N-Alkylation of 2,3-dihydroimidazo[2,1-*b*]quinazolin-1(10)*H*-5-one. On the cryptoanionic mechanism of *N*-substitution

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Quantum chemical methods involving studies of transition states of the reaction showed that the main products of *N*-alkylation of prototropic 2,3-dihydroimidazo[2,1-*b*]quinazolin-1(10)*H*-5-one (**1**) in the gas phase and under neutral conditions in solution occurring *via* the S_N2 mechanism should be *N*(10)-alkyl-substituted derivatives formed from the 1*H*-tautomer. Minor *N*(1)-substituted derivatives in solution can be produced from both tautomers. For the alkylation of the free *N*-anion of compound **1**, position 1 is attacked first. Validity of conclusions concerning the overall regioselectivity of the reaction was confirmed experimentally. In the absence of solvent, the alkylation proceeds abnormally with a sharp increase in the content of the 1-substituted isomers up to inversion of the regioselectivity of the reaction, which is explained by the participation in the process of the H-bonded dimer of the substrate $(\mathbf{1a})_2$, which undergoes alkylation *via* the cryptoanionic mechanism.

Key words: 2,3-dihydroimidazo[2,1-*b*]quinazolin-1(10)*H*-5-one, quantum chemical calculations, density functional method, transition states, prototropic tautomerism, *N*-alkylation, H-bonded dimers, cryptoanionic reaction mechanism, mechanism of alkyltransferase action.

N(10)-Substituted 2,3-dihydroimidazo[2,1-*b*]quinazolin-5-ones possess diverse biological activity. They have been synthesized up to presently mainly by ring closure of the corresponding isatoic anhydrides.[1—6] Direct *N*(10)-substitution in 2,3-dihydroimidazo[2,1-*b*]quinazolin-1(10)*H*-5-one (**1**) under neutral conditions, which could result in the formation of these compounds, have not been studied previously. Only the *N*(1)-alkylation and *N*(1)-acylation of compound **1** in the presence of bases are known[1,7—9] and involve, probably, the *N*-anion of the substrate as intermediate.

In the present work, the reactivity of different forms of compound **1** and their role in *N*-alkylation with allowance for the solvent effect were analyzed by quantum chemical methods. The calculated data were compared with the experimental results of *N*-alkylation, and a preparative method for the synthesis of *N*(10)-substituted quinazolinones **2** was developed.

Results and Discussion

Although annelated quinazolinone **1** should yield only two types of the final products of *N*-alkylation, namely, *N*(10)- (**2**) and *N*(1)-alkyl-substituted (**3**) derivatives, the reaction can include six variants of the electrophilic attack, because compound **1** has three potentially ambidentate forms (1*H*- (**1a**), 10*H*-tautomer (**1b**), and *N*-anion (**1c**)). It is most probable that the main contribution to the overall yield will be made by the alkylation routes involving attacks to the nitrogen atoms with non-conjugated lone electron pairs (LEP).

Evidently, the positional and tautomeric-substrate selectivity of the *N*-alkylation of imidazoquinazolinone **1** is determined by the three main factors: nucleophilicity of the N(1) and N(10) nitrogen atoms in each of its two tautomers, mobility of the prototropic equilibrium, and its position. Possible routes of the *N*-alkylation of tautomers **1a,b** and *N*-anion of **1c** in the composition of the ion pair with the alkaline metal cation *via* the S_N2 mechanism, transition states (TS) **TS1—TS6** corresponding to these routes, and the corresponding *N*-alkyl derivatives **2**, **3** and salts of their protonated form **4—7** are presented in Scheme 1.

Quantum chemical studies were performed mainly for the reaction of electroneutral and *N*-anionic forms **1a—c** with methyl halides (Hal = Cl, Br, I) and dimethyl sulfate (DMS). In addition, we studied the benzylation of tautomer **1a** with benzyl bromide. The calculations were mainly performed by the Hartree—Fock (RHF) and density functional (DFT) methods with the B3LYP functional in the 6-31G** basis set.

The results of calculation of the starting molecules **1a,b**, *N*-anion **1c**, and its lithium, sodium, and potassium salts (M-**1c**; M = Li, Na, K), alkylating agents, TS of

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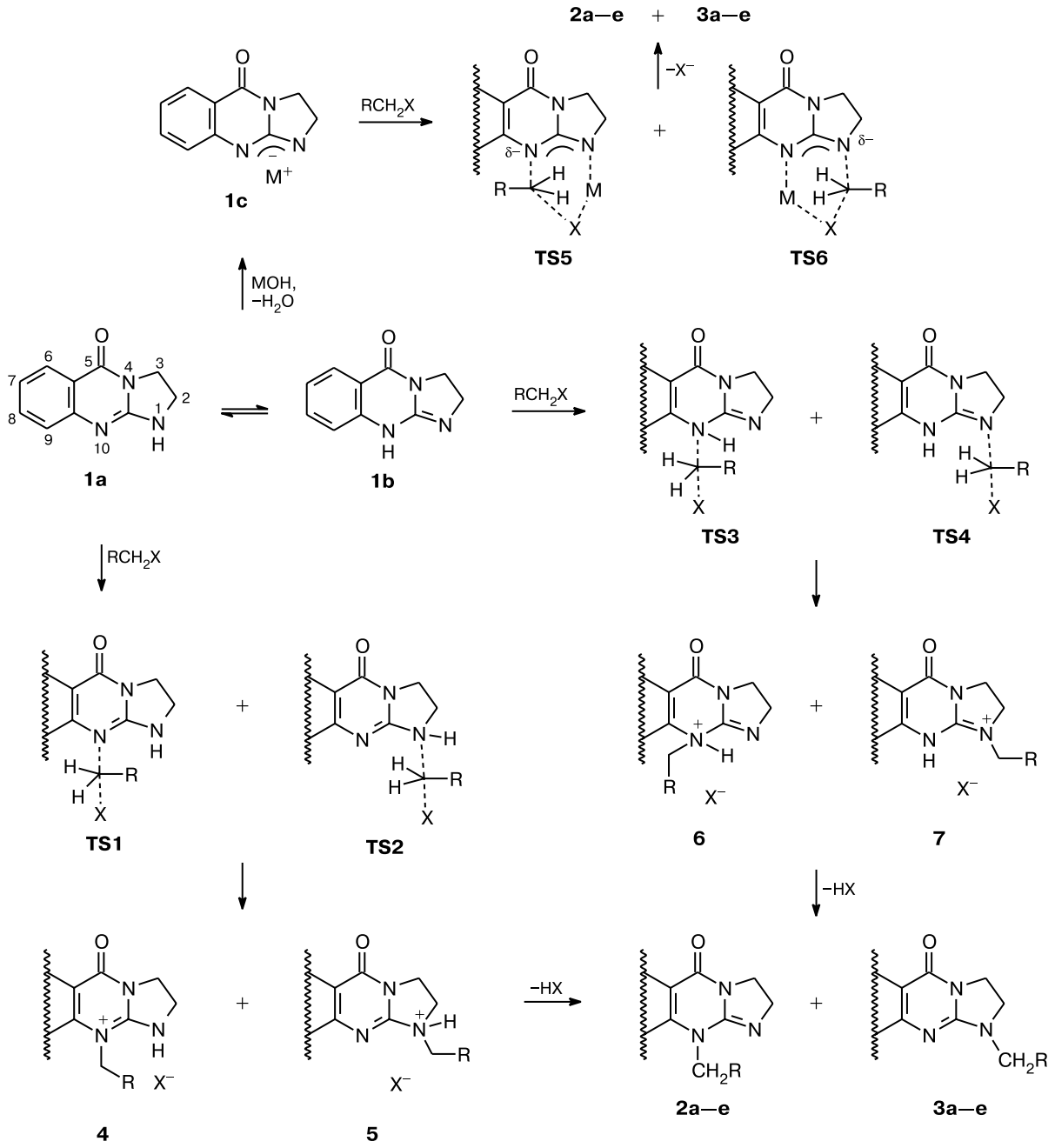
Scheme 1



X = Hal, OSO_3Me; M = Li, Na, K
2—7: R = H (**a**), Ph (**b**), *p*-ClC_6H_4 (**c**), $PhOCH_2$ (**d**), *p*-$BrC_6H_4OCH_2$ (**e**)

reactions, and salt-like products **4—7** (R = H, X = Cl) in the gas phase are presented in Tables 1 and 2. Imidazoquinazolone structures **1a—c** have the planar or nearly planar structures of the tricyclic framework. In this case, 1*H*-tautomeric form **1a** of compound **1**, as compared to 10*H*-tautomer **1b**, is characterized by a substantially lower total energy and thus should be predominant. Imidazoquinazolinone **1** forms no 1- and 10-metal-substituted forms similar to prototropic tautomers **1a,b**, because the metal atoms in its *N*-metal-substituted derivatives are not localized at any nitrogen atom but are arranged approximately in the middle between them. In other words, the *N*-metallation of each tautomer **1a,b** affords the same metal derivative with the symmetry C_s. In this case, the

Table 1. Geometric characteristics and dipole moments of the reactants, products, and transition states and the frequencies of imaginary modes of the TS (ν_i) (DFT, B3LYP/6-31G**)

Structure	R in RCH_2X	X	μ_{calc} /D	*d*/Å		Angle N—C—X[a] /deg	ν_i /cm^{-1}
				C—N[b]	C—X		
1a	—	—	3.7	—	—	—	—
1b	—	—	2.5	—	—	—	—
1c	—	—	2.3	—	—	—	—
Li-**1c**	—	—	6.4	—	—	—	—
Na-**1c**	—	—	8.8	—	—	—	—
K-**1c**	—	—	11.3	—	—	—	—
MeCl	H	Cl	2.1	—	1.80	—	—
MeBr	H	Br	1.9	—	1.96	—	—
MeI[c]	H	I	1.6	—	2.19	—	—
Me_2SO_4	H	OSO_3Me	4.9	—	1.45	—	—
BnBr	Ph	Br	2.3	—	2.00	—	—
4	H	—	8.9	1.47	—	—	—
5	H	—	10.4	1.51	—	—	—
7	H	—	7.9	1.46	—	—	—
TS1	H	Cl	10.4	1.87	2.46	172.3	473.5
	H	Br	9.9	1.87	2.59	168.0	470.7
	H	I	11.4	1.94	2.80	175.6	448.3
	Ph	Br	11.3	1.86	2.72	161.6	379.9[d]
	H	OSO_3Me	5.4	2.04	1.94	170.5	543.6
TS2	H[e]	Cl	13.4	1.76	2.47	177.5	550.1
	H[e]	Br	13.5	1.76	2.61	177.4	547.3
	H	I	14.2	1.92	2.87	177.4	559.5
	Ph[f]	Br	14.1	1.87	2.81	159.3	456.9[d]
	H	OSO_3Me	10.9	1.92	2.07	173.8	507.2
TS4	H	Cl	11.0	1.88	2.43	176.0	485.0
TS5[g]	H	Cl	8.5	2.08	2.32	179.2	436.0
TS5 (M = Li)	H	Cl	3.0	2.22	2.21	154.6	424.2
TS5 (M = Na)	H	Cl	5.8	2.22	2.19	161.8	405.6
TS5 (M = K)	H	Cl	8.8	2.20	2.20	167.3	409.7
TS6[g]	H	Cl	8.0	2.11	2.27	178.4	440.0
TS6 (M = Li)	H	Cl	1.9	2.22	2.19	154.5	430.4
TS6 (M = Na)	H	Cl	3.2	2.23	2.17	161.5	407.6
TS6 (M = K)	H	Cl	5.3	2.22	2.18	167.0	409.9
TS7[h]			9.4	2.12	2.35	171.4	570.4

[a] The angle formed with participation of the attacked N atom.
[b] The length of the forming bond in the TS and reaction products.
[c] The 6-311G* basis set was used for the iodine atom in all iodine-containing structures.
[d] The calculation of ν_i was performed by the RHF/6-31G* method.
[e] Data of the calculation by the MP2/6-31G** methods (for ν_i, RHF/6-31G**).
[f] Calculations were performed by the RHF/6-31G** methods.
[g] Transition state of the free *N*-anion.
[h] Calculations were performed by the RHF/6-31G method.

metal cation is coordinated by the N(1) and N(10) nitrogen atoms forming the five-membered chelate cycle. The metal cation in the chelate cycle is somewhat closer to the N(1) atom. This fact and a comparison of the calculated orders of two M—N bonds in all the three salts M-**1c** under study indicate that the M—N(1) bond in them is somewhat stronger. The structures of salts Li-**1c** and K-**1c** are shown in Fig. 1. In the series of metals Li, Na, and K, the sum of orders of two M—N bonds decreases significantly due to an increase in the ionic character of *N*-metal-substituted derivatives M-**1c**, and the effective positive charge on the metal atom increases, by contrast, from +0.45 for Li to +0.72 for K.

When analyzing the data obtained for the methylation products of compound **1** with methyl chloride, *viz.*, hydrochlorides **4—7** (see Table 2), it is noteworthy that the product of the endothermic reaction of 10*H*-tautomer **1b** at position 10, namely, hydrochloride **6** (R = H), is ther-

Table 2. Total energies in the gas phase (E^{tot}) of the reactants, products, and TS and the energy barriers ($\Delta E^{\neq}$) of the *N*-alkylation of quinazolinone **1** in the gas phase obtained by the RHF/6-31G** and DFT (B3LYP/6-31G**) methods

Structure	R in RCH_2X	X	$-E^{tot}$ (au)		$\Delta E^{\neq}$ (ΔE^{tot})[a]/kcal mol^{-1}	
			RHF	DFT	RHF	DFT
1a	—	—	622.02709	625.47758	—	—
				623.992256[b]		
1b	—	—	622.01717	625.46969	—	—
1c	—	—	621.45668	624.91910	—	—
Li-**1c**	—	—	628.95222	632.45766	—	—
Na-**1c**	—	—	783.33771	787.18618	—	—
K-**1c**	—	—	1220.61574	1224.76327	—	—
MeCl	H	Cl	499.06154	499.97802	—	—
				499.34180[b]	—	—
MeBr	H	Br	2609.50967	2611.45244	—	—
				2609.77590[b]	—	—
MeI [c]	H	I	6956.41925	6959.28270	—	—
Me_2SO4	H	OSO_3Me	776.00858	778.48437	—	—
BnBr	Ph	Br	2838.98590	2842.28569	—	—
4	—	—	1121.09183	1125.46557	—	—
5	—	—	1121.03743	1125.41244	—	—
3a···HCl[d]	—	—	1121.09374	1125.46583	—	—
6	—	—	1120.98489	—	—	—
7	—	—	1121.10266	1125.47565	—	—
TS1	H	Cl	1121.02711	1125.40497	38.6 (−2.0)	31.8 (−6.3)
	H	Br	3231.47861	3236.88167	36.5	30.3
	H	I	7578.40212	7584.72345	27.7	23.1
	Ph	Br	3460.95270	3467.714857	37.8	30.4
	H	OSO_3Me	1398.00018	1403.93811	22.3	15.0
TS2	H	Cl	1121.00738	1123.26140[b]	51.0 (32.1; −3.2[e])	45.6 (27.0; −6.4 [e])[b]
	H	Br	3231.45846	3233.70283[b]	49.1	41.0 [b]
	H	I	7578.38371	—	39.3	—
	Ph	Br	3460.93716	—	47.6	—
	H	OSO_3Me	1397.97624	1403.91322	37.3	30.6
TS3	H	Cl	1120.98450	—	59.1	—
TS4	H	Cl	1121.02464	1125.40256	33.9 (−15.0)	28.3 (−17.5)
TS5[f]	H	Cl	1120.50632	1124.89259	7.5	2.8
TS5 (M = Li)	H	Cl	1127.97208	1132.40919	26.2	16.6
TS5 (M = Na)	H	Cl	1282.35969	1287.13799	24.8	16.4
TS5 (M = K)	H	Cl	1719.63997	1724.71595	23.4	15.9
TS6[f]	H	Cl	1120.50969	1124.89575	5.4	0.9
TS6 (M = Li)	H	Cl	1127.96940	1132.40683	27.8	18.1
TS6 (M = Na)	H	Cl	1282.35858	1287.13767	25.5	16.6
TS6 (M = K)	H	Cl	1719.64026	1724.71720	23.2	15.1
TS7[g]	H	Cl	1742.45077	—	28.3	—

[a] ΔE^{tot} is the difference of E^{tot} of the products and reactants; when calculating E^{tot} of the products, we used the structures of hydrochlorides obtained by the IRC method and being local but not necessarily global minima, because their optimization in the framework of the most favorable localization of the Cl^- anion was not performed.

[b] Calculation by the MP2/6-31G** method.

[c] The 6-311G* basis set was used for the iodine atom in all structures.

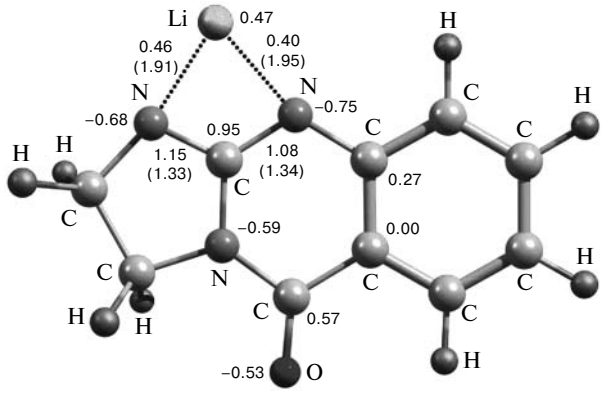
[d] The structure of **5** in the gas phase is unstable and easily transformed into a considerably more stable molecular complex **3a**···HCl.

[e] Change in the total energy relatively to complex **3a**···HCl.

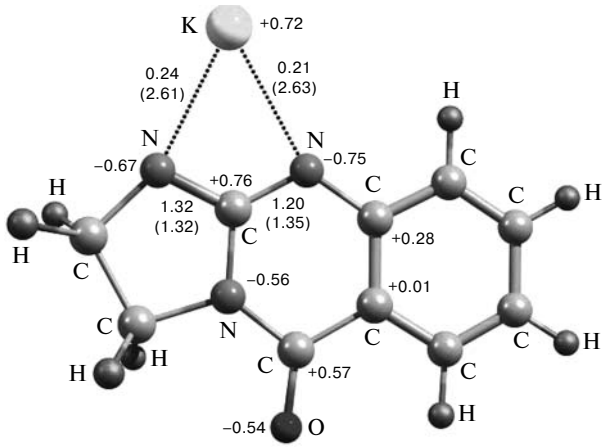
[f] Transition state for the free *N*-anion.

[g] Calculation by the RHF/6-31G method.

modynamically very unfavorable compared to both the starting compounds and isomeric salts **4**, **5**, and **7**. The main reason for this phenomenon is conjugation in the partially aromatic pyrimidinone ring. Although the RHF/6-31G** method gives the energy minimum for this product, the more precise DFT calculation shows that



A



B

Fig. 1. Structures of *N*-lithium (Li-**1c**; **A**) and *N*-potassium (K-**1c**; **B**) salts of imidazoquinazolinone **1** (B3LYP/6-31G**). For some bonds, their orders and lengths in Å (in parentheses) are presented; charge values are also given for several atoms.

salt **6** is unstable, at least in the configuration corresponding to methylation. This is caused by its affinity to the barrierless decomposition to the starting compounds **1b** and MeCl, when the cation of the salt acts toward the Cl^- ion as the methylating agent. Thus, the methylation of tautomer **1b** with methyl chloride through **TS3** in the gas phase, most likely, is impossible; however, it occurs with reactants that give less nucleophilic counterions during the reaction.

Unlike salt **6**, isomeric hydrochloride **5** (R = H), which is also formed by the endothermic attack at the conjugated LEP of the nitrogen atom, corresponds to a minimum on the potential energy surface (PES), although this compound in the gas phase is prone to exothermic deprotonation with the chloride ion to form molecular complex **3a**···HCl. The remaining two methyl-containing hydrochlorides **4** and **7** correspond to the exothermic routes of methylation with methyl chloride and are rather stable to the nucleophilic attack by the Cl^- ion.

For all reactions of *N*-alkylation, we succeeded to localize the corresponding TS (**TS1**—**TS6**) by the RHF method. However, the calculation at the higher level (DFT) did not reveal the most thermodynamically unfavorable **TS2** (R = H, X = Cl, Br, I and R = Ph, X = Br) and **TS3** (R = H, X = Cl) for the methylation and benzylation of tautomers **1a,b**, although **TS2** (R = H, X = OSO_3Me) for the reaction with DMS was found. This result does not mean that some of the **TS2** structures are impossible as transition states, because for R = H, X = Cl, Br we succeeded to obtain **TS2** by the MP2/6-31G** method (see Tables 1 and 2). An unsuccessful attempt to localize **TS3** (R = H, X = Cl) by the DFT method seems understandable if we take into account the above-mentioned instability of the assumed product of **TS3** transformation, namely, salt **6**, which was revealed by just this method.

Selected geometric characteristics of the obtained TS, the frequencies of their imaginary vibrational modes (ν_i), total energies (E^{tot}), and the energy activation barriers $\Delta E^{\neq}$ calculated from E^{tot} are given in Tables 1 and 2. The structures of **TS1, TS2, TS5**, and **TS6** for the methylation of tautomer **1a** and *N*-lithioimidazoquinazolinone Li-**1c** with DMS and MeCl, respectively, are shown in Figs 2 and 3 as illustrations for the TS structure.

As can be seen from the data in Figs 2 and 3 and Table 1, all the TS under study have the trigonal bipyramidal configuration of the reaction center. The TS containing no metal usually exhibit an insignificant deviation of three atoms of the reaction site N, C, Hal from the ideal linear arrangement (see Table 1). The exceptions are the TS of *N*-benzylation **TS1** and **TS2** (R = Ph, X = Br) for which this deviation is pronounced and achieves ~20°.* This effect has an electrostatic nature and is related to the mutual repulsion of the negatively charged bromine atom and neighboring π-electron cloud of the phenyl group, which represents a continuous region of the negative electrostatic potential.[10] ** Taking into account published data for imidazole and pyridine[11] and our results, we can conclude that this effect is probably inherent in *N*-benzylation as a whole and is virtually independent of the nature of the halogen atom.

The second case of electrostatic deformation of the reaction center is observed in metal-containing TS: **TS5** and **TS6** (R = H, X = Cl, M = Li, Na, K) corresponding to the methylation of contact ion pairs (CIP) M-**1c** with

* Hereinafter if is not specially mentioned, the data obtained by the DFT method (B3LYP/6-31G**) are discussed.

** Validity of this explanation could be verified by studying the TS containing benzyl halides with strong electron-withdrawing substituents in the benzene ring for which the electrostatic potential of the π-electron cloud is known[10] to decrease sharply.

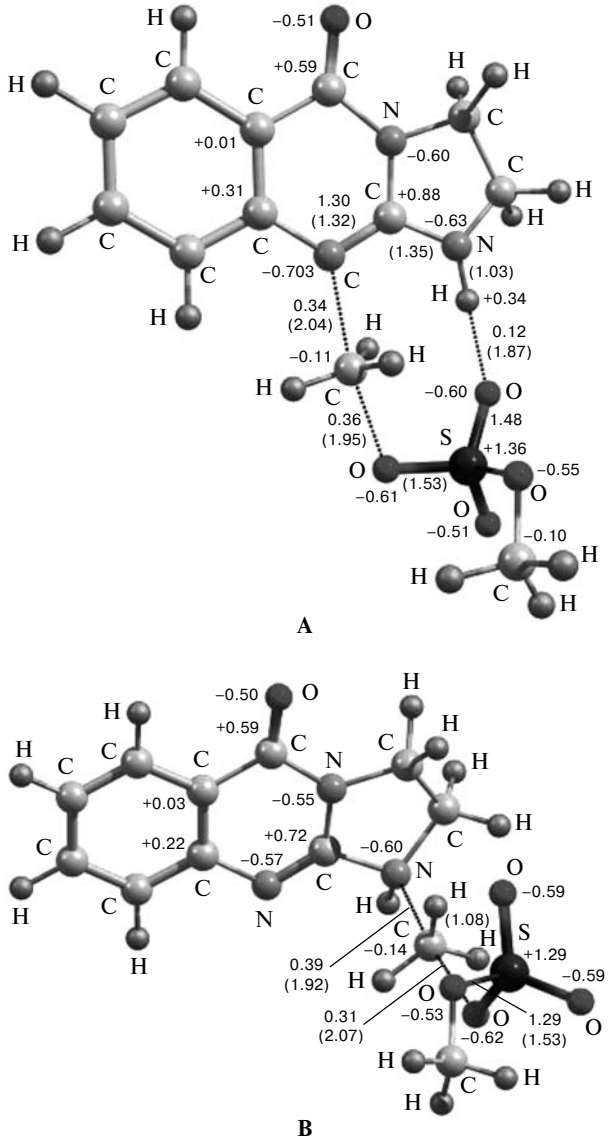


Fig. 2. Transition states **TS1** (**A**) and **TS2** (**B**) for the methylation of tautomer **1a** with dimethyl sulfate (B3LYP/6-31G**). Designations are the same as in Fig. 1.

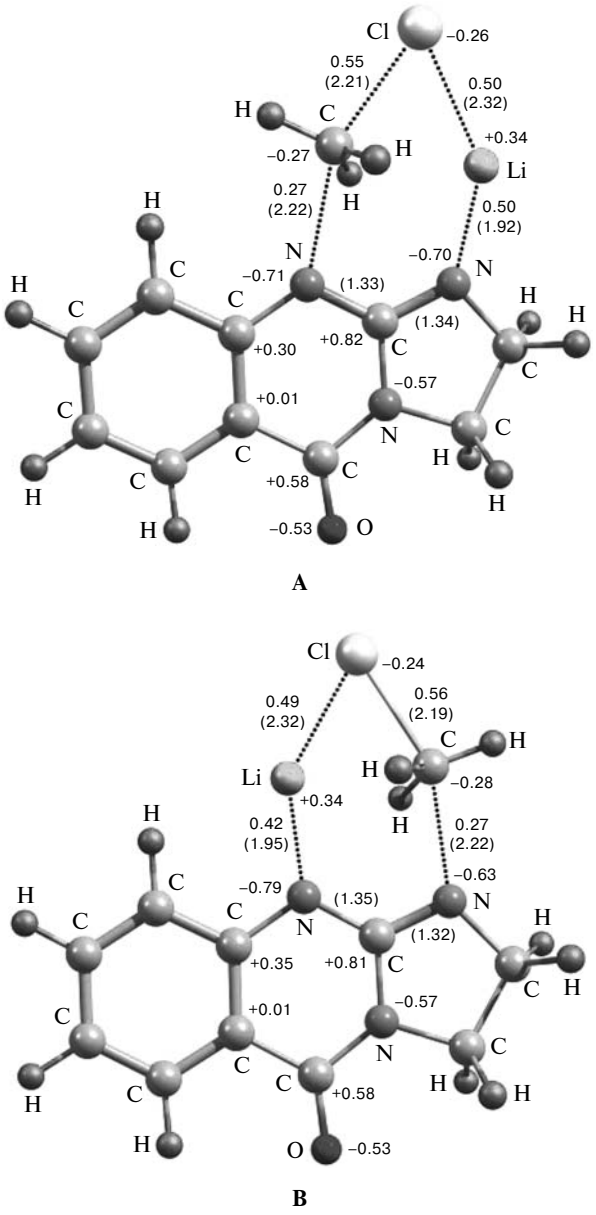


Fig. 3. Transition states **TS5** and **TS6** for the *N*-methylation of *N*-lithium-2,3-dihydroimidazo[2,1-*b*]quinazolin-5-one (Li-**1c**; **A** and **B**) with methyl chloride (B3LYP/6-31G**). Designations are the same as in Fig. 1.

methyl chloride. Their metal atom, regardless of its nature and direction of the electrophilic attack of the reactant, is always localized at the nitrogen atom adjacent to the electrophilic carbon atom of alkyl halide. In this case, the C—Cl bond of methyl chloride and the metal atom lie virtually in the plane of the heterocyclic framework of the *N*-anion. The obvious exception is only **TS6** (M = K) in which both MeCl and the K^+ ion lie substantially higher than the heterocycle plane due to steric repulsion of the bulky K^+ ion from the nearest H(9) hydrogen atom. The deformation of the reaction site in the metal-containing TS is also accompanied by a decrease in the N—C—Hal angles and caused by the shift of the negatively charged chlorine atom attracting to the metal cation. This deformation, unlike that observed in the TS of *N*-benzylation, manifests the attractive interaction (see Fig. 2). The degree of angular distortion of the N—C—Hal fragment is close to that detected in the TS of benzylation and depends on the metal nature, decreasing moderately with an increase in the size of its atom (see Table 1).

In the TS of alkylation under study, the central fragment CH_2R is also deformed, which appears as the shift of the carbon atom from the trigonal plane toward the nitrogen atom. The degree of distortion in all TS containing no metal increases, as a whole, with an increase in the

energy barriers of the reactions $\Delta E^{\neq}$. This effect is maximum in **TS2** (R = H, X = Cl, Br), whose C—H—H—R dihedral angle is about 20°. At the same time, in the low-energy **TS1**, **TS2** (R = H, X = OSO_3Me) and **TS5, TS6** (R = H) for the *N*-anion, which is characterized by the longest C—N bond (>2 Å), virtually no deformation is observed (see Table 1). Evidently, this type of distortions can be explained in the framework of the Hammond postulate determining the relationship of energetic of the reaction and geometry of its TS.[12]

For all the reactions under study, the DFT method gives substantially lower values of the internal energy barriers $\Delta E^{\neq}$ as compared to those found by the RHF method, which is a consequence of the much higher energy of electron correlation in the TS than in the starting reactants.

Going to considerations of the energetic of alkylation in the absence of solvation, note that in both tautomers the nitrogen atoms with non-conjugated LEPs are much more nucleophilic than those, whose LEPs are conjugated with the π-system (the difference in $\Delta E^{\neq}$ is ~10—15 kcal mol^{-1}; see Table 2). In this case, the *N*-alkylation of tautomers **1a,b** with halides MeCl, MeBr, and BnBr even to the most nucleophilic nitrogen atoms is a very slow reaction, approximately as the gas-phase methylation of ammonia with methyl chloride for which $\Delta E_{calc}^{\neq} \approx 32$—38 kcal mol^{-1} (see Refs 13—16); MeI and DMS are much more reactive in this case. As a whole, the reactivity of RCH_2X for the attack to both nucleophilic positions of tautomer **1a** changes in the order MeCl < MeBr ≈ $PhCH_2Br$ < MeI < < Me_2SO_4 in which the activation energy of substitution for the attack of the N(10) atom decreases from 31.8 to 15.0 kcal mol^{-1}. In this case, the reactivity of benzyl bromide is unexpectedly low, although this halide is usually more reactive than primary alkyl bromides. This is related, most likely, to the fact that steric factors created by a rather bulky (compared to MeBr) BnBr molecule unfavorably affect the energy of **TS1** and **TS2** and to the already mentioned angular distortion of the N—C—Br reaction site in these TS, which impedes overlapping of the p-orbital of the attacked carbon atom with AOs of the nitrogen and bromine atoms. This effect is absent in **TS1** and **TS2** in the reactions with MeBr. Note that the highest reactivity of DMS toward tautomer **1a** is partially due to the stabilization of **TS1** by the NH···O hydrogen bond, whose formation involves the N(1) nitrogen atom and one of the oxygen atoms of DMS (see Fig. 2, **A**).

Of the two tautomers of compound **1**, 10*H*-tautomer **1b** is more nucleophilic, and its $\Delta E^{\neq}$ for the attack by methyl chloride to the more reactive position 1 is ~28.3 kcal mol^{-1}. Since the formation of this tautomer from the main 1*H*-form **1a** requires a consumption of additional ~5.3 kcal mol^{-1} (see Table 2), the total energy expenses in this reaction route increase to 33.6 kcal mol^{-1}, which already exceeds noticeably an energy barrier of 31.8 kcal mol^{-1} for the most favorable (as it turned out) direct *N*-methylation at position 10 of although less reactive but predominant tautomeric form **1a**. The third principally possible reaction route involving the attack of the tetrahedral N(1) nitrogen atom in 1*H*-tautomeric form **1a** is not competitive in the gas phase ($\Delta E^{\neq}$ = 45.6 kcal mol^{-1}). Thus, the formation of the *N*(10)- (**2**) and *N*(1)-alkyl-substituted (**3**) derivatives as the main and secondary products, respectively, is most probable in the gas-phase *N*-alkylation of the molecular form of the substrate.

By contrast to electroneutral forms of the substrate **1a,b**, *N*-anion **1c** is characterized by close nucleophilicity of the N(1) and N(10) atoms and, being an isolated particle, is extremely reactive toward alkylating agents ($\Delta E^{\neq}$ for the reaction with MeCl is ~1 kcal mol^{-1}). This is explained, from the one hand, by a higher (as a whole) nucleophilicity of the *N*-anions compared to the corresponding molecular forms[17] and, on the other hand, by the absence of a counterion and a solvate shell (*cf.* Ref. 18). In "bare" *N*-anion **1c**, judging from the obtained data (see Table 2), the N(1) nitrogen atom is somewhat more nucleophilic than the N(10) atom (the corresponding $\Delta E^{\neq}$ values for methylation with MeCl are 0.9 and 2.8 kcal mol^{-1}).

In the presence of the contact counterion M^+, the nucleophilicity of *N*-anion **1c** decreases sharply, because the metal cation, as mentioned above, is localized, in this case, near the sites of electrophilic attack and impedes the interaction of the CIP with the alkylating agent. This effect appears quantitatively as an increase in the energy activation barriers $\Delta E^{\neq}$ for the attack of MeCl to each of the two nucleophilic nitrogen atoms of the CIP to values about 15 kcal mol^{-1}. The reactivity of the CIP, which depends moderately on the metal nature, increases in the order Li, Na, K in which $\Delta E^{\neq}$ ranges from 13.6 to 16.6 kcal mol^{-1}.

To the contrary of the free *N*-anion, the N(10) atom in its lithium and sodium salts is more nucleophilic, because the attack of methyl chloride at this atom is conjugated with the cleavage of a weaker M—N(10) bond and, hence, requires a lower (by 1.5 and 0.2 kcal mol^{-1}, respectively) activation energy $\Delta E^{\neq}$ than the attack at the N(1) atom. For the potassium salt (K-**1c**), this factor is not decisive because of low orders of the K—N bonds and their more ionic character, due to which this salt, as well as the free anion, should react preferentially at position 1 ($\Delta\Delta E^{\neq}_{(TS5,TS6)}$ for K-**1c** is −0.8 kcal mol^{-1}; see Table 2).

Thus, for the free *N*-anion and its CIP with the potassium cation, the N(1) atom should be a more reactive position, while an opposite ratio of nucleophilicities of the N(1) and N(10) atoms can be expected for the lithium and sodium salts.

On going from the gas phase to solutions, the *N*-alkylation of ammonia, according to available calculated data,

is extremely accelerated and becomes strongly exothermic due to the efficient solvation of the TS and cationic forms of the alkyl-substituted derivatives.[13—16] A similar influence of solvation should be predicted for the *N*-alkylation of tautomers **1a,b**, because the transition states of the S_N2 type **TS1**, **TS2**, and **TS4** have considerable dipole moments, and the starting reactants are low-polarity (see Table 1). The alkylation of free *N*-anion **1c**, by contrast, depends on the solvent to a considerably less extent, because here not only **TS5** and **TS6** but also *N*-anion **1c** are strongly solvated. These conclusions are confirmed by the calculation of the free activation energies $\Delta G^{\neq}$ of *N*-alkylation of the considered forms of the substrate in nitromethane. The polarized continuum model (PCM) and DFT/B3LYP method (Table 3) were used in the calculation. Although it is believed[16] that the PCM method somewhat underestimates the energy barriers of *N*-alkylation, the results obtained by this method can be used for qualitative and comparative estimations. It follows from the $\Delta G^{\neq}$ values presented in Table 3 (taking into account that $\Delta G^{\neq} > \Delta E^{\neq}$ in this case)[13] that all three possible processes of alkylation of tautomers **1a,b** (but not *N*-anion **1c**) are strongly accelerated indeed. Nevertheless, the most probable direction of *N*-methylation of the molecular form of **1** under these conditions remains to be the attack of the main tautomer **1a** to position 10. The *N*(1)-methylation of minor tautomer **1b** *via* the scheme **1a** → **1b** → **3a**, judging from the overall energy expenses, is less favorable (by ~1.9 kcal mol^{-1}). At the same time, unlike the gas phase, the attack of the main tautomer **1a** at the N(1) nitrogen atom can also be significant, because it demands only by 5.0 kcal mol^{-1} more energy than *N*(1)-substitution in the minor tautomer **1b** and by 6.9 kcal mol^{-1} more energy than in the main tautomer. This is explained by the maximum polarity of **TS2** (R = H, $\mu_{calc} \approx 14$ D; see Table 1), whose energy decreases upon solvation more strongly than in the case of other TS. As shown by the data in Table 3, a considerable increase in exothermicity of *N*-alkylation processes should be expected on going to solutions. In addition, note that a small difference in nucleophilicity of the N(1) and N(10) nitrogen atoms in free *N*-anion **1c** with an advantage for the N(1) atom is retained in solutions (see Table 3).

Table 3. Total free energies (G^{tot}) of the reactants, TS, and products and the free energies for the reaction in solution $\Delta G^{\neq}$ and ΔG° (PCM/B3LYP/6-31G**, $MeNO_2$, 25 °C)

Structure	R in RCH_2X	X	$-G^{tot}$ [a] (au)	$\Delta G^{\neq}$ (ΔG°) /kcal mol^{-1}
1a	—	—	625.448968	—
1b	—	—	625.440048	—
1c	—	—	624.962166	—
MeCl	—	—	499.966389	—
MeBr	—	—	2611.440130	—
MeI	—	—	6959.26773	—
Me_2SO_4	—	—	778.467981	—
BnBr	—	—	2842.257023	—
4	—	—	1125.442390	—
5	—	—	1125.405446	—
7	—	—	1125.450712	—
TS1	H	Cl	1125.390765	15.4 (−17.0)
	H	Br	3236.864904	15.2
	H	I	7584.701289	9.7
	Ph	Br	3467.684522	13.5
	H	OSO_3Me	1403.896651	12.7
TS2	H	Cl	1125.379783[b]	22.3 (6.2)
	H	Br	3236.854991[b]	21.4
TS4	H	Cl	1125.387723	11.7 (−27.8)
TS5	H	Cl	1124.916588	7.5
TS6	H	Cl	1124.917936	6.7

[a] Somewhat higher (by ~1.0—1.5 kcal mol^{-1}) $\Delta G^{\neq}$ values were obtained when nitromethane is replaced by methanol; if is not specially mentioned, the geometry of the structure calculated at the B3LYP/6-31G** level was used.

[b] Calculated using the TS geometry obtained by the MP2/6-31G** method.

Unlike the reactions of tautomers **1a,b**, the *N*-alkylation of CIP M-**1c** should become slower on going to solutions, because the starting ion pairs are much more polar than their **TS5** and **TS6** (see Table 1). However, this effect will not play, most likely, a substantial role, because the overall alkylation rate of *N*-anions in polar media depends mainly on the presence of solvate-separated ion pairs (SIP) and free *N*-anions, whose concentration under standard conditions of such reactions should be much higher than that of the CIP and, in addition, the reactivity of the SIP should be higher than that of the CIP. Taking into account the initially low difference in nucleophilicity of the N(1) and N(10) nitrogen atoms in *N*-anion **1c** and its ion pairs and the spatial separation of the anion and cation upon the transformation of CIP M-**1c** into the corresponding SIP, we can assume that the regioselectivities of the electrophilic attack of the SIP and free solvated *N*-anion are close. The contribution to alkylation of different types of ion pairs and the free *N*-anion should depend on the reaction conditions. According to literature data for the *O*- and *S*-anions, when the solution simultaneously contains dissociated anions and SIP, situations of alkylation of virtually only free *N*-anions are possible, whereas either SIP do not react,[19] or mainly only SIP react due to concentration predomination.[20]

Thus, it can be assumed that the *N*-alkylation of the molecular form of compound **1** in both the solution and gas phase has approximately the same regioselectivity, and similar reactions of *N*-anion **1c** in polar media proceed predominantly at the N(1) nitrogen atom regardless of the counterion nature.

The results of experimental studies of the alkylation of quinazolinone **1** confirm these conclusions. The action of both active alkylating agents (DMS, *p*-chlorobenzyl bro-

mide) and less reactive β-aryloxyethyl bromides in $MeNO_2$ or DMF on this compound affords mainly *N*(10)- (**2**) and (to a less extent) *N*(1)-substituted 2,3-dihydroimidazo[2,1-*b*]quinazolin-5-ones (**3**). Here the highest regioselectivity is observed for alkylation with DMS and β-aryloxyethyl bromides for which the content of 1-substituted compounds in a mixture of isomers does not exceed 10%. The *p*-chlorobenzylation of compound **1** with *p*-chlorobenzyl bromide is less selective. In $MeNO_2$ the reaction affords a mixture of 10- and 1-isomers **2c** and **3c** in a ratio of ~2 : 1, while under more drastic conditions (boiling DMF) this ratio is already ~1.5 : 1, which is related, most likely, to a decrease in the regioselectivity of the reaction because of the influence of the temperature factor.

Despite a low selectivity of alkylation, it can be used successfully for the preparation of 10-alkylquinozolinones **2**, which are considerably less soluble than their 1-isomers **3** and can be rather easily purified by recrystallization.

The β-aryloxyethylation or *p*-chlorobenzylation of compound **1** in DMF in the presence of NaH, when *N*-anion **1c** is subjected to alkylation, affords almost only 1-substituted derivatives **3a,c—e**.

The *N*-(*p*-chlorobenzylation) of the molecular form of compound **1** occurs rather nontrivial, with inversion of regioselectivity, in the absence of solvent at 140 °C and affords almost pure 1-(*p*-chlorobenzyl)imidazoquinazolinone **3c** in high yield (an admixture of 10-isomer **2c** is ~5%). We believe that this fact reflects the replacement of the reaction mechanism on going from the alkylation of substrate **1** to the alkylation of its H-bonded dimer $(\mathbf{1a})_2$. This is caused, most likely, by a low solubility of compound **1** in *p*-chlorobenzyl bromide and the involvement of only dimer $(\mathbf{1a})_2$ in the heterogeneous reaction, because the crystalline lattice of compound **1** is formed of this dimer.* In the dimer, the LEP of the N(10) atom is blocked by a hydrogen bond and, therefore, the reaction is directed to the N(1) nitrogen atom, which is free for the electrophilic attack. It is known[22] that ambident ions in media of solvents prone to hydrogen bonding are usually alkylated predominantly to less electronegative nucleophilic centers for an analogous reason. Under similar conditions, when β-phenyloxyethyl bromide is used as the reactant, a mixture of phenoxyethyl-substituted derivatives **2d** and **3d** is formed, which is enriched in 1-isomer **3d**, whose content, however, is only ~40% in this case. The lower yield of the *N*(1)-substitution product in this reaction is caused, most likely, by a higher solubility of quinazolinone **1** in β-phenoxyethyl bromide, due to which the process also proceeds to a substantial extent in the homogeneous regime.

Probably, molecular forms of the reactants act as alkylating agents toward dimer $(\mathbf{1a})_2$, although for *p*-chlorobenzylation we cannot exclude the participation of the *p*-chlorobenzyl cation in the reaction. Although the role of similar cations is usually insignificant in benzylation (for example, imidazole and pyridine react with BnBr *via* the S_N2 mechanism[11,23]), for substrates with a low reactivity this channel can be rather important or even the main (*cf.* Ref. 24). Also note that dimer $(\mathbf{1a})_2$, probably, takes some part in homogeneous alkylation, especially in concentrated solutions; however, under these conditions, the dimeric route of the reaction is evidently lowly competitive.

A possibility of the *N*-alkylation of the dimer was confirmed by the study of a $(\mathbf{1a})_2$—MeCl bimolecular system by the RHF/6-31G method, which made it possible to find **TS7** corresponding to the *N*(1)-methylation of associate $(\mathbf{1a})_2$ on the PES of this system (Fig. 4). As compared to free dimer $(\mathbf{1a})_2$, the dimeric fragment of this TS is considerably distorted, which appears as the loss of the planar symmetric structure and a considerable elongation of the N—H distance in the attacked NH group. The latter is expressed to such an extent that we can speak about the real migration of a proton in the TS to the opposite N(1) nitrogen atom of the second monomer. Evidently, the migration is caused by a comparatively high acidity of the N—H bond in compound **1a** and its further enhancement during TS formation. As a result of the transformation of the starting reactant—substrate complex in **TS7**, the dimer undergoes transformation into the tight ion pair $\mathbf{1c}\cdots\mathbf{1H}^+$ consisting of *N*-anion **1c**, at which the electrophilic attack of the reactant is directed, and the protonated form of the substrate $\mathbf{1H}^+$ (Scheme 2). The total charges on the cation, *N*-anion, and MeCl are +0.87, −0.70, and −0.18, respectively. Since the *N*-anionic

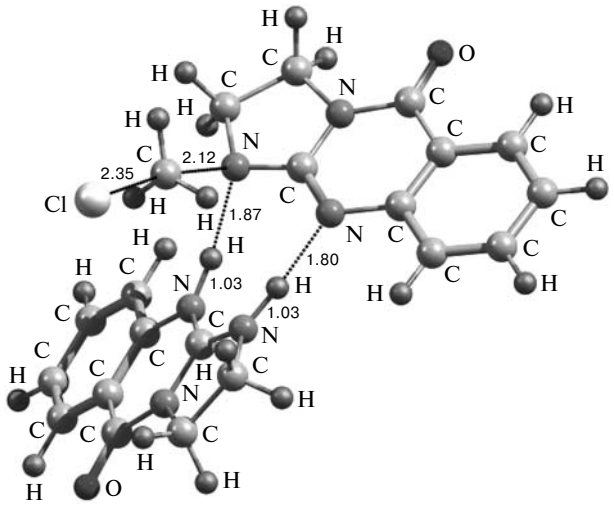
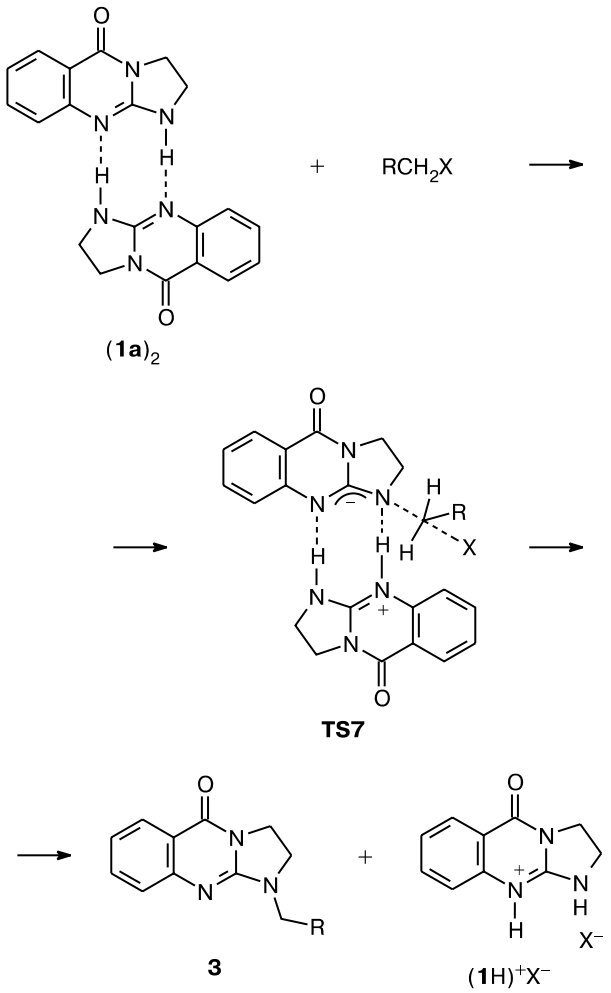


Fig. 4. Transition state **TS7** for the *N*-alkylation of dimer $(\mathbf{1a})_2$ with methyl chloride (RHF/6-31G); bond lengths are given in Å.

* It is known[21] that structurally close 1,2,3,4-tetrahydropyrimido[2,1-*b*]quinazolin-1(11)*H*-6-one exists in the crystalline state just as a dimer similar to $(\mathbf{1a})_2$.

form **1c** is much more reactive than the molecular form, the electrophilic attack at the sp^3-N(1) nitrogen atom is strongly facilitated.

Scheme 2



The data presented suggest the autocatalytic effect, which is exerted by the second molecule of **1a** in the dimer, and the reaction itself by its mechanism can be classified as cryptoanionic *N*-alkylation. The catalytic influence of the second molecule of the monomer can be illustrated by the calculated values of the energy barriers $\Delta E^{\neq}$ (RHF/6-31G) for the gas-phase *N*(1)-methylation of tautomer **1a** with methyl chloride *via* the scheme with the intermediate formation of the dimer (28.3 kcal mol^{-1}) and by the direct methylation (39.6 kcal mol^{-1}). Therefore, it is not surprising that in **TS7**, as in other low-energy transition states of *N*-alkylation, the C—N bond is considerably elongated (~2.12 Å).

It should be mentioned that activation processes of weak nucleophiles similar to that described above for the molecular form of compound **1** can form a basis for the mechanism of catalytic effect of alkyltransferases, *viz.*, enzymes providing the transfer of alkyl groups between biochemical substrates, which usually proceeds *via* the scheme of S_N2-substitution.[25,26] To the present time, the detailed mechanism of functioning of transferases remains to be poorly studied, and a possibility of the cryptoanionic reaction route is not revealed yet. However, the quantum chemical study of the biochemical *N*-methylation of glycine and guanidylacetic acid (GAA)[25—28] by the simulation of the reaction site of the reacting system showed that in the TS of the enzymatic reactions the alkylating NH group of the substrate forms the N—H···O hydrogen bond with the oxygen atom of the enzyme. It was also demonstrated[27,28] that this bond forms no $N^-\cdots H—X^+$ ion pair in the TS, as in the case of dimer $(\mathbf{1a})_2$, because of the insufficient basicity of the oxygen atom and acidity of the NH group; nevertheless, it provides a noticeable decrease in the energy barrier of the transfer of the methyl group. According to data of the quantum chemical simulation, the elongation of the N—H bond of GAA upon the transformation of the starting ternary substrate—reactant—enzyme complex into the TS, unlike the $(\mathbf{1a})_2$—MeCl system, is relatively small, being only ~0.02 Å.[28] However, although this TS retains the N—H bond, the *N*-methylation of GAA with adenosylmethionine, which is the last step of the biosynthesis of creatine, is also accompanied by the deprotonation of the attacked NH fragment but only after the system has passed through the TS.[28] Therefore, the formation of the TS and deprotonation proceed although *via* the concerted mechanism but asynchronically.

Thus, the $(\mathbf{1a})_2$—MeCl system can be considered as a simple model that clearly illustrates the principal possibility of functioning of alkyltransferases *via* the cryptoanionic mechanism as applied to substrates with a sufficiently high acidity of the alkylating NH fragment. The most obvious biochemical target of cryptoanionic *N*-alkylation could be the amide-type NH groups containing a mobile proton in the composition of peptides and proteins.

* * *

The present study indicates sufficient adequacy and prospects of the modern quantum chemical methods for studies of *N*-alkylation reactions in the series of nitrogen-containing heterocycles. The further use of these methods will unambiguously serve for considerably deeper insight into fine but substantial details of the processes occurring in molecular systems during these practically significant transformations and, in particular, it should provide more clear understanding of mechanisms of the catalytic action of different alkyltransferases.

Table 4. Physicochemical properties of *N*-alkylquinazolinones **2c—e** and **3a,c—e**

Compound	M.p./°C (solvent)	^{1}H NMR ($CDCl_3$), δ (*J*/Hz)							
		H(2) (1 H)	H(3) (1 H)	H(6) (1 H)	H(7) (1 H)	H(8) (1 H)	H(9) (1 H)	NCH_2R (2 H)	Other protons
2c	226—228[1] (MeCN)	3.93—4.00 (m)	4.18—4.23 (m)	8.10 (dd, *J* = 7.8, *J* = 1.7)	7.09 (td, *J* = 7.5, *J* = 0.9)	7.43 (t, *J* = 7.5)	6.83 (d, *J* = 8.3)	5.26 (s)	7.19—7.33 (m, 4 H, H arom.)
2d	191—193 (MeOH)	3.94 (t, *J* = 9.1)	4.13 (t, *J* = 9.0)	8.09 (dd, *J* = 7.9, *J* = 1.6)	7.11 (t, *J* = 7.3)	7.57 (t, *J* = 7.9)	7.35 (d, *J* = 8.2)	4.34 (t, *J* = 5.5)	4.46 (t, 2 H, OCH_2, *J* = 5.5); 6.84 (d, 2 H, *o*-H arom., *J* = 7.9); 6.94 (t, 2 H, *p*-H arom., *J* = 7.5); 7.24 (t, 2 H, *m*-H arom., *J* = 7.9)
2e	218.5—220.5 (EtOH—DMF)	3.89—4.00 (m)	4.10—4.19 (m)	8.10 (dd, *J* = 7.9, *J* = 1.8)	7.12 (td, *J* = 7.5, *J* = 1.0)	7.58 (t, *J* = 7.9)	7.31 (d, *J* = 7.9)	4.30 (t, *J* = 5.6)	4.45 (t, 2 H, OCH_2, *J* = 5.7); 6.72 (d, 2 H, *o*-H arom., *J* = 9.0); 7.34 (d, 2 H, *m*-H arom., *J* = 9.0)
3a	172.5—174.0 (i-C_8H_{18}—Pr^iOH)	3.68 (t, *J* = 8.3)	4.17 (t, *J* = 8.3)	8.12 (dd, *J* = 7.9, *J* = 1.2)	7.16 (td, *J* = 7.6, *J* = 1.2)	7.57 (td, *J* = 7.7, *J* = 1.7)	7.38 (t, *J* = 8.2)	3.08* (s)	—
3c	141—142 (MeCN)	3.53 (t, *J* = 8.3)	4.15 (t, *J* = 8.3)	8.13 (dd, *J* = 8.0, *J* = 1.6)	7.19 (t, *J* = 7.7)	7.59 (t, *J* = 7.7)	7.41 (d, *J* = 8.0)	4.65 (s)	7.28—7.38 (m, 4 H, H arom.)
3d	125—126 (i-C_8H_{18}—Pr^iOH)	3.91 (t, *J* = 8.6)	4.16 (t, *J* = 8.6)	8.12 (d, *J* = 8.0)	7.17 (td, *J* = 8.0, *J* = 1.1)	7.57 (td, *J* = 7.6, *J* = 1.8)	7.37 (d, *J* = 8.1)	3.91 (t, *J* = 5.0)	4.28 (t, 2 H, OCH_2, *J* = 5.0); 6.91 (d, 2 H, *o*-H arom., *J* = 7.7); 6.97 (t, H, *p*-H arom., *J* = 7.5); 7.29 (t, 2 H, *m*-H arom., *J* = 7.5)
3e	179—180.5 (i-C_8H_{18}—Pr^iOH)	3.89 (t, *J* = 8.2)	4.19 (t, *J* = 8.8)	8.12 (dd, *J* = 7.9, *J* = 1.2)	7.17 (td, *J* = 7.5, *J* = 1.3)	7.58 (td, *J* = 7.6, *J* = 1.6)	7.36 (d, *J* = 7.6)	3.90 (t, *J* = 5.2)	4.24 (t, 2 H, OCH_2, *J* = 5.7); 6.80 (d, 2 H, *o*-H arom., *J* = 9.1); 7.39 (d, 2 H, *m*-H arom., *J* = 8.9)

* Signals from protons of the NMe group.

Experimental

^{1}H NMR spectra were recorded on a Varian Unity-300 instrument (300 MHz) in the regime of internal stabilization of the polar-resonance line of ^{2}H of the deuterated solvent.

The ratio of isomers during alkylation was determined by the ^{1}H NMR method. Authentic samples of 10-methyl- (**2a**) and 10-(*p*-chlorobenzyl)-substituted (**2c**) derivatives were synthesized by ring closure of the corresponding *N*-substituted isatoic anhydrides with 4,5-dihydro-2-methylthioimidazole.[1] 1-Methyl-substituted isomer **3a** was synthesized by analogy to the preparation of other 1-substituted derivatives of compound **1** (see Ref. 1). The physicochemical properties of all newly synthesized compounds are presented in Table 4. The energies of molecules were calculated, the TS structure was optimized, and calculations by the method of internal reaction coordinate were performed using the PC GAMESS (6.4) version* of the GAMESS quantum chemical program package (US).[29] In the calculation of iodine-containing structures for the iodine atom, the intrinsic 6-311G* basis set was used in all cases.[30] Stationary points on the PES were identified as TS on the basis of the presence of the imaginary vibrational mode in the calculation by the DFT/B3LYP/6-31G** method (except for **TS7**), and the corresponding reactions were identified using the study of the reaction route in both directions from the TS. In this case, the RHF/6-31G method was used because of voluminous calculations. Since it is difficult to optimize the TS in solutions, non-relaxed structures of TS and reactants obtained for the isolated molecules were applied in the calculations by the PCM model. The values of effective charges on atoms and bond orders calculated according to Mulliken were used in discussion. All values of total energies and their changes were determined with corrections to the zero-point vibrational energy (ZPE). In these calculations we used the scaling coefficient values presented in Ref. 31.

1-Methyl-2,3-dihydroimidazo[2,1-*b*]quinazolin-5-one (3a). Sodium hydride (0.25 g, 11 mmol) (from 0.42 g of a 60% suspension of NaH in Nujol) was added by portions with stirring for

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

10 min to a suspension of quinazolinone **1** (1.87 g, 10 mmol) in anhydrous DMF (30 mL), and then a solution of DMS (0.95 mL, 10 mmol) in DMF (2 mL) was added. The mixture was stored for 30 min at 25 °C and cooled. Water (100 mL) was added, and methyl-substituted derivative **3a** was filtered off. The yield was 1.45 g (78%). Found (%): C, 65.93; H, 5.64; N, 20.75. $C_{11}H_{11}N_3O$. Calculated (%): C, 65.66; H, 5.51; N, 20.88.

Methylation of 2,3-dihydroimidazo[2,1-*b*]quinazolin-1(10)*H*-5-one (1). A solution of quinazolinone **1** (1.87 g, 10 mmol) and DMS (0.95 mL, 10 mmol) in $MeNO_2$ (20 mL) were refluxed for 12 h. After the solvent was distilled off, the residue of salts of compounds **2a** and **3a** was treated with a 10% solution of NH_4OH, and the precipitate was filtered off. The yield of a mixture of *N*-methyl-substituted derivatives **2a** and **3a** was 1.85 g (92%), and the ratio of isomers was **2a** : **3a** = 13 : 1. After double recrystallization from ethyl acetate, the yield of 10-methyl-substituted isomer **2a** was 1.5 g (75%), m.p. 214—215 °C.[1] A sample of **2a** mixed with the authentic sample melts without depression.

p*-Chlorobenzylation of quinazolinone 1.** ***A. A solution of compound **1** (1.87 g, 10 mmol) and *p*-chlorobenzyl bromide (2.05 g, 10 mmol) in $MeNO_2$ (25 mL) was refluxed for 14 h. The solvent was evaporated, the residue was treated with a 10% solution of NH_4OH, and a mixture of *p*-chlorobenzyl-substituted derivatives **2c** and **3c** was separated from an admixture of the starting quinazolinone **1** by chromatography on a column with Al_2O_3 (eluent $CHCl_3$), collecting the fraction with R_f 0.4. The yield of a mixture of the isomers was 2.1 g (67%); ratio **2c** : **3c** ≈ 2 : 1.

B. A solution of compound **1** (1.87 g, 10 mmol) and *p*-chlorobenzyl bromide (2.05 g, 10 mmol) in DMF (100 mL) was refluxed for 3 h, and a mixture of 10- and 1-*p*-chlorobenzyl-substituted derivatives **2c** and **3c** in a ratio of ~1.5 : 1 (0.8 g, 25%) was isolated by a standard procedure.

C. A mixture of quinazolinone **1** (1.87 g, 10 mmol) and *p*-chlorobenzyl bromide (2.05 g, 10 mmol) were melted together for 1 h at 140 °C. After cooling, the resulting melt was triturated with Et_2O (20 mL), a precipitate of hydrobromides of compounds **2c** and **3c** was filtered off, and 1-substituted derivative **3c** (2.6 g, 84%) was isolated as described for entry ***A***; an admixture of 10-isomer **2c** was 5%. After recrystallization from a $Pr^iOH—C_6H_{14}$ (1 : 10) mixture, the yield of 1-(*p*-chlorobenzyl)quinazolone **3c** was 2.0 g (65%). Found (%): C, 65.43; H, 4.77; N, 14.04. $C_{17}H_{14}ClN_3O$. Calculated (%): C, 65.49; H, 5.30; N, 13.48.

D. Sodium hydride (0.25 g, 11 mmol) (from 0.42 g of a 60% suspension of NaH in Nujol) was added by portions with stirring for 10 min to a suspension of quinazolinone **1** (1.87 g, 10 mmol) in anhydrous DMF (30 mL), and then *p*-chlorobenzyl bromide (2.05 g, 10 mmol) was added. The mixture was stored for 30 min at 25 °C and for 15 min at 40 °C, cooled, and treated with water (100 mL). A precipitate of 1-(*p*-chlorobenzyl)quinazolinone **3c** was filtered off. The yield was 2.6 g (84%). A sample of **3c** mixed with the sample obtained in entry ***C*** shows no depression of the melting point.

β-Phenoxyethylation of quinazolinone 1. ***A.*** A solution of quinazolinone **1** (1.87 g, 10 mmol) and β-phenoxyethyl bromide (2.05 g, 10 mmol) in $MeNO_2$ (25 mL) was refluxed for 14 h. A mixture of isomers **2d** and **3d** was isolated as in the case of *p*-chlorobenzyl bromide in entry ***A***. The yield was 2.06 g (67%). The ratio was **2d** : **3d** ≈ 12 : 1. After recrystallization from methanol, pure 10-substituted isomer **2d** was obtained. Found (%): C, 69.89; H, 5.87; N, 14.02. $C_{18}H_{17}N_3O_2$. Calculated (%): C, 70.34; H, 5.58; N, 13.67.

B. The reaction without solvent was carried out as a similar process with *p*-chlorobenzyl bromide (entry ***C***) but at 150 °C. The yield of a mixture of **2d** and **3d** was 68%, and the ratio was **2d** : **3d** ≈ 1.5 : 1.

C. The reaction in the presence of NaH was carried out as described above for a similar process involving *p*-chlorobenzyl bromide (entry ***D***). The yield of 1-(β-phenoxyethyl)-substituted derivative **3d** after recrystallization from an i-$C_8H_{18}—Pr^iOH$ (10 : 1) mixture was 73%. Found (%): C, 70.00; H, 5.74; N, 13.73. $C_{18}H_{17}N_3O_2$. Calculated (%): C, 70.34; H, 5.58; N,13.67.

10-[β-(4-Bromophenoxy)ethyl]-2,3-dihydroimidazo[2,1-*b*]quinazolin-5-one (2e) was synthesized from quinazolinone **1** and β-(4-bromophenoxy)ethyl bromide by refluxing in $MeNO_2$ similarly to methyl-substituted derivative **2a** in 74% yield. Found (%): C, 55.56; H, 4.02; Br, 20.89. $C_{18}H_{16}BrN_3O_2$. Calculated (%): C, 55.97; H, 4.18; Br, 20.69.

1-[β-(4-Bromophenoxy)ethyl]-2,3-dihydroimidazo[2,1-*b*]quinazolin-5-one (3e) was synthesized from quinazolinone **1** and β-(4-bromophenoxy)ethyl bromide in DMF in the presence of NaH similarly to derivative **3c** in 82% yield. Found (%): C, 56.07; H, 3.91; Br, 20.77. $C_{18}H_{16}BrN_3O_2$. Calculated (%): C, 55.97; H, 4.18; Br, 20.69.

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