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QUANTUM CHEMICAL INVESTIGATION OF THE EFFECT OF CATION SIZE ON THE COURSE OF THE METHYLATION OF 2,4-DIOXOQUINAZOLINE SALTS

M. A. Ashirmatov, B. A. Urakov, and Kh. M. Shakhidoyatov

The effect of cation size on the dual reactivity of the lithium, sodium, and potassium salts of 2,4-dioxoquinazolines in liquid and solid phase methylation reactions has been studied. The results obtained were confirmed by data of quantum chemical calculations and IR spectroscopy.

It is known that compounds containing the grouping $-CH_2-C{=}X$, $-NH-C{=}X$ (X=O, S, NH), etc. display dual (multiple) reactivity in electrophilic substitution reactions [1-3]. The nature of the counter ion and the leaving group, the effect of the medium, and the electronic properties of the substituents prove to exert a significant influence on this. There are literature data on the qualitative composition and quantitative ratio of the methylation products of heterocyclic amides and thioamides [4, 5], however, the role of any particular nucleophilic center in alkylation reactions was not discussed.

Results are given in the present paper of our model investigations on the reactivity of 2,4-dioxoquinazoline (DOQ) salts in methylation reactions. We conducted the methylation of salts of 2,4-dioxoquinazoline in liquid and solid phases to clarify the effect of the nature of the counter ion on the course of the reaction. Reactions were carried out in dimethylformamide solution (concentration 0.6 M), where the substrate interacted with the electrophilic reagent and acted as a contract ion pair. Methyl iodide and dimethyl sulfate were used as alkylating agents. If the solvation effect is neglected, the mechanism of reaction of ion pairs with the electrophile must be identical in the liquid and solid phases. Consequently, salts of 2,4-dioxoquinazoline in the solid phase may be modeled by contact ion pairs.

Reaction was carried out in the solid phase by maintaining a dry substrate sample in an atmosphere of methyl iodide or dimethyl sulfate. As is seen from Table 1, the yield of product methylated at the N^1 atom increases as the size of the cation increases. The reduction in yield of product methylated at the N^1 atom in the liquid phase compared to solid is probably explained by solvation and subsequent partial ionization of the reaction centers of the substrate by solvent molecules. Salts of 2,4-dioxoquinazoline are not methylated in the solid state by methyl iodide. This is linked in all probability with the relatively weak electrophilicity of methyl iodide.

There are several studies in the literature devoted to the study of the effect of the counter ion on the dual reactivity of ambident anions using rhodanines, acetoacetic esters, and pyrroles as examples [1, 6, 7]. However there are no data on the action of the nature of the counter ion on the direction of the reaction under heterophase conditions. We have carried out quantum chemical calculations by the MNDO method [8] to explain the influence of the counter ion on the reactivity of 2,4-dioxoquinazoline salts and to analyze the possible mechanism of the process in the gas phase.

As mentioned above, the reactivity of polydentate anions is determined by many factors. Calculation of the quantitative contribution of each factor is very complex. In this work we have attempted to separate out and to assess quantitatively the role of only one factor, viz. the influence of the nature of the counter ion on the direction of the methylation of 2,4-dioxoquinazoline. In the absence of other factors linked with the properties of the medium (nature of the solvent) and with structural and other factors (temperature, concentration, characteristics of the alkylating agent, etc.) remaining constant, the reaction begins with the formation of a complex by coordination of the quinazolone anion with the metal cation.

When modeling the influence of the nature of the counter ion on the reaction direction of salts of 2,4-dioxoquinazoline in the gaseous state, it is possible to use known structural data [9], putting into effect a procedure for complete optimization

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TABLE 1. Dependence of the Ratio of Isomeric Methylation Products of 2,4-Dioxoquinazoline Salts on the Nature of the Cation and the Alkylating Agent

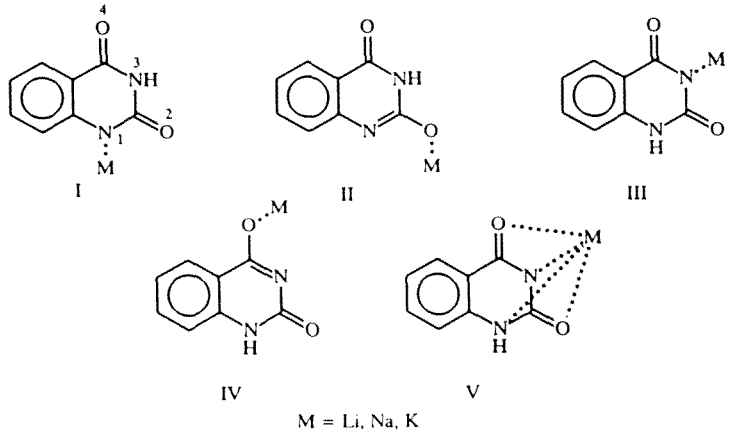
Cation	Alkylating agent	Isomer composition, %			
		liquid phase		solid phase	
		N^1	N^3	N^1	N^3
Li^+	CH_3I	6	94	—	—
	$(CH_3O)_2SO_2$	13	87	25	75
Na^+	CH_3I	18	82	—	—
	$(CH_3O)_2SO_2$	26	74	40	60
K^+	CH_3I	28	72	—	—
	$(CH_3O)_2SO_2$	42	58	50	50

TABLE 2. Enthalpies of Formation and Charges on the Atoms of 2,4-Dioxoquinazoline Salts Calculated by the MNDO Method

Compound	M	ΔH_f, kcal/mole	N^1	O^2	N^3	O^4	H^1	H^3	M
DOQ	—	-53,1	-0,35	-0,37	-0,41	-0,33	0,22	0,22	—
Anion	—	-85,1	-0,38	-0,47	-0,51	-0,45	0,16	—	—
I	Li	-79,1	-0,48	-0,45	-0,35	—	—	0,21	0,56
	Na	-98,4	-0,47	-0,44	-0,39	-0,36	—	0,21	0,58
	K	-145,8	-0,51	-0,38	-0,39	-0,37	—	0,20	0,58
II	Li	-66,4	-0,42	-0,52	-0,40	-0,38	—	0,20	0,66
	Na	-98,4	-0,47	-0,44	-0,39	-0,36	—	0,21	0,58
	K	-145,8	-0,51	-0,38	-0,40	-0,37	—	0,20	0,58
III	Li	-74,7	-0,33	-0,45	-0,53	-0,37	0,21	—	0,56
	Na	-94,5	-0,36	-0,41	-0,51	-0,41	0,20	—	0,56
	K	-135,6	-0,34	-0,38	-0,50	-0,36	0,20	—	0,51
IV	Li	-77,1	-0,36	-0,40	-0,53	-0,42	0,20	—	0,56
	Na	-94,5	-0,36	-0,41	-0,52	-0,41	0,19	—	0,57
	K	-135,6	-0,34	-0,38	-0,50	-0,35	0,20	—	0.51
V	Li	-34,8	-0,40	-0,37	-0,47	-0,35	0,10	—	0,60
	Na	-89,8	-0,39	-0,38	-0,47	-0,37	0,19	—	0,58
	K	-169,2	-0,38	-0,38	-0,38	-0,45	0,38	—	0,57

of the geometry by the MNDO method. Several variants were considered for the structures of complexes of the 2,4-dioxoquinazoline anion (DOQ^N) with a metal cation (M^+) depending on its orientation in relation to the reactive nucleophilic centers at N^1, O^2, N^3, and O^4. The cation M^+ was located both in the plane of the molecule (I)-(IV) and above it (V), coordinating with all the heteroatoms in the latter case.

According to the calculated data (Table 2) the N^3-H bond is more polarized than N^1-H in the ground state of the molecule. Consequently the proton of the N^3-H bond must be more easily and more rapidly subject to replacement by the metal cation, which was confirmed experimentally by studying the acid–base properties of 2,4-dioxoquinazoline derivatives [10].

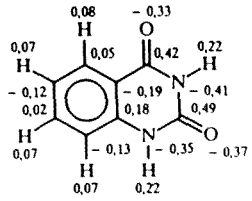


I II III

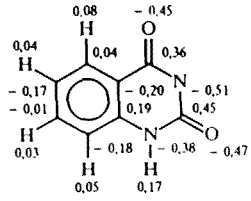
IV V

M = Li, Na, K

It may therefore be proposed that the structure in which the H at N^3 is replaced by M is the most probable. This is also indicated by the IR spectra of 2,4-dioxoquinazoline salts from which the absorption bands at 3200 cm^{-1} characteristic of the N^3-H group have disappeared. Calculation shows that 2,4-dioxoquinazoline anion (DOQ^-) displays a polydentate character indicated by the significant concentration of additional negative charge on all the reaction centers N^1, O^2, N^3, and O_4.



DOQ



DOQ^-

We now consider the possible changes in electronic structure of the systems being investigated as a function of the nature of the metal ion. In the case of the lithium salt of 2,4-dioxoquinazoline, the lithium ion is coordinated preferentially with the N^1 atom [structure (I) with a Li^+-DOQ^- ion pair is more stable than (II) by ~0.6 eV, than (III) by ~0.2 eV, than (IV) by ~0.1 eV, and than (V) by ~1.9 eV]. However the experimental data indicate a lower probability for the coordination of Li^+ at N^1 than at O^4. Disappearance from the IR spectra of 2,4-dioxoquinazoline lithium salt of absorption bands for the $C^4{=}O$ carbonyl group at 1715 cm^{-1} and the appearance of a new peak near 1550 cm^{-1}, corresponding to a carbonyl group in a chelated compound, indicates binding of the Li^+ ion with O^4 and N^3 atoms. The diffuse and split absorption bands with single maxima near 3200-3300 cm^{-1} are caused by the presence of the intermolecular hydrogen bond of the NH group.

The intermolecular interactions therefore exclude the possibility of forming an ion pair. Evidently this very circumstance also hinders substitution of the proton at N^1 by lithium cation to a larger extent than at N^3. Since the quantum chemical calculations were carried out for the free ion pair in which intermolecular forces are not acting, it is entirely possible that in such a state coordination of Li^+ cation at N^1 is the most favorable, but in other cases when it is impossible to disregard the surroundings O^4 is favored (as proved experimentally). The low stability of structures (II) and (V) was confirmed by data of IR spectra which exclude the coordination of lithium cation with DOQ^- anion outside the plane of the molecule and at the oxygen atom of the $C^2{=}O$ group (absorption bands at 1660-1665 cm^{-1} corresponding to the $C^2{=}O$ bond did not disappear).

The electron density distribution and the sizes of the energy characteristics for the sodium and potassium salts of 2,4-dioxoquinazoline show that the metal ion is capable of coordination with the two nucleophilic centers at O^2 and N^1 (Table 2), possibly being located symmetrically between them, which is favored by the volumes of the K^+ and Na^+ cations being larger than Li^+.

In reality the structure most probable for the sodium salt is that in which the sodium ion is coordinated with the O^4 and N^3 atoms. This is indicated by the IR spectra in which the absorption band for the $C^4{=}O$ group is shifted to lower frequency by 160-165 cm^{-1} and the band for $C^2{=}O$ by 20-25 cm^{-1}. Other variants, such as location of the sodium ion on an axis perpendicular to the plane of the anion, are not excluded.

According to the MNDO calculations the K^+ ion in the potassium salt of 2,4-dioxoquinazoline must be located above the plane of the anion (somewhat closer to N^3 and O^4 than to N^1 and O^2) since structure (V) is the most stable compared to the others (I)-(IV). In this the potassium ion is coordinated with all the reaction centers of the polydentate anion, raising their electron density significantly. It is seen from Table 2 that the additional electron density is localized to a greater extent on the O^4 atom than on N^1 and O^2.

On interacting the potassium salt of 2,4-dioxoquinazoline with alkylating agents, the leaving group is linked with the potassium ion and the electrophilic residue, with all the nucleophilic centers having high basicity in relation to proton. The yield of methylation products is therefore determined primarily by the basicity of the reaction center. Since the basicity of nitrogen atoms is greater than oxygen, the reaction proceeds at a nitrogen atom.

The experimental data show that the yield of product methylated at N^3 is low. This is linked with the close proximity of the potassium ion to N^3, i.e. this center is shielded. On carrying out the reaction in the liquid or solid phase the yield of methylation products at reaction centers N^3 and N^1 are balanced. Similarly, on attack of the lithium salt of 2,4-dioxoquinazoline by alkylating agent, its leaving group interacts with the lithium ion but the electrophilic residue is directed towards the reaction center having the greatest electron density and basicity relative to proton. As a result the product methylated at N^3 is formed preferentially.

According to the calculated data the lithium ion of the lithium salt of 2,4-dioxoquinazoline is bonded with the N^1 atom in the gaseous phase and with O^4 in the liquid and solid phases. The electrophile attacks the N^3 atom forming the product methylated at N^3 predominantly. The sodium and potassium cations may be coordinated symmetrically with the O^4 and N^3 atoms. The more preferred structure for the potassium ion is that in which it interacts with all the nucleophilic centers. In the case of the potassium ion the electrophilic agent adds to the N^3 and N^1 atoms forming methylation products. Due to partial shielding of the N^3 reaction center, the yield of both alkyl substituted derivatives is balanced. The yield of methylation product at the N^1 reaction center increases with an increase in cation size. Methylation of 2,4-dioxoquinazoline salts with the participation of ion pairs, irrespective of the aggregate state of the substrate or alkylating agent, proceeds at two reaction centers, viz. the nitrogen atoms in positions 1 and 3.

EXPERIMENTAL

The IR spectra were taken on a UR 20 spectrometer in KBr disks and on an UR 29 instrument in solution. The PMR spectra were taken on an INM 4H 100 instrument (solvent CF_3COOH, internal standard TMS). Silufol UV 254 plates were used for TLC. The system was chloroform–methanol (5:1).

1-Methyl-2,4-dioxoquinazoline was obtained by the reaction of N-methylanthranilic acid with potassium cyanate in the presence of acetic acid [11]. Yield was 48%, mp ~230°C (water–alcohol). PMR spectrum (CF_3COOH): 3.65 (3H, s), 7.1-7.6 ppm (4H, m).

3-Methyl-2,4-dioxoquinazoline was obtained by the methylation of 2,4-dioxoquinazoline and subsequent separation of it from the isomeric 1-methyl-2,4-dioxoquinazoline on a column. Yield was 16%, mp 218-219°C (alcohol). PMR spectrum (CF_3COOH): 3.33 (3H, s), 7.0-7.7 ppm (4H, m).

Methylation Reaction in the Liquid Phase. The metal hydride (0.01 mole) was added to a solution of 2,4-dioxoquinazoline (1.62 g, 0.01 mole) and the mixture stirred for 20 min at room temperature. The methylating agent (0.01 mole) was then added dropwise and the mixture stirred for 4 h. At the end of the reaction the solvent was distilled off in vacuum and the mixture of alkylated products was analyzed by TLC and PMR spectroscopy.

Methylation Reaction in the Solid Phase. A weighed sample of salt (0.2 g) was maintained in an atmosphere of dimethyl sulfate or methyl iodide in a vacuum desiccator for 24 h. The reaction mixture was then analyzed by TLC with reference samples and by PMR spectroscopy.

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