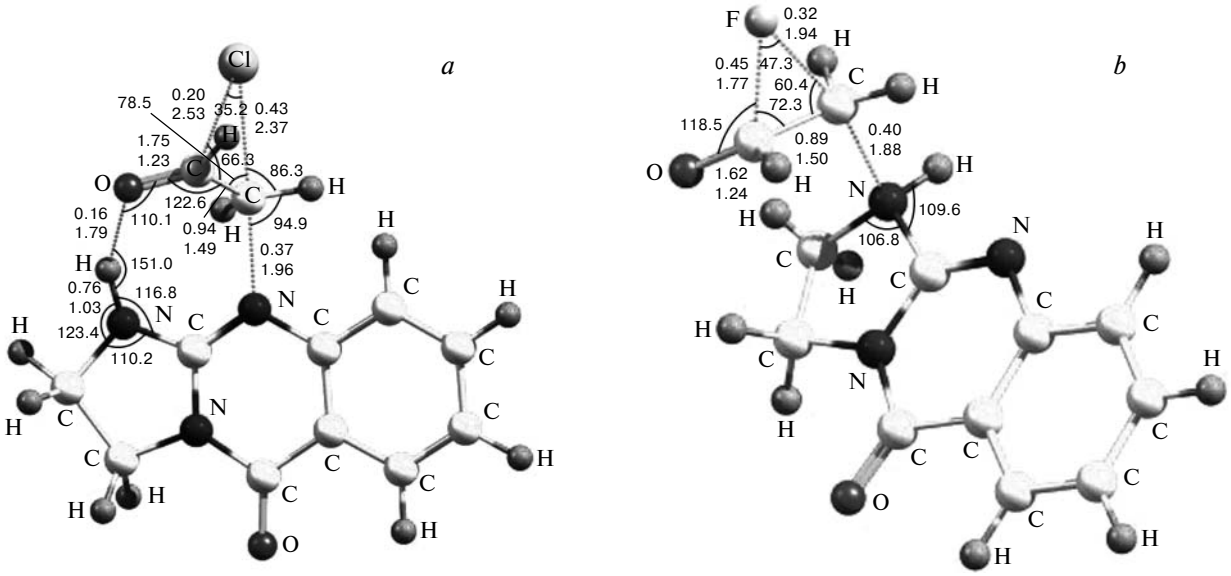


Fig. 1. Transition states **TS7** (X = Cl) (*a*) and **TS8** (X = F) (*b*) for the S_N2 formylmethylation of tautomer **1a** with aldehydes **2a,b** (B3LYP/6-31G** calculations). Here and in Figs 2—7, the bond orders (upper values), bond lengths/Å (lower values), and bond angles/deg (indicated by arcs) are given.

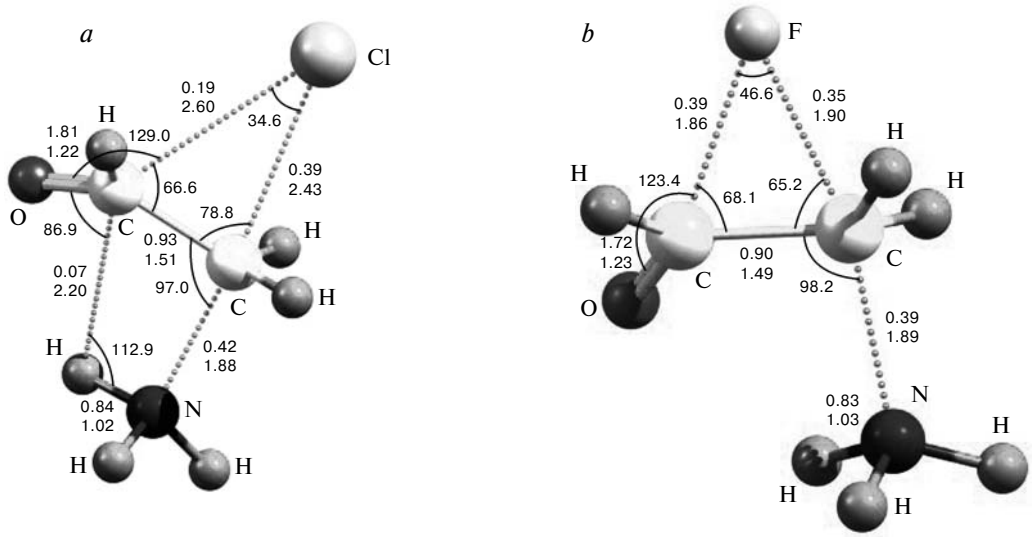


Fig. 2. Transition states **TS9** for the S_N2 formylmethylation of ammonia with chloride **2a** (*a*) and fluoride **2b** (*b*) (B3LYP/6-31G** calculations).

N-nucleophiles containing the primary or secondary amino group. These hydrogen bonds are present, in particular, in transition states **TS7**—**TS9** (X = Cl and F) (see Figs 1 and 2).* The total stabilizing effect of the carbonyl group in these TS due to the above-mentioned two factors is significant and can be estimated from the activation energy difference ($\Delta\Delta E^{\neq}$) between the *N*-alkylation of the substrates with methyl halides[49a] and haloaldehydes **2** (see Table 3). For substrates **1a** and NH_3 with X = Cl in the absence of solvation, $\Delta\Delta E^{\neq}$ is ~10—15 kcal mol^{-1}. In the presence of solvation, this difference and, consequently, the difference in the reactivity of AH and alkyl halides should be substantially smaller due to a much higher polarity and solvation stabilization of TS of *N*-methylation compared to TS for formyl-containing analogs (TS of the reaction of **1a** with MeCl have μ_{calc} ~13.4 and ~10.4 D).[49a] It should be emphasized that double bridge bonds analogous to those present in hypothetical structures **TS3** were found in none of the TS under consideration.

* The hypothesis about the presence of this type of hydrogen bonds in TS of *N*-acylalkylation of amines has been made earlier.[51]

Further studies of structures **TS7**—**TS9** showed that there is virtually no conjugation with the carbonyl group, which was generally considered as a factor responsible for stabilization of TS of acylalkylation in modern investigations (see above). Actually, the C—CO bond order in **TS7**—**TS9** is even smaller than unity (0.89—0.96). For comparison, the C—C bond order in the enolate anion CH_2=CH—O^- calculated by the B3LYP/6-31G** method is 1.59. Like in the above-mentioned TS $[Hal...CH_2(CHO)...Hal]^-$,[10] the C—C and C=O bond lengths in **TS7**—**TS9** (1.48—1.51 and 1.22—1.24 Å, respectively) are intermediate between the calculated bond lengths in free aldehydes **2a,b** (1.52 and 1.21 Å, respectively) and the enolate anion CH_2=CH—O^- (1.38 and 1.27 Å, respectively). However, this is not due to conjugation but due to the presence of halogen bridges in TS. In particular, a slight elongation of the C=O bond compared to that in free aldehydes **2a,b** is associated with a decrease in the order of this bond as a result of additional bonding between the CO group and the halogen atom.

The conjugation with the carbonyl fragment is hindered because the corresponding p-AO of the carbon atom of the methylene group is already involved in the bonding with the entering and leaving groups and, to a lesser extent, because of a deviation of the C—Hal bond from the optimal (orthogonal with respect to the plane of the formyl group) direction (by ~20—30°). Apparently, these factors are also responsible for the virtually complete absence of conjugation in S_N2-type TS involving allyl halides, *viz.*, C analogs of AH **2**.[52]

According to the results of calculations for chloroaldehyde **2a**, the latter is characterized by a much higher reactivity in the *N*-formylmethylation by the S_N2 mechanism compared to fluoroaldehyde **2b** ($\Delta\Delta E^{\neq} \approx$ −14——16 kcal mol^{-1}, see Table 3).

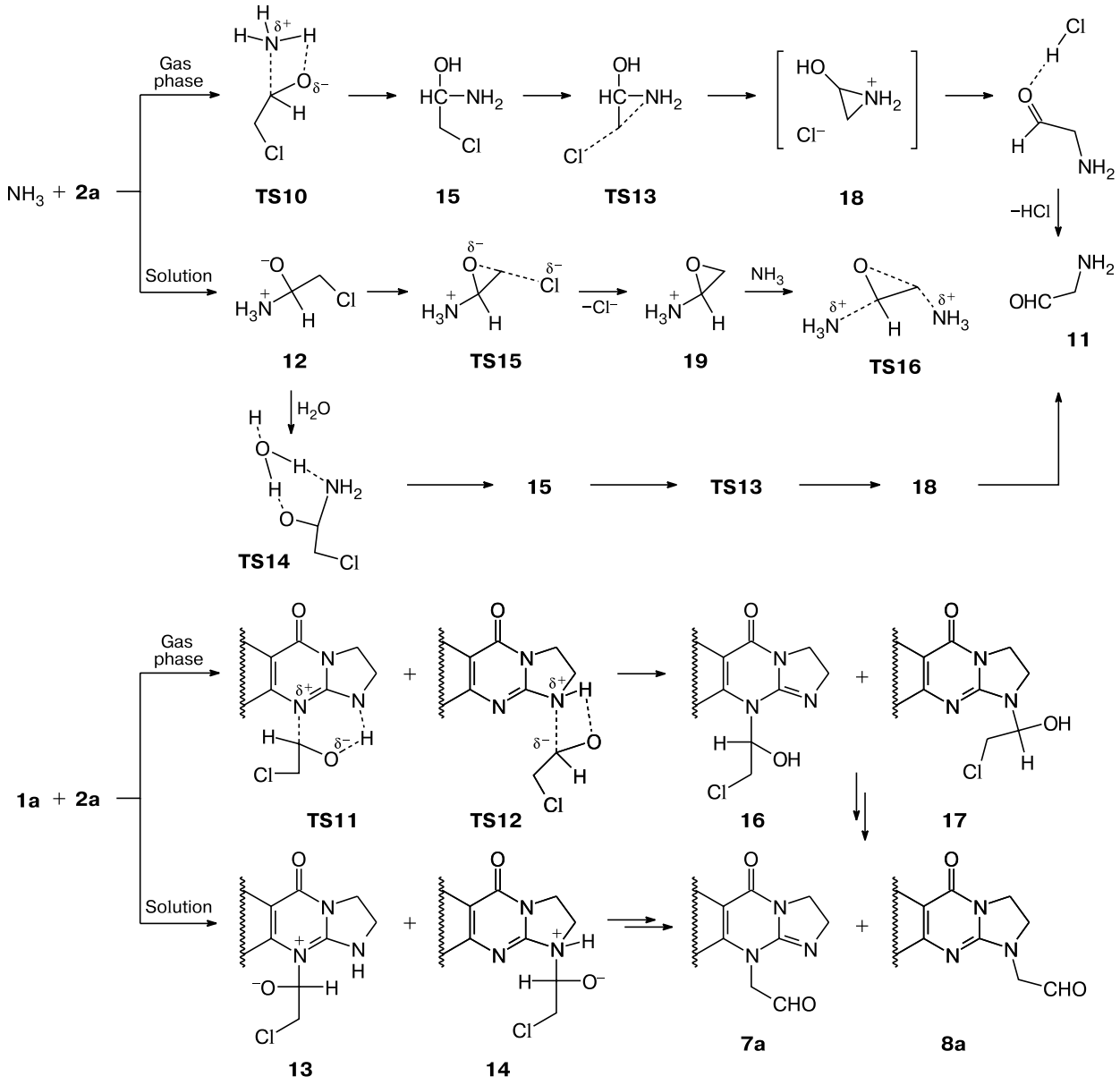
Therefore, the S_N2 mechanism accounts for the rather efficient *N*-acylalkylation of nucleophiles and directly relates the high reactivity of AH to particular structural features of TS of the reaction.

***N*-Acylalkylation by the S_NAE mechanism.** Calculations by the RHF/6-31G** and DFT (B3LYP/6-31G**) methods showed that the potential intermediates of *N*-formylmethylation of substrates **1a** and NH_3 by the S_NAE mechanism, *viz.*, α-haloalkyl-substituted zwitterions **12**—**14** (Scheme 3), like the parent zwitterion H_3N^+—CH_2O^-,[32a,33] are absolutely unstable in the absence of solvation and do not exist as isolated species. Most likely, this is also true for zwitterions of nitrogen bases with carbonyl compounds as a whole. Consequently, it can be concluded that the mechanism involving the intermediate formation of zwitterions is impossible for the gas-phase *N*-acylalkylation of neutral N-nucleophiles.

However, the *N*-acylalkylation through the direct formation of haloalkylaminocarbinols is, in principle, possible under gas-phase conditions (see Schemes 1 and 3). This is confirmed by the results of investigation of the NH_3—**2a** and **1a**—**2a** systems. For these systems, there are stationary points **TS10**—**TS12** and **15**—**17** on the potential energy surface corresponding to TS of *N*-hydroxyalkylation and haloalkylaminocarbinols generated from these TS, respectively (see Scheme 3 and Tables 2 and 3). Transition states **TS10** and **TS12** (Fig. 3) correspond to the *N*-hydroxyalkylation of ammonia and position 1 of quinazolinone **1a**. These transition states have a structure with the four-membered 1,3-prototropic reaction unit typical of such transformations[33,47] and a rather high energy (see Table 3). To the contrary, transition state **TS11** for hydroxyalkylation of quinazolinone **1a** at the N(10) atom (see Fig. 3) contains the weakly strained six-membered 1,5-prototropic reactive ring formed with the involvement of the adjacent NH group and, consequently, has a rather low energy relative to the reagents. The nature of this TS is indicative of a rather unusual reaction mechanism characterized by the attack on the tertiary N(10) atom and the prototropic shift of the H atom from the N(1) atom rather than from the attacked N atom, which is observed in the case of the usual *N*-hydroxyalkylation by the 1,3-prototropic mechanism.[33,47] The activation energies $\Delta E^{\neq}$ for transition states **TS10**—**TS12** are 27.7, 8.5, and 36.2 kcal mol^{-1}, respectively. Unlike **TS11**, isomeric **TS12** is diastereomeric because it contains the tetrahedral N(1) atom and was localized for the stereo forms *R*(N),*S*(C) (**TS12a**) and *R*,*R* (**TS12b,c**) (see Tables 1 and 2). The *R*,*R* structures **TS12b,c** are formally conformers of each other and differ in the angle of rotation of the formyl group characterized by the O=C—C—Cl dihedral angle (−82 and 178°, respectively). All three forms are similar in energy, and structure **TS12c** corresponding to the reaction pathways with the minimal energy consumption has the lowest energy (see Table 3).

The fact that the S_N2 *N*-acylalkylation and the *N*-hydroxyalkylation of quinazolinone **1a** with chloroaldehyde **2a** in the absence of solvation are mutually competitive can be estimated by a pairwise comparison of the total energies or the energies $\Delta E^{\neq}$ of the corresponding isomeric TS. For four TS involved in these reactions, these energies decrease in the series **TS12c** > **TS8** > **TS7** > > **TS11**, in which the energies of the states **TS7**, **TS8**, and **TS12c** are 8.5, 22.8, and 27.7 kcal mol^{-1}, respectively, relative to the most stable structure **TS11**. Therefore, in the case of the attack of tautomer **1a** on the N(10) atom, the S_N2-substitution reaction is noncompetitive with the *N*-hydroxyalkylation ($\Delta\Delta E^{\neq} = \Delta E^{\neq}_{S_N2} - \Delta E^{\neq}_{Add} =$ 8.5 kcal mol^{-1}). This is not surprising taking into account the above-mentioned specific features of **TS11**. To the contrary, based on the negative energy differences $\Delta\Delta E^{\neq}$ (−4.9 and −4.7 kcal mol^{-1}), the S_N2-acylalkylation reaction dominates in the case of the attack of quinazolinone

Scheme 3



1a on the less nucleophilic N(1) atom, as well as in the case of the attack of ammonia (and, apparently, of other N-nucleophiles). In the latter case, the *N*-acylalkylation through the *N*-hydroxyalkylation becomes even more noncompetitive because the second step of this reaction, *viz.*, the intramolecular nucleophilic substitution in haloalkylaminocarbinols, is even more unfavorable because of the presence of the strained three-membered ring in TS. Actually, the activation energy $\Delta E^{\neq}$ of the simplest TS of this type (**TS13**) for haloalkylaminocarbinol **15** is ~38 kcal mol^{-1}, which is almost 15 kcal mol^{-1} higher than $\Delta E^{\neq}$ for the direct *N*-acylalkylation of ammonia with chloride **2a** by the S_N2 mechanism (see Table 3). In the absence of solvation, **TS13** is transformed, not into the expected chloride of aziridinium cation **18**, but immediately into the *N*-formylmethylation product, to be more precise, into its hydrochloride associate (**11** · HCl), which was demonstrated by the intrinsic reaction coordinate (IRC) method. Cyclic structure **18** is generated in the course of the reaction but it does not correspond to the energy minimum. This structure immediately undergoes the barrierless *O*-deprotonation with the Cl^- counterion accompanied by the three-membered ring opening, so that all transformations are involved in a single elementary reaction event (see Scheme 3). To the contrary, salt **18** in solutions, where the nucleophilicity of the anions is

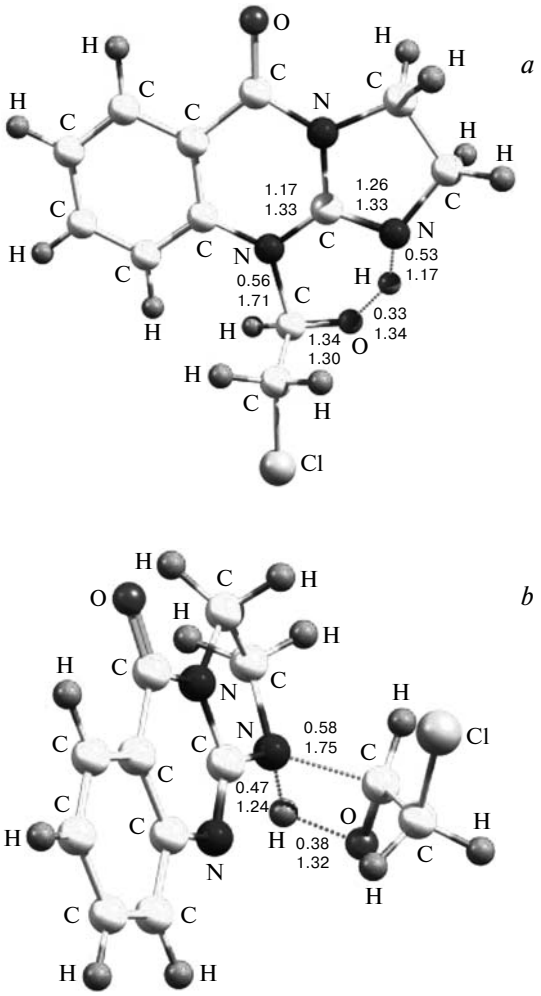


Fig. 3. 1,5-Prototropic transitions states **TS11** (*a*) and **TS12c** (*b*) for the addition of 1*H*-imidazoquinazolinone **1a** at the carbonyl group of chloroaldehyde **2a** (B3LYP/6-31G** calculations).

sharply decreased, most likely corresponds to the minimum on the potential energy surface and serves as an intermediate of the reaction.

The fundamental difference of the *N*-acylalkylation reaction in solution is that zwitterions stabilized by solvation can be formed under these conditions, and these zwitterions can serve as both intermediates of the reaction and precursors of different by-products. Calculations for zwitterionic structures **12**—**14** by the RHF/6-31G** method taking into account solvation (the PCM model; $MeNO_2$ as the solvent) confirmed that these structures in solution correspond to energy minima. However, it appeared that zwitterions **12**—**14** cannot be optimized in terms of the PCM model in calculations by the more precise DFT (B3LYP/6-31G**) method. This is because the energy minima corresponding to these zwitterions are shallow and, consequently, they are not revealed, because the solvation energy of zwitterions as well as of other compounds, which are prone to specific interactions with the solvent or hydrogen bonding, are underestimated in terms of the PCM model (*cf.* Refs 53—55). This conclusion is confirmed by the fact that even the tetrasolvates of zwitterion **12** with H_2O, $MeNO_2$, and $CHCl_3$ having the minimum solvation shell are characterized by the energy minima in calculations by both of the above-mentioned methods without the use of the PCM model. All three tetrasolvates are stabilized by hydrogen bonds between the solvents and the NH_3^+ or CO group of the zwitterion (*cf.* Ref. 33) (Fig. 4). According to the results of calculations by the semiempirical PM3 method, both icosahydrate of zwitterion **12** containing 20 H_2O molecules and icosahydrate of the analogous pyridine zwitterion ($C_5H_5N^+$—$CH(O^-)$—CH_2Cl) are stabilized, even despite the absence of a hydrogen-bond donor (the NH group) in pyridine. The length of the resulting C—N bond in these

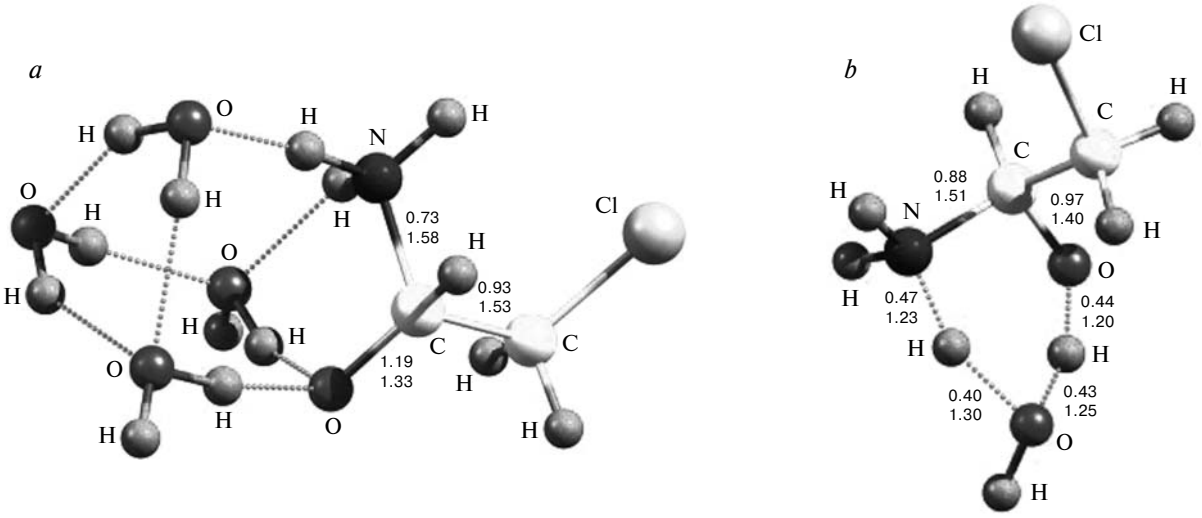


Fig. 4. Tetrahydrate of zwitterion **12** (*a*) and prototropic transition state **TS14** (*b*) for its catalytic isomerization giving tetrahydrate of hydroxyalkyl derivative **15** (only the catalyzing water molecule is shown) (B3LYP/6-31G** calculations).

two zwitterions is 1.59 and 1.63 Å, respectively, which is evidence of its substantial weakening.

Let us emphasize that we failed to find TS for the formation of the zwitterion hydrate **12**·4H_2O from the corresponding three-component system NH_3—**2a**—4H_2O by the restricted Hartree—Fock method. This is, apparently, because only of technical difficulties (the complex character of the potential energy surface in the vicinity of TS, the low energy barrier of the reaction, and the necessity of varying a large number of geometric parameters reflecting the mutual arrangement of the reagent and solvent molecules) or because the solvation shell is insufficiently representative. We also did not find TS for the direct transformation of **12**·4H_2O into tetrahydrate of *N*-acylalkyl derivative **11**, which is analogous to **TS4**. This is circumstantial evidence that the existence of such nitrogen-bridged neutral structures is highly improbable, as has been mentioned above. At the same time, we located **TS14**—**TS16** (Figs 4 and 5) corresponding to the formation of *N*-formylmethyl derivative **11** from **12**·4H_2O in the three-step reaction involving the prototropic isomerization of tetrahydrate **12**·4H_2O into tetrahydrate of haloalkylaminocarbinol **15** catalyzed by one water molecule, the cyclization of **15** to tetrahydrate of amino oxirane **19**, and the nucleophilic cleavage of **19** (see Scheme 3). Investigations of the character of the reaction pathway accompanied by the minimal energy consumption in the vicinity of **TS14** demonstrated that the catalytic isomerization of zwitterions proceeds as the concerted two-proton transfer, during which one of the protons of the ammonium group in the zwitterion migrates to the H_2O molecule acting as the catalyst, whereas one of protons of the latter molecule migrates to the O atom of the zwitterion. This transformation is characterized by $\Delta E^{\neq}$ of 7.4 and 18.8 kcal mol^{-1} relative to the starting configuration of the tetrahydrate **12**·4H_2O (**TS14** is directly generated from this tetrahydrate) and its more stable form, which is presented in Tables 2 and 3 and shown in Fig. 4.

The activation energies $\Delta E^{\neq}$ for the processes **12**·4H_2O → **19**·4H_2O and **19** → **11** are 30.6 and 2.7 kcal mol^{-1}, respectively. Therefore, the above-considered results show that the cyclization of the zwitterion to amino oxirane is most likely the rate-determining step of the amino oxirane pathway of the *N*-acylalkylation involving zwitterions. However, TS of this step (**TS15**), even despite the partially solvated character, has a much higher energy relative to the reagents than unsolvated highly polar transition state **TS9** (23.0 kcal mol^{-1}) of direct S_N2 formylmethylation of ammonia. Hence, the *N*-acylalkylation accompanied by the intermediate formation of haloalkylcarbinol is presumably the noncompetitive reaction channel in solution as well.

***N*-Acylmethylation of N-anions.** For this type of *N*-acylalkylation, the principal possibility of the S_NAE mechanism and its ability to compete with the substitution by the S_N2 mechanism were demonstrated. Investigations of TS of the reactions of the amide ion and the N-anion of imidazoquinazolinone **1c** with AH **2a** demonstrated that the N-acylmethylation of the unsolvated N-anions proceeds by either the S_N2 or S_NAE mechanism depending on the nature of the anionic substrate, primarily, on its nucleophilicity. There is no sharp boundary between two mechanisms because their TS are structurally similar and the *N*-acylalkylation in both processes starts with the more or less pronounced electrophilic attack of the CO group on the reagent. The direct S_N2 substitution, which excludes this attack, at least in the step of formation of the prereaction complex, apparently cannot proceed.

Based on the data for the NH_2^- ion, it can be concluded that highly nucleophilic N-anions are acylalkylated by the two-step S_NAE mechanism through the anionic tetrahedral intermediate. For the NH_2^-—**2a** system,

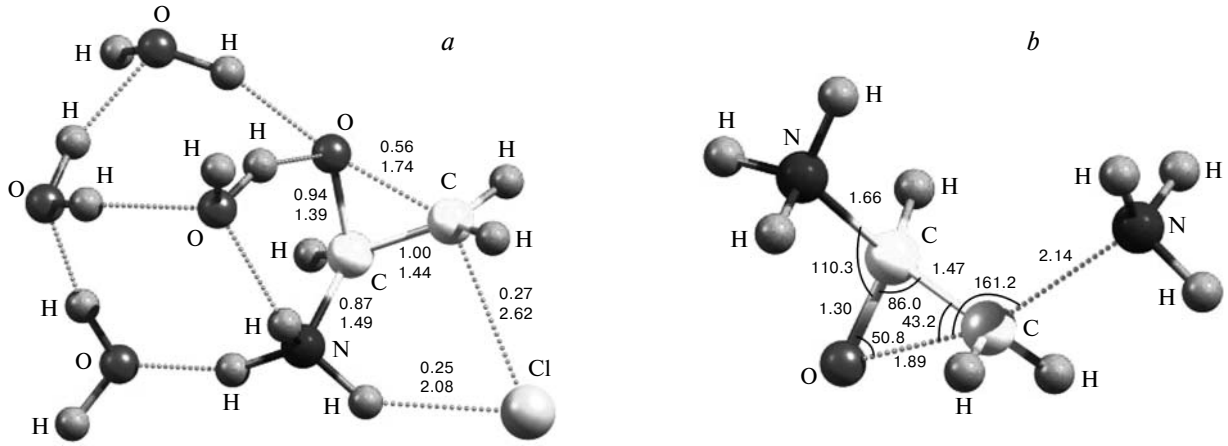
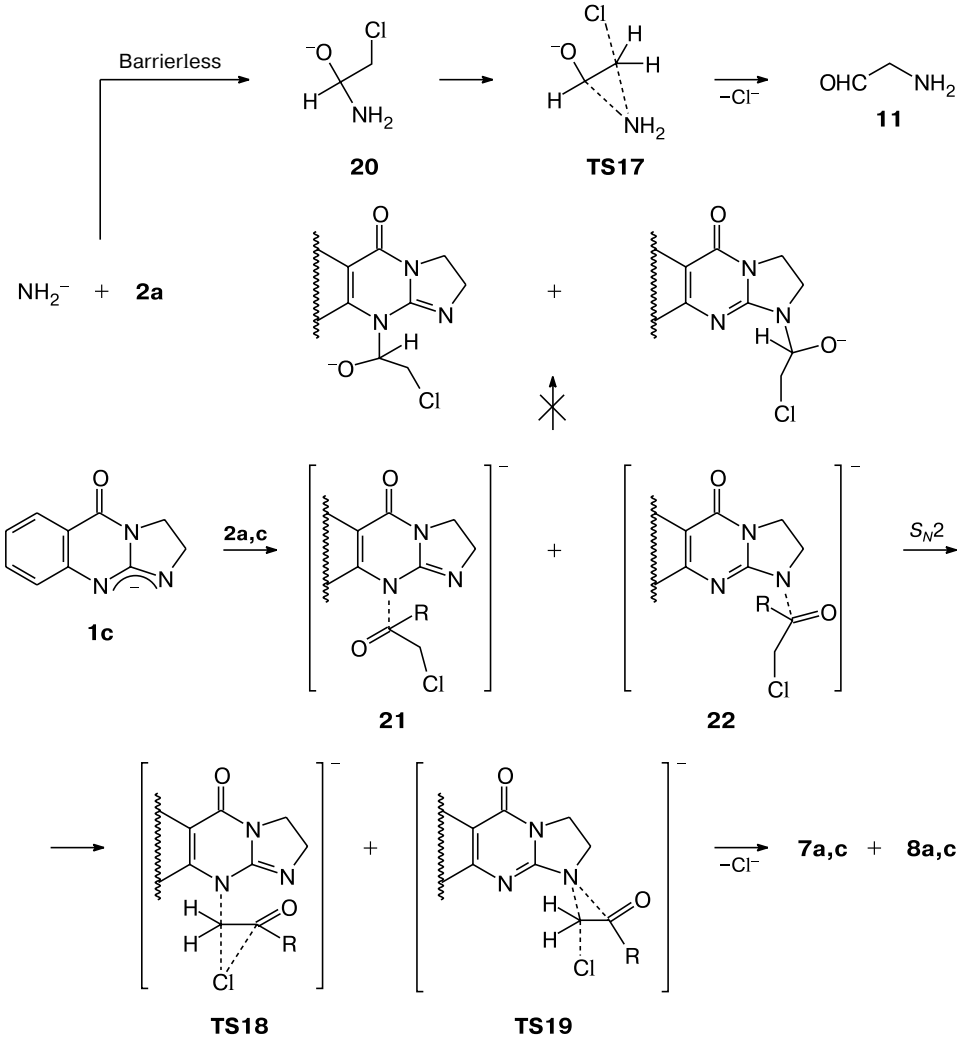


Fig. 5. Transition state **TS15** for the cyclization of zwitterion hydrate **12**·4H_2O giving amino oxirane hydrochloride tetrahydrate **19** (*a*) and transition state **TS16** for the nucleophilic ring opening in unhydrated cation **19** (*b*) (B3LYP/6-31G** calculations).

Scheme 4



R = H, Ph

O-anion **20** is formed as such an intermediate (Scheme 4, Fig. 6). Due to high nucleophilicity of the amide anion, the C—N bond in anion **20** is rather strong, although it is substantially loosen (the bond length is 1.57 Å and the bond order is 0.81). The formation of tetrahedral intermediate **20** is strongly exothermic and barrierless, whereas its transformation into *N*-formylmethylation product **11** proceeds through low-barrier ($\Delta E^{\neq} = 7.6$ kcal mol^{-1}) **TS17** (see Fig. 6). The latter contains the nitrogen-centered bridge and is structurally very similar to the above-discussed hypothetical neutral **TS4**,[22–24] the N—CO bond in **TS17** being substantially stronger than the N—CH_2 bond (the bond orders are 0.43 and 0.21, respectively).

Therefore, anionic N-nucleophiles, unlike neutral nucleophiles, can react with AH in the absence of solvation by the two-step S_NAE mechanism. Taking into account the barrierless character of the initial step of the

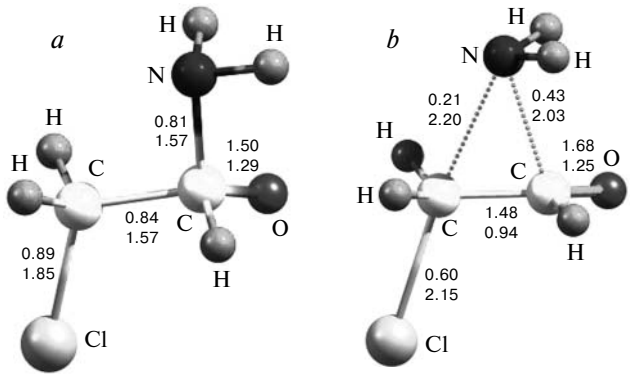


Fig. 6. Tetrahedral intermediate **20** for the *N*-formylmethylation of the amide ion with chloroaldehyde **2a** by the S_NAE mechanism (*a*) and **TS17** for the second reaction step relating intermediate **20** to *N*-formylmethyl derivative **11** (*b*) (B3LYP/6-31G** calculations).

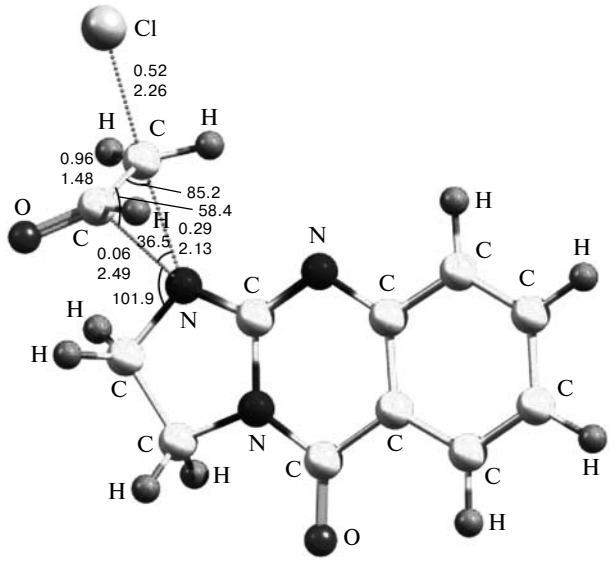


Fig. 7. Transition state **TS19** for the *N*-formylmethylation of the N-anion of quinazolinone **1c** with chloroaldehyde **2a** by the S_N2 mechanism (B3LYP/6-31G** calculations).

reactions involving highly nucleophilic N-anions analogous to NH_2^-, it is reasonable to suggest that there is no special TS corresponding to the substitution by the S_N2 mechanism for these processes.

The *N*-acylalkylation of the weakly nucleophilic N-anion of quinazolinone **1c** is radically different. This anion reacts with AH **2a** by the concerted S_N2 mechanism through isomeric **TS18** and **TS19** (Fig. 7; see Scheme 4). The latter transition state corresponding to the substitution at the N(1) atom is 3.5 kcal mol^{-1} more favorable, which is consistent with the above-mentioned fact that anion **1c** undergoes the N(1)- rather than N(10)-phenacylation with phenacyl bromide (**2c**).

Transition state **TS19** contains the nitrogen bridge with the weak N—CO bond (the bond order is 0.06) and with the substantially stronger N—CH_2 bond (the order is 0.29). Nevertheless, even this bond with the carbonyl group causes a noticeable deformation of the N—C—CO bond angle in the reaction unit in the direction opposite to that observed in the halogen-bridged TS. As a result, this angle in **TS19** is smaller than 90° (~85°), whereas the Cl—C—CO angle is, on the contrary, larger than 90° (~94°).

Transition state **TS18** contains the halogen bridge with the weak Cl—CO bond (the order is 0.07) instead of the nitrogen bridge, which, at first glance, is somewhat unexpected. However, this structure of TS is, apparently, attributed to a particularly strong conjugation between the second lone electron pair of the N(10) atom and the π system in N-anion **1c**, which does not allow this lone pair to form an additional bond with the CO group.

It should be noted that both transition states of ion **1c** are formed from prereaction ion-molecular complexes **21** and **22** (see Scheme 4). Both these complexes, like tetrahedral intermediate **20**, correspond to the attack of the CO group of compound **2a** on the lone electron pair of the nitrogen atom and are stabilized not only by the ion-dipole interaction but also by the weak N—CO bond (the order is 0.07 and 0.15, respectively). Evidently, these complexes can be considered, on the one hand, as structures analogous to the prereaction complexes of the usual S_N2 alkylation[56,57] and, on the other hand, as strongly loosen analogs of tetrahedral intermediate **20**.

Apparently, the reactions with weakly nucleophilic N-anions cannot proceed by the S_NAE mechanism, at least in the absence of solvation, because these N-anions are, most likely, unable to form tetrahedral intermediates. For anion **1c**, this is confirmed by investigations of the structures corresponding to its addition at the CO group of chloroaldehyde **2a**. It appeared that these structures show characteristic features of the dominant repulsion between the substrate and the reagent and the tendency to undergo barrierless decomposition.

Hence, neutral N-nucleophiles cannot, in principle, undergo *N*-acylalkylation by the addition—elimination (S_NAE) mechanism involving zwitterionic intermediates in the absence of solvation because of absolute instability of these intermediates. In solution, zwitterions can be formed and involved in the *N*-acylalkylation, at least *via* the amino oxirane pathway. However, this reaction pathway is noncompetitive with the S_N2 mechanism. Depending on the nucleophilicity, N-anionic substrates react with AH in the absence of solvation by either the addition—elimination or S_N2 mechanism. The high activity of AH in reactions with N-nucleophiles is not associated with the presence of conjugation in the acylalkyl halide fragment of TS but is determined by stabilization of TS due to the formation of halogen or nitrogen bridges as well as in the presence of necessary structural prerequisites, *viz.*, hydrogen bonding between the substrate and the reagent.

Experimental

The ^{1}H NMR spectra were recorded on a Varian XL-300 instrument in $CDCl_3$. The energy calculations of the molecules, the structure optimization of TS, and calculations by the IRC method were carried out with the use of the quantum chemical GAMESS (US) program package[58] (PC GAMESS version).★ The stationary points on the potential energy surface were identified as TS from the presence of the imaginary vibrational mode in DFT B3LYP/6-31G** calculations and in calculations with the use of the IRC method in both directions from TS. Because of a large body of calculations, most of the latter calculations were performed by the RHF/6-31G method. However, in the most important cases (for **TS17** and **TS18**) and also for all

★ A. A. Granovsky, http://www.classic.chem.msu.su/gran/gamess/index.html.

reactions with the involvement of NH_3 and NH_2^-, the calculations were carried out at the B3LYP/6-31G** level of theory. The transition states, reagents, and intermediates were described using the Mulliken bond orders and charges. The force matrices for all structures were calculated by the B3LYP/6-31G** method. All energy characteristics are given with the zero-point energy (ZPE) correction obtained using the scaling coefficient of 0.961.[59]

Compound **1** was synthesized by analogy with its 7-chloro derivative[60] starting from isatoic anhydride and 2-methylthio-4,5-dihydroimidazole. The yield was 75%, m.p. 264—266 °C (Pr^iOH—DMF). Found (%): C, 63.92; H, 4.99; N, 22.66. $C_{10}H_9N_3O$. Calculated (%): C, 64.16; H, 4.85; N, 22.45. ^1H NMR ($CDCl_3$), δ: 3.84 and 4.30 (both t, 2 H each, CH_2, J = 8.3 Hz); 6.88 (br.s, 1 H, NH); 7.19 (t, 1 H, H(7), J = 7.0 Hz); 7.25 (d, 1 H, H(9), J = 7.8 Hz); 7.58 (t, 1 H, H(8), J = 7.7 Hz); 8.13 (d, 1 H, H(6), J = 7.9 Hz).

The physicochemical constants of the newly synthesized compounds are given in Table 1.

Phenacylation of the molecular form of quinazolinone 1. ***A.*** A solution of quinazolinone **1** (1.87 g, 10 mmol) and phenacyl bromide (**2c**) (2.00 g, 10 mmol) in MeCN (20 mL) was refluxed for 29 h. The solvent was distilled off, the residue was treated with a concentrated ammonia solution (15 mL), and the reaction product was extracted with chloroform and chromatographed on an alumina column. The resulting mixture of isomeric substitution products was recrystallized from ethanol, and 10-phenacyl-substituted product **7c** was obtained in a yield of 1.80 g (58.8%). Found (%): C, 70.55; H, 5.17; N, 13.85. $C_{18}H_{15}N_3O_2$. Calculated (%): C, 70.81; H, 4.95; N, 13.76.

B. The reaction was carried out analogously but in nitromethane for 8 h. A mixture of isomers **7c** and **8c** was obtained in 75.0% yield.

Phenacylation of the N-anion of quinazolinone 1. Quinazolinone **1** (1.87 g, 10 mmol) and phenacyl bromide (**2c**) (5.97 g, 30 mmol) were successively added with stirring to a solution of KOH (0.67 g, 12 mmol) in DMSO (20 mL) at ~20 °C. After 10 min, water (50 mL) was added to the reaction mixture, and the reaction product was extracted with chloroform (2×20 mL). Chloroform was distilled off under reduced pressure. The residue was thoroughly triturated with MeCN (10 mL), and 1-phenacyl derivative **8c** was filtered off in a yield of 1.16 g (38.0%). Found (%): C, 70.74; H, 5.17; N, 14.03. $C_{18}H_{15}N_3O_2$. Calculated (%): C, 70.81; H, 4.95; N, 13.76.

***p*-Chlorophenacylquinazolinone (7d).** A mixture of quinazolinone **1** (0.94 g, 5 mmol) and *p*-chlorophenacyl bromide (**2d**) (1.71 g, 5 mmol) in MeCN (25 mL) was refluxed for 42 h, during which compound **1** was gradually transferred into solution followed by precipitation of the reaction products. After completion of the reaction, the precipitate was filtered off and recrystallized from ethanol. Hydrobromide of compound **7d** was obtained in a yield of 1.20 g (53.3%). Found (%): C, 51.39; H, 3.59; N, 9.99. $C_{18}H_{15}BrClN_3O_2$. Calculated (%): C, 50.07; H, 3.61; N, 10.21.

2,6-Di-*tert*-butyl-4-hydroxyphenacylquinazolinone (7e). A mixture of compound **1** (0.94 g, 5 mmol) and bromo ketone **2e** (1.64 g, 5 mmol) in MeCN (20 mL) was refluxed for 22 h. The reaction mixture was cooled, and the precipitate that formed was filtered off and washed with a small amount of MeCN. Hydrobromide **7e** containing an impurity of the starting compound **1** was obtained in a yield of 1.97 g. The product was purified by the treatment with boiling $MeNO_2$ (10 mL), and undissolved quinazolinone **1** (0.13 g) was filtered off. After cooling of the filtrate, hydrobromide of compound **7e** was obtained in a yield of 1.34 g (52.0%). Found (%): C, 60.6; H, 6.5; N, 8.3. $C_{26}H_{32}BrN_3O_3$. Calculated (%): C, 60.7; H, 6.3; N, 8.2.

10-Pivaloylmethylquinazolinone (7f). A mixture of quinazolinone **1** (0.94 g, 5 mmol) and bromopinacolone (1 mL, 7.5 mmol) in MeCN (30 mL) was refluxed for 28—30 h. After completion of the reaction, the solvent was distilled off, and the residue was successively treated with Me_2CO (10 mL) and boiling $MeNO_2$ (20 mL). Poorly soluble starting quinazolinone **1** (0.4 g) was separated. After cooling, hydrobromide of compound **7f** was filtered off from the filtrate in a yield of 0.99 g (54.0%). Found (%): C, 54.5; H, 6.5; N, 12.0. $C_{16}H_{22}BrN_3O$. Calculated (%): C, 54.6; H, 6.3; N, 11.9.

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