Photoinduced bimolecular cyclization of diarylamines with polyhalomethanes into acridines

4.* A comparison of the reactivity of different intermediates at intermediate reaction stages

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It is shown on the basis of measurements of the activation parameters for the reaction of nucleophilic substitution, an intermediate stage of photochemical reactions, that the entropy factor makes the main contribution to the decrease in the reactivities of the intermediates that occurs on going from $CHBr_3$ to CBr_4. The low efficiency of *N*-alkyl-substituted diarylamines in these photochemical transformations is explained by taking into consideration another intermediate stage (cyclization) and by quantum chemical modeling of the preceding isomerization.

Key words: diarylamine; tetrabromomethane; bromoform; acridine; diarylaminoacridine; photoinduced synthesis; nucleophilic substitution; MNDO; *cis*—*trans*-isomerization.

A mechanism for the photoinduced formation of diarylaminoacridines (**2**) in the reactions of diarylamines (**Am**) with CBr_4 has been suggested previously.[1] A comparison of the results of these studies with the data[2] obtained from studying the photoinitiated reaction of **Am** with $CHBr_3$, which results in the formation of acridines (**1**) not substituted at position 9, has shown that in both cases the reaction occurs according to the same scheme to form intermediates **In** with structures **In1** and **In2** (Scheme 1). It has also been found that in the reaction with $CHBr_3$, the reaction of **In1x** with **Am** (nucleophilic substitution stage) is rather fast and the rate of the whole process is limited[2] by the cyclization of **In2x**. In the reaction with CBr_4, the ratio of the rates of the last two stages is reversed, and nucleophilic substitution becomes the rate-determining step.[1]

In this work, the reasons for the fact that the reactivity of **In1y** in the photochemical reaction of **Am** with CBr_4 is lower than that of **In1x** in the reaction with $CHBr_3$ are studied. Two amines are studied: di-*p*-tolylamine (DTA), which forms **In1a** and di-(*p*-cumylphenyl)amine (DCPA), which forms **In1b**.

The second question discussed is related to a comparison of two mechanisms of photoinduced bimolecular cyclization. According to Scheme 1 previously suggested,[1,2] the recombination of the primary radicals occurs with the participation of the nitrogen atom of the radical cation and/or the neutral amine radical $Ar_2N^{\bullet}$, and compound **In2**, which in fact is a derivative of aza-*o*-quinodimethane, is involved in the cyclization. According to Scheme 2 (using diphenylamine and CBr_4 as an example),[3] the recombination occurs at the *ortho*-position of the benzene ring of the amine radical cation, and compound **In3**, which is also a derivative of aza-*o*-quinodimethane, participates in the cyclization.

Based on the similarity of structures **In3** and **In2**, it could be assumed that their activities in the cyclization should also be comparable. However, the experimental data indicate the opposite situation. For tertiary amines Ar_2NR, the cyclization of **In3** *via* Scheme 2 is the only channel of acridine formation, because the reaction center for the recombination of radicals and the formation of **In2** *via* Scheme 1 is blocked. The yield of the cyclization products on going from Ar_2NH to Ar_2NR decreases sharply.[1,2] As shown below on the basis of the quantum chemical model, this fact can be explained by the inertness of **In3** type structures to cyclization, which in turn is associated with the higher energy barrier to **In3** isomerization. Isomerization precedes cyclization in both **In2** and **In3** and is necessary to transform these compounds from the thermodynamically stable ground state *trans*-isomers to *cis*-isomers that are active toward cyclization.

* For Part 3, see Ref. 1.

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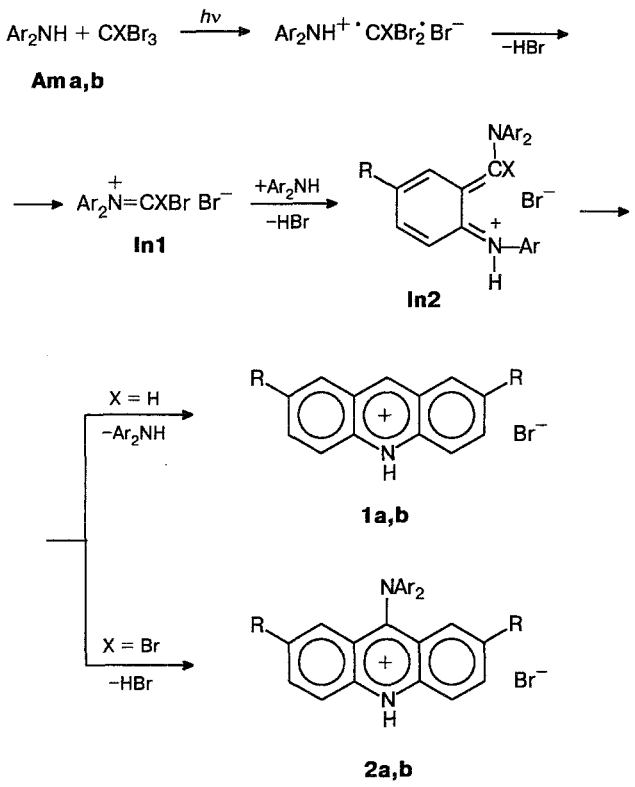
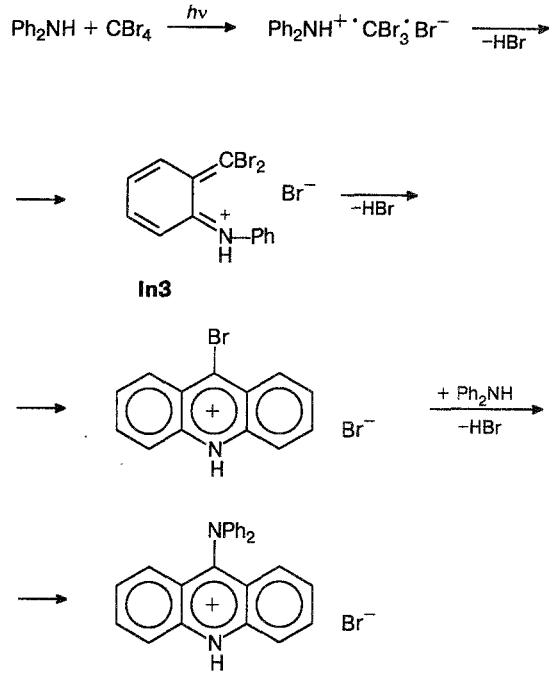
Scheme 1



Ar = R— , R = Me (**a**), $PhCMe_2$ (**b**)

$CXBr_3$: X = H (**x**), Br (**y**)

Scheme 2



Experimental

Prior to use, amines were recrystallized from hexane or ethanol, and CBr_4 was recrystallized from aqueous ethanol. Bromoform was distilled *in vacuo*. Toluene (spectroscopically pure grade) was used. A thermostated quartz cell was irradiated with the light from a DRSh-1000 lamp using a UFS-5 light filter. The kinetics of dark reactions were followed on a Specord UV-VIS spectrophotometer coupled with a PC 8020 computer. The accuracy of measurements of rate constants was 20 %. Pseudo-monomolecular rate constants were measured from an increase in the optical density at the following wavelengths: 540 for the reaction with $CHBr_3$ and 525 (for DTA) and 515 nm (for DCPA) for the reaction with CBr_4. The temperature was varied from 275 to 314 K. The values obtained for the observed rate constants are presented in Tables 1 and 2.

The quantum chemical calculations of the activation barriers to isomerization were performed by the MNDO method (see Ref. 4) with a standard set of parameters.

Table 1. Effect of temperature on the observed rate constant k' measured from an increase in the optical density D_{540}

DTA		DCPA	
T/K	$k' \cdot 10^2$/s^{-1}	T/K	$k' \cdot 10^2$/s^{-1}
275	3.8	274	6.5
280	5.0	280	9.0
286	7.5	286	12.0
292	10.0	292	18.0
293	10.8		

Note. Conditions of measurements: [**Am**] = 0.01, [$CHBr_3$] = 0.4 *M*, toluene.

Table 2. Effect of temperature on the observed rate constant k' measured from an increase in the optical density D_{525} (for DTA) and D_{515} (for DCPA)

DTA		DCPA	
T/K	$k' \cdot 10^3$/s^{-1}	T/K	$k' \cdot 10^3$/s^{-1}
279	2.0	279	1.2
286	2.6	286	1.6
293	3.2	293	2.6
300	4.3	300	3.6
307	5.7	307	5.3
314	7.3		

Note. Conditions of measurements: [**Am**] = 0.01, [CBr_4] = 0.025 *M*, toluene.

Results and Discussion

As follows from the previous studies,[1,2] the bimolecular rate constants k for nucleophilic substitution can be obtained directly from the observed constants k', using the correlation $k = k'[\mathbf{Am}]^{-1}$. The k values calculated from the data of Tables 1 and 2 for the four reactions studied under standard conditions are presented in Table 3. It can be seen from a comparison of these values that varying substituents R in the amine molecules (in parallel in the aromatic part of **In1**) has a slight effects on the rate constant, and compounds **In1x** and **In1y** exhibit similar activities in the reactions with the corresponding amines. At the same time, varying the substituent X in polyhalomethane, namely replacing H with Br, results in a decrease in the rate constant by more than an order of magnitude for both amines. This effect is probably associated with the fact that X is located directly at the reaction center, the carbon atom of the methyleneimine salt **In1**, *i.e.*, when it changes not only does the electron density distribution at this center change, but the spatial surroundings change as well.

The analysis of the activation parameters (see Table 3) shows that these parameters have values typical of bimolecular reactions: fairly low activation enthalpies and high negative activation entropies. It can be seen from the comparison that the entropy factor makes the main contribution to the decrease in the reactivity of **In1y** compared to **In1x**, and in the reaction with DTA the decrease in the activation entropy is so high that it is not compensated for by the simultaneous decrease in the activation enthalpy. Apparently, the two bromine atoms at the reaction center in **In1y** compared to one bromine atom in **In1x** considerably increase the steric hindrance to the attack of **In1** to the *ortho*-position of the amine molecule, which results in more rigid restrictions to the arrangement of the reagent and solvent molecules in the formation of the activated complex in the substitution reaction.

One more interesting conclusion can be drawn from the data of Table 3. In the reaction with amines, both intermediates formed in the reaction with $CHBr_3$, **In1ax** and **In1bx**, have the same activities, because both the activation enthalpies (~36 kJ mol^{-1}) and entropies (~−100 J mol^{-1} K^{-1}) are nearly equal. However, in the reactions of compounds **In1ay** and **In1by** (formed in the reactions with CBr_4) with amines, the similarity of the values of the rate constants is explained only by the fact that the chosen temperature range is near the isokinetic temperature (39.5 °C for these two reactions), because the activation enthalpy decreases and the loss in the entropy in the formation of the activated complex simultaneously increases on going from DTA to DCPA. Therefore, at −68.3 °C the rate constant of the reaction of intermediate **In1ay** with DTA is an order of magnitude higher than that of the reaction of **In1by** with DCPA. In this connection, it is interesting to study the "cross-coupling" reactions: **In1ay** (formed from DTA) with DCPA and **In1by** (formed from DCPA) with DTA. However, the method for the generation of these intermediates restricts the variation of substituents in the aromatic rings of their molecules.

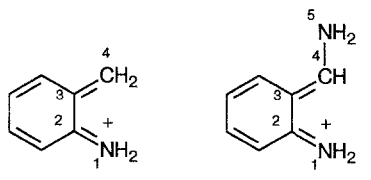
Table 3. Rate constants k of the reactions of compounds **In1** with amines in the reaction of nucleophilic substitution (toluene, 20 °C) and activation parameters of this reaction

Compound	Am	k /L mol^{-1} s^{-1}	$\Delta H^{\neq}$ /kJ mol^{-1}	$-\Delta S^{\neq}$ /J mol^{-1} K^{-1}
In1ax	DTA	10.8	36±4	101±13
In1ay	DTA	0.32	25±2	169±6
In1bx	DCPA	18.0*	37±4	95±16
In1by	DCPA	0.26	36±4	133±13

* T = 19 °C.

Now let us consider the question of the activity of compounds **In2** and **In3** during cyclization. The analysis of the structures of these compounds and a comparison with similar reactions of thermal intramolecular cyclization[5,6] show that the cyclization reactions of **In2** and **In3** are possible only with the participation of the *cis*-isomers. Obviously, at room temperature both of the compounds exist as the more thermodynamically stable *trans*-forms. Therefore, the overall sequence of the reactions should include isomerization around the double C=N bond, which was omitted in Schemes 1 and 2. For **In2** it is the nitrogen atom that enters into the acridine ring as a result of cyclization. In **In2** the positive charge is stabilized by the unpaired electrons of the two nitrogen atoms, while in **In3** it is stabilized by those of only one atom. Therefore, it can be assumed that the order of the C=N π-bond in **In2** should be lower than that in **In3** and, hence, the energy barrier to *trans—cis*-isomerization around the "less" double C=N bond in **In2** should be lower than in **In3**.

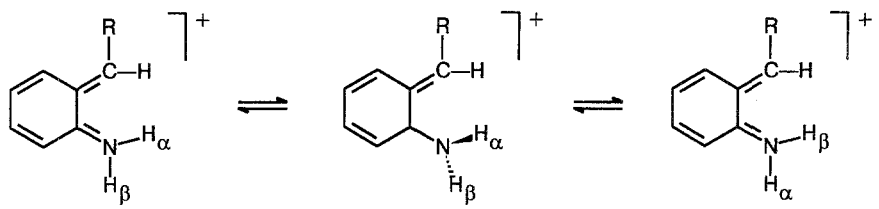
To check this assumption, the isomerization of compounds **In2** and **In3** was modeled by the MNDO method. The simplest structural analogs of **In2** and **In3**, molecules **M1** and **M2**, respectively, were chosen as models.



M1 **M2**

The *trans—cis*-isomerization of **M1** and **M2** can be expressed by the general scheme in which the transition state $\mathbf{M}_i^{\neq}$ is shown (Scheme 3). In this state, the hydrogen atoms of the amino group are shifted out of the plane of the molecule, and the p-orbital of the nitrogen atom, by contrary, is coplanar with the benzene ring.

Scheme 3



M_i-«*trans*» $M_i^{\neq}$ M_i-«cis»

R = H (**M1**); NH_2 (**M2**)

In the calculations, the value of the dihedral angle θ between the plane of the aromatic ring and the plane in which the amino group lies was fixed. Then the minimum of the total energy of the molecules was found by optimizing the geometry. The values obtained for the energies, some bond lengths, and the charges on the amino and methylene (methine) groups in the ground (θ = 0°) and transition (θ = 90°) states for compound **M1** are presented in Table 4.

It can be seen from these data that in the ground state of **M1** the N(1)—C(2) and C(3)—C(4) bond lengths are close to the mean values of the double C=N (1.32 Å) and C=C (1.34 Å) bond lengths, whereas in the transition state **M1**$^{\neq}$ the C=N bond lengthens sharply and the C(3)—C(4) bond lengthens somewhat less. In the transition state, the strong positive mesomeric effect of the nitrogen atom is switched off, because the p-orbital of the nitrogen atom is orthogonal to the π-orbitals of the benzene ring. As a result, the weaker negative inductive effect of the nitrogen atom begins to predominate over the mesomeric effect, and the whole amino group takes a negative charge. The positive charge increases simultaneously at the methylene group, at which nearly half of the total charge of the system is concentrated in the transition state.

The calculated parameters for model compound **M2** are presented in Table 5. In this model, the double-bonding state of the N(1) and C(2) atoms is decreased (the bond length is increased) already in the ground state, and in the transition state this bond becomes nearly single. At the same time, in the ground state the bond between the C(4) and N(5) atoms has substantial double bond character, which increases still more in the transition state. The C(3)—C(4) bond lengthens. The charge redistribution in the molecule corresponds to these changes in the bond lengths and, hence, in the bond orders. Already in the initial state of **M2**, the charge on the $NH_2(1)$ group is two times smaller than that in **M1**. The main positive charge in **M2** is concentrated on the $CHNH_2$ group, and in the transition state this group carries 3/4 of the total charge on the molecule.

The comparison of the energies of the model compounds in the ground and transition states shows that the potential barrier to rotation around the N(1)—C(2) bond in **M1** is higher (nearly two times) than in **M2**; $\Delta E^{\neq}$(**M1**) > $\Delta E^{\neq}$(**M2**). The variation in the molecular energy with the movement along the reaction coordinate is shown in Fig. 1. The value of the dihedral angle θ is used as the reaction coordinate. Since in the model compounds both of the substituents at the N(1) atom are the same, the initial and final states of **M1** and **M2** are degenerate and the M_i-"*trans*" and M_i-"*cis*" energies

Table 4. Total energies (E), bond lengths (R), and charges on the groups of atoms calculated by the MNDO method for compound **M1** at different values of the dihedral angle θ

Model	θ /deg	E /kJ mol^{-1}	R_{12} /Å	R_{34} /Å	q_{NH_2}	q_{CH_2}
M1	0	870.1	1.3467	1.3697	0.215	0.352
M1$^{\neq}$	90	947.6	1.3970	1.3825	−0.034	0.475

Table 5. Total energies (E), bond lengths (R), and charges on the groups of atoms calculated by the MNDO method for compound **M2** at different values of the dihedral angle θ

Model	θ /deg	E /kJ mol^{-1}	R_{12} /Å	R_{34} /Å	R_{45} /Å	$q_{NH_2(1)}$	$q_{CH(4)}$	$q_{NH_2(5)}$
M2	0	813.1	1.3631	1.4216	1.3419	0.121	0.421	0.213
M2$^{\neq}$	90	857.5	1.4033	1.4417	1.3334	−0.062	0.485	0.251

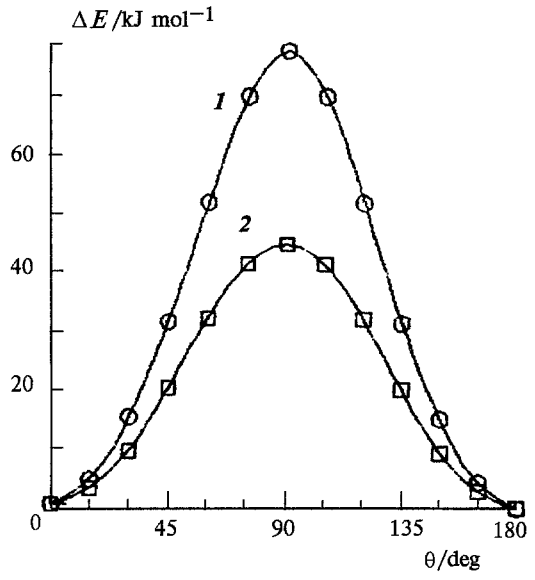


Fig. 1. Energy barriers to rotation around the double C=N bond for compounds **M1** (*1*) and **M2** (*2*) calculated by the MNDO method.

are equal to one another. In the real compounds **In3** and **In2**, the place of the H_β atom is occupied by a phenyl (aryl) group. Therefore, the energy of the *cis*-form should be greater than the energy of the *trans*-form due to steric hindrances. The barrier to isomerization should also increase proportionally if the correlation $\Delta E^{\neq}$(**In3**) > $\Delta E^{\neq}$(**In2**) remains true.

It should be mentioned that the isomerization of the positively charged compounds **In2** and **In3**, each of which has three substituents at the nitrogen atom, is possible only *via* rotation around the double C=N bond, and this is the route that was modeled above. In the neutral compounds, two substituents remain at the nitrogen atom after deprotonation and the unshared electron pair appears on the sp^2-orbital. Therefore, isomerization due to inversion of this orbital *via* the intermediate p-state is possible. The quantum chemical calculations show that the activation energy of inversion may be considerably lower than the activation energy of rotation, and the thermal isomerization of azomethines[7] and azobenzene[8] occurs *via* inversion, while rotation occurs only due to photoexcitation of the π,π^* absorption band.[9]

Isomerization *via* inversion increases the inequality $\Delta E^{\neq}$(**In2**) < $\Delta E^{\neq}$(**In3**) still more in the comparison of the reactivities of secondary and ternary amines, because deprotonation is possible for **In2** formed from Ar_2NH, while there is no proton in **In3** formed from Ar_2NR and, hence, isomerization is possible only *via* rotation around the C=N bond.

Thus, the kinetics of nucleophilic substitution, which is one of the thermal stages of photoinduced bimolecular cyclization, has been studied. Varying the alkyl substituents in the amine molecule is shown to have a slight effect on the activities of the intermediates in the substitution reaction, and the entropy factor makes the main contribution to the decrease in their activities during variations of halomethane, namely on going from $CHBr_3$ to CBr_4. The reaction of *trans—cis*-isomerization that precedes the cyclization of the different intermediates was studied by quantum chemical modeling. It is shown that the potential barrier to isomerization of the intermediate increases on going from secondary to tertiary amines, which makes it possible to explain the low efficiency of *N*-alkylated diarylamines in the photoinduced reaction.

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