Transformations of 3,4-bisindolylmaleimides with differently bonded indole and maleimide moieties under the action of protic acids: a quantum chemical study

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Intramolecular cyclization reactions of 3,4-bis(indol-3-yl)maleimides **1**, 3-(indol-1-yl)-4-(indol-3-yl)maleimides **2**, and 3,4-bis(indol-1-yl)maleimides **3** under the action of protic acids were studied in order to estimate the parameters of the interaction between protonated and unprotonated indole moieties. Geometric parameters, charge distributions, energy characteristics, and information concerning the frontier orbitals of bisindolylmaleimides **1**—**3** were obtained from density functional B3LYP/6-31G(d) quantum chemical calculations. Alternative pathways of protonation of bisindolylmaleimides with differently bonded indole and maleimide moieties were studied and pathways of cyclization of corresponding conjugated acids leading to polyannelated compounds were analyzed. All the key intermediates of the cyclization reactions correspond to stationary points on the potential energy surfaces (minima and transition states). Analysis of the potential energy surfaces revealed almost linear dependences of the activation energies of the cyclization reactions under study on the distances between the reaction centers, on the angle of approach of intramolecular electrophile, and on the energy gap (energy difference between frontier orbitals). The key role in the cyclization reactions is played by structural similarity between the starting indoleninium cations and the activated complexes of the reactions under study.

Key words: bisindolylmaleimides, protonation, cyclization, potential energy surface, activated complex, frontier orbitals, indoleninium cation, annulation.

Research on the chemical properties and reactivity of 3,4-bisindolylmaleimides is of interest in connection with the fact that some compounds of this series and related indolo[2,3]carbazoles possess valuable biological properties.[1,2] Earlier,[3,4] it was shown that intramolecular cyclizations of 3,4-bis(indol-3-yl)maleimides **1**, 3-(indol-1-yl)-4-(indol-3-yl)maleimides **2**, and 3,4-bis(indol-1-yl)maleimides **3** under the action of protic acids proceed differently and result in different types of compounds. 3,4-Bis(indol-3-yl)maleimides **1** under acid catalysis conditions and after dehydrogenation form indolo[2,3]carbazole derivatives **4** (Scheme 1). In the absence of oxidant (DDQ) intermediate **5** undergoes isomerization into aminophenylcarbazole **6** (see Scheme 1). Possible mechanisms of the cyclization and isomerization of system **1** are shown in Scheme 2.

Unlike 3,4-bis(indol-3-yl)maleimides **1**, 3-(indol-1-yl)-4-(indol-3-yl)maleimides **2** and 3,4-bis(indol-1-yl)maleimides **3** under the action of protic acids undergo 2—4′- or 2—7′-cyclization to give 8b,9-dihydroindolo[4′,3′:3,4,5]pyrrolo[3′,4′:6,7][1,4]azepino[1,2-*a*]indol-1,3(2*H*,5*H*)-diones **7** or 9b,10-dihydroindolo[1′,7′:4,5,6]pyrrolo[3′,4′:2,3][1,4]diazepino[1,7-*a*]indol-1,3-diones **8**, respectively (Scheme 3). Compounds **7** and **8** under the action of DDQ in toluene were converted to indolo[4′,3′:3,4,5]pyrrolo[3′,4′:6,7]azepino[1,2-*a*]indol-1,3(2*H*,5*H*)-diones **9** and 1*H*-indolo[1′,7′:4,5,6]pyrrolo[3′,4′:2,3][1,4]diazepino[1,7-*a*]indol-1,3(2*H*)-diones **10**, respectively. Possible cyclization mechanisms[3,4] are shown in Scheme 3.

Since the cyclization reactions of differently fused bisindolylmaleimides proceed in different fashion, it was interesting to establish the electronic, steric, and other factors responsible for the cyclization pathways that lead to maleimidoindolocarbazoles or maleimidoindolo[1,4]diazepines (-azepines).

Orientation of protonation of the molecules of 3,4-bis(indol-3-yl)maleimides 1, 3-(indol-1-yl)-4-(indol-3-yl)maleimides 2, and 3,4-bis(indol-1-yl)maleimides 3. Usually, the indole ring is protonated at position 3. Therefore one can assume that most probably a proton will attack molecules **1**—**3** also at position 3 of the indole ring. However, the effect of a strong electron acceptor, namely, the maleimide ring bonded to the indole moieties should

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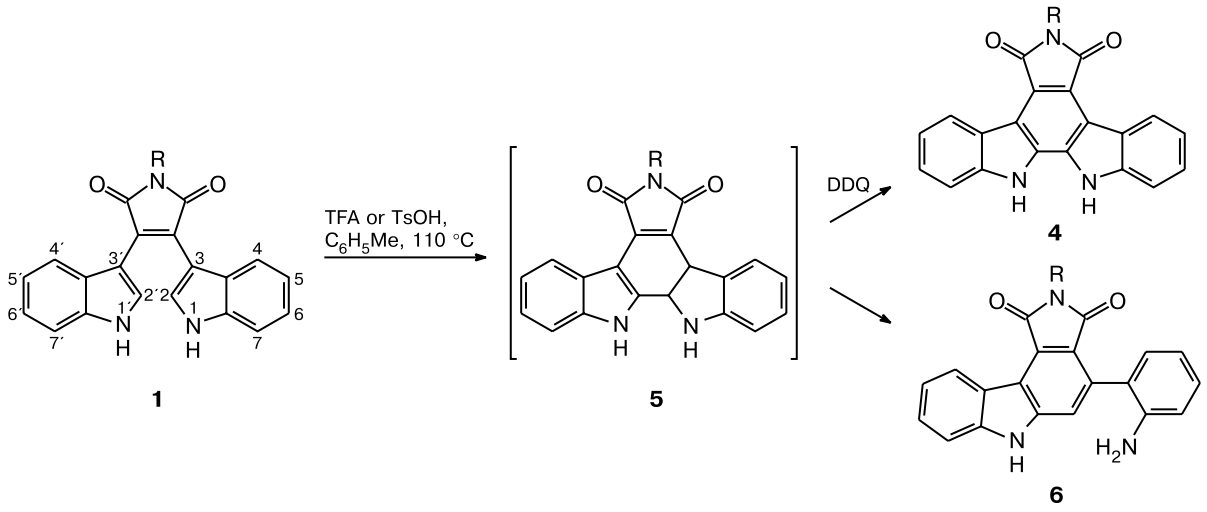
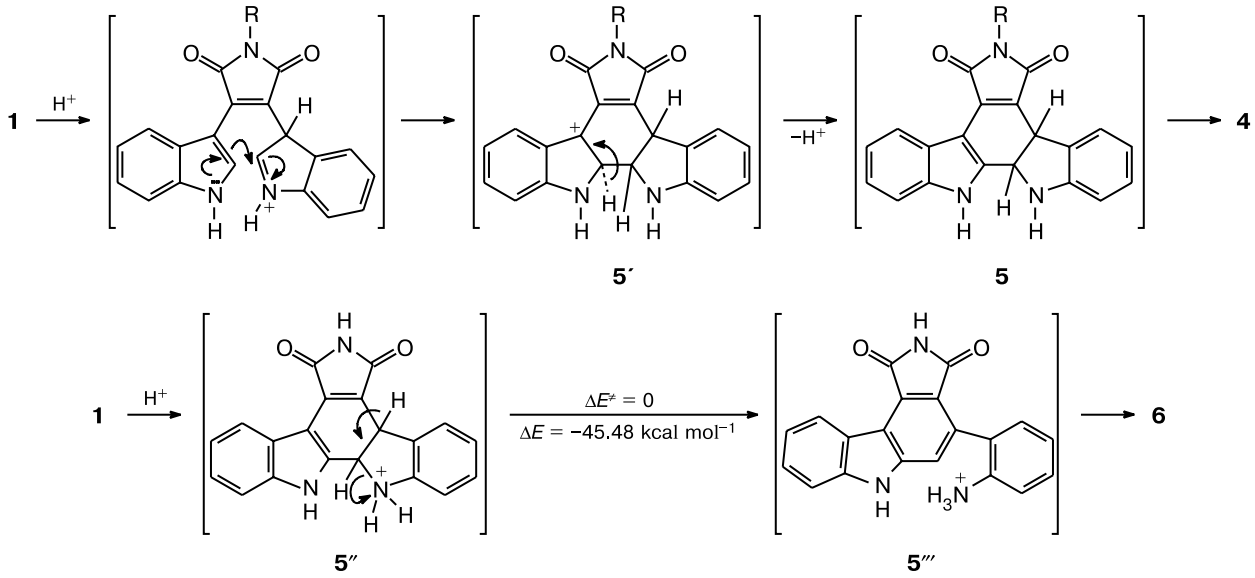
Scheme 1



R = H, Alk, Ar

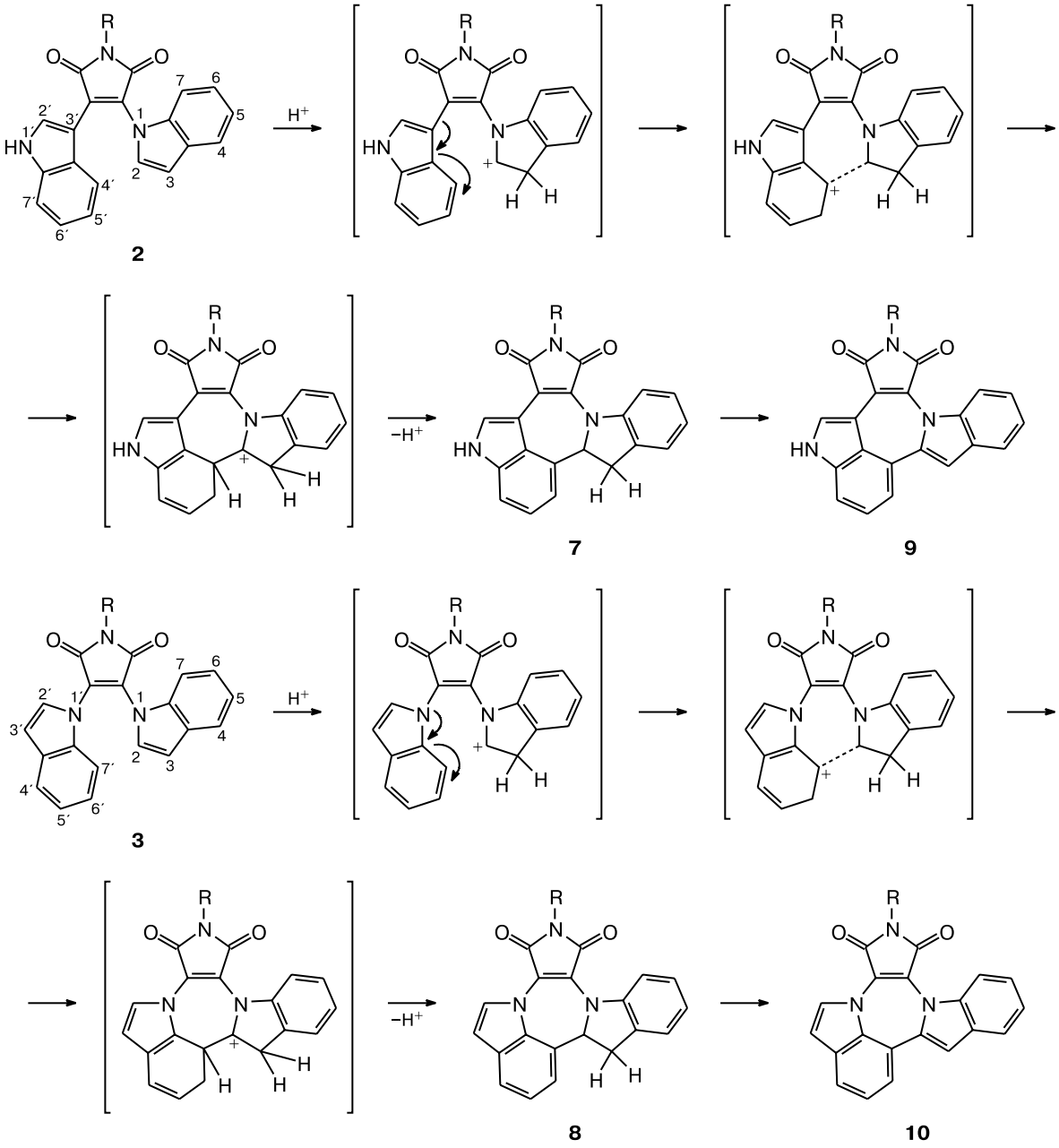
Scheme 2



R = H, Alk, Ar

be taken into account. Indeed, calculations showed that all three bisindolylmaleimide molecules **1—3** bear formal negative charges at position 3 of the indole rings, which favors a proton attack on this position. The largest negative atomic charge of C(3) was obtained for molecule **2** (−0.232); the next is molecule **3** (−0.224) followed by molecule **1** (−0.036) (Fig. 1). Interestingly, if the indole moiety is bonded to the maleimide fragment through the nitrogen atom, the charge distribution in the indole system is very similar to that in the unsubstituted indole. If the bonding occurs through the carbon atom, its formal charge becomes too lowered, but this does not preclude the proton attack on position 3 even in bisindolylmaleimide **1**. Molecule **2** has two alternative positions for proton attack, that is, position 3 of the indole moiety bonded to the maleimide moiety through the nitrogen atom and position 3′ of the other indole moiety bonded through the carbon atom. Since the negative charge of the C(3) atom (−0.232) is much larger than that of the C(3′) atom (−0.026), we can assume a proton attack on the C(3) atom. This pathway of protonation of compound **2** was proved experimentally. Despite the fact

Scheme 3



that the calculated formal charges of the indole nitrogen atoms are much larger than those of all other atoms in the system (see Fig. 1), we excluded these nitrogens from consideration. Indeed, they cannot be treated as potential protonation sites because they have no p-orbitals containing a free electron pair which would be involved in aromatic π-conjugation. (Here, mention should be made of the assumption[5] of initial proton attack on the N(1) atom; but the lack of a free p-orbital to be filled with an electron pair similarly to the "pyridine" nitrogen atom required that the proton be rapidly transferred to the C(3) atom through conventional 1—3-delocalization over the π-electron system). According to calculations, protonation at position 3 causes the appearance of a positive charge on the C(2) atom and the formation of an electrophilic center which participates in further intramolecular cyclization. The atomic charges of C(2) in the indole-indoleninium structures **1′—3′** are +0.214, +0.148, and +0.137, respectively (see Fig. 1). Thus, the results of our calculations are in reasonable agreement with the initial assumptions of the protonation pathways of bisindolylmaleimides.

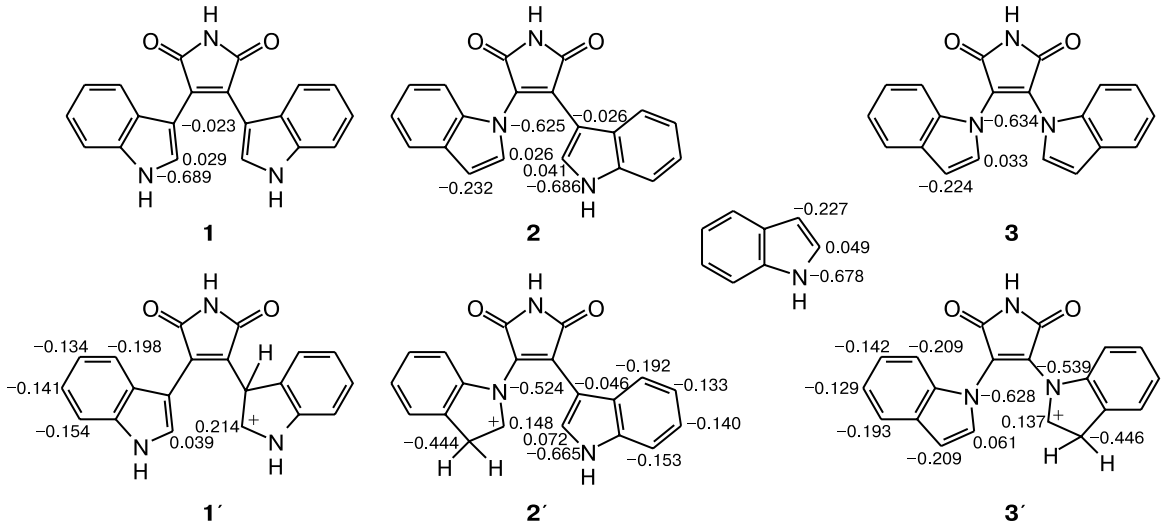


Fig. 1. Charges on the reaction centers in bisindolylmaleimides **1—3**, corresponding indoleninium cations, and unsubstituted indole.

Analysis of cyclization of protonated bisindolylmaleimides. Cyclization of the *N*-indolyl-*N*-indoleninium system **3′** and *C*-indolyl-*N*-indoleninium system **2′** leads to formation of the 1,4-diazepine or azepine central rings that adopt a chair conformation, whereas cyclization of the *C*-indol-*C*-indoleninium intermediate **1′** under identical conditions gives a nearly planar cyclohexadiene central ring. Both the starting bisindolylmaleimides **1—3** and the corresponding indoleninium cations **1′—3′** exhibit some interesting structural features. They belong to so-called "propeller" structures in which the indole rings do not lie in the same plane with each other and with the maleimide moiety, being rotated by some angle with respect to its plane, despite the possibility of realization of a longer π-conjugation chain in the case of monoplanar arrangement of the three rings. The "propeller" type of spatial arrangement occurs in, *e.g.*, triphenylmethane and related structures.[6] It is due to the fact that planar arrangement of aromatic rings is precluded by steric van der Waals interactions between the eclipsed hydrogen atoms. Such eclipsed interactions hamper free rotation of the indole rings about the C—N and C—C bonds.

The reactions under study are intramolecular versions of aminoalkylation (Mannich reaction), being a particular case of electrophilic substitution in the aromatic nucleus, which involves an intermediate formation of a σ-complex followed by the loss of proton.[7] With allowance for intramolecular character of the process under study, this reaction mechanism is favored by three factors, namely, 1) optimum electron density distribution over the attacked π-system; 2) optimum angle between the attacking electrophile and the plane of the attacked aromatic ring (~115—120°); and 3) optimum distance between the interacting reaction centers.

For instance, the formal negative atomic charges of C(7′) in cation **3′** (–0.209) and of C(4′) in cation **2′** (–0.192) favor the attack of intramolecular electrophilic center on these positions (see Fig. 1).

Since the angle of attack of the electrophile and the distance between the reaction centers are affected by steric hindrances to rotation of the indole rings about the C—N and C—C bonds in the indoleninium cations **1′—3′**, we can assume that the intramolecular ring closure under study will be a compromise between all the factors listed above. For instance, earlier[8] quantum chemical calculations of intramolecular cyclization reactions showed that similarity in spatial configurations between the initial structure and the corresponding transition state (activated complex) is the main condition for the reaction to occur. In other words, in most cases the reaction system should overcome difficulties (steric hindrances, see above) and attain a favorable overlap of the frontier MOs. According to Fukui,[9] the efficiency of the overlap between interacting orbitals depends on the energy characteristics (energy difference between the frontier orbitals of the reactants or the "energy gap") and geometric parameters (distance between the reaction centers and the angle of attack). For instance, intramolecular reaction systems can be extremely sensitive to angular parameters of the reaction center;[8] in this case the reaction centers are separated by a sufficiently short distance and the electron density on the reaction centers formally favors the reaction, but it does not occur.

Because of this, we studied the potential energy surfaces (PES) — energy profiles — of the 2—7′-, 2—4′-, and 2—2′-cyclizations of the indoleninium systems **1′—3′**. The energy profiles obtained for all the systems under study represent typical PESs of low-barrier reactions (Figs 2 and 3) that in essence occur at the bottom of the

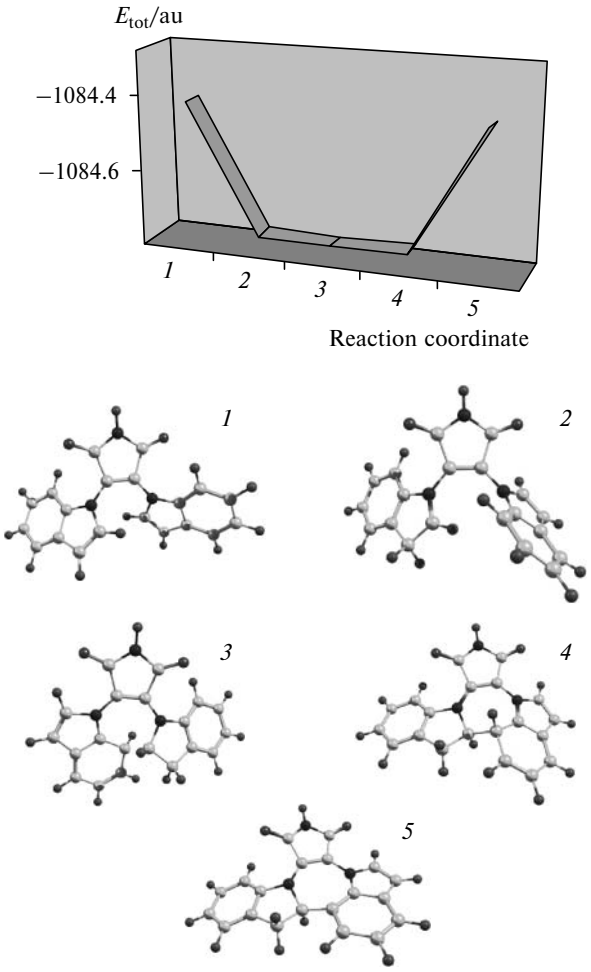


Fig. 2. Total energy (E_{tot}) plotted *vs.* reaction coordinate (PES profile) for 2—7′-cyclization of indoleninium system **3**′. Shown are strictural correlations for the following species: initial molecule **3** (*1*), indoleninium cation **3**′ (*2*), intermediate local energy minimum (*3*), seven-membered cyclic cation (*4*), and product **8** (*5*).

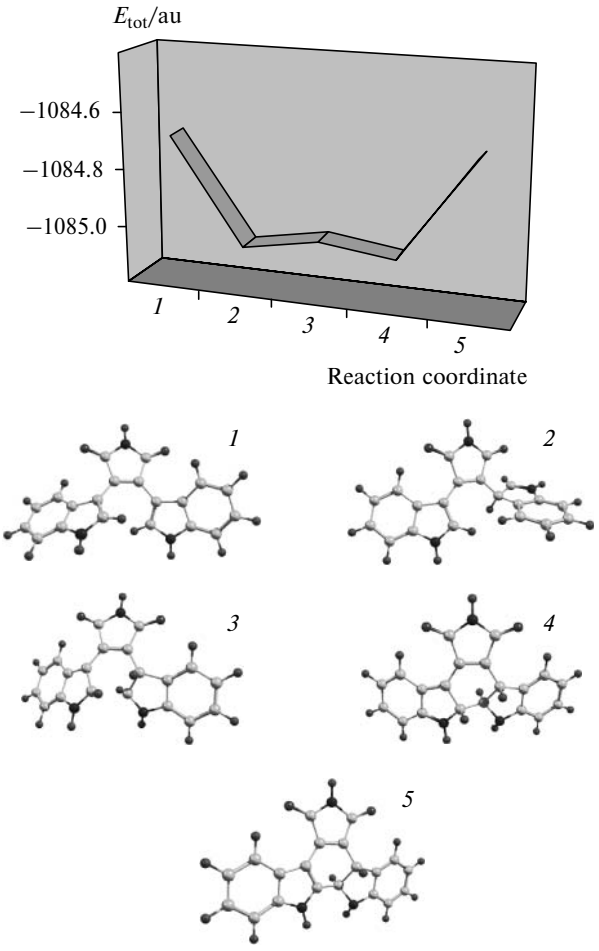


Fig. 3. Total energy (E_{tot}) plotted *vs.* reaction coordinate (PES profile) for 2—2′-cyclization of indoleninium system **1**′. Shown are strictural correlations for the following species: initial reagent (*1*), product (*5*), transition state (*3*), and intermediate cations (*2* and *4*).

valley; *i.e.*, there is a nearly flat portion of the potential curve in the vicinity of the transition state (intermediate) *3*.

Our closed-shell, or restricted B3LYP/6-31G(d) (RB3LYP), calculations of the transition state of the 2—7′-cyclization of system **3**′ failed to locate a transition state between the indoleninium cation **3**′ and a cyclic cationic intermediate of the type *4* (see Fig. 2 and Scheme 3). In structure *3*, which precedes the cyclic cationic intermediate *4*, the reaction centers are separated by a distance of 1.63 Å. We found that this structure corresponds to a local minimum on the potential curve (its energy level is ~1.5 kcal mol^{-1} lower than the energy levels of the reagents and products) rather than the transition state. We assumed that this is a consequence of the onset of triplet instability in the course of the search for a saddle point and that, probably, the reaction proceeds by a radical cation mechanism rather then pure ionic mechanism (S_E). This gave us an impetus to carry out calculations in the open-shell approximation (unrestricted method, UB3LYP). The UB3LYP calculations of this system gave a high activation barrier (41.57 kcal mol^{-1}) for the reaction under mild conditions at room temperature. Based on this result, we excluded the radical ion mechanism and assumed that the reaction occurs almost barrierlessly. Such reactions are sensitive to the mutual position of hydrogen atoms at the reacting centers. Namely, a "spiral-like" *trans*-attack (hydrogen atoms are in *trans*-position relative to the reaction centers on the C atoms) (Fig. 4, *a*) occurs almost barrierlessly, whereas a "V-shaped" *cis*-attack (*cis*-arrangement of hydrogen atoms relative to the C atoms) (Fig. 4, *b*) is characterized by an activation energy of 17.98 kcal mol^{-1}. This seems to be due to the fact that hydrogen atoms in this situation eclipse each other. According to our calculations with the same basis set, the 2—2′-cyclization of system **3**′ should pro-

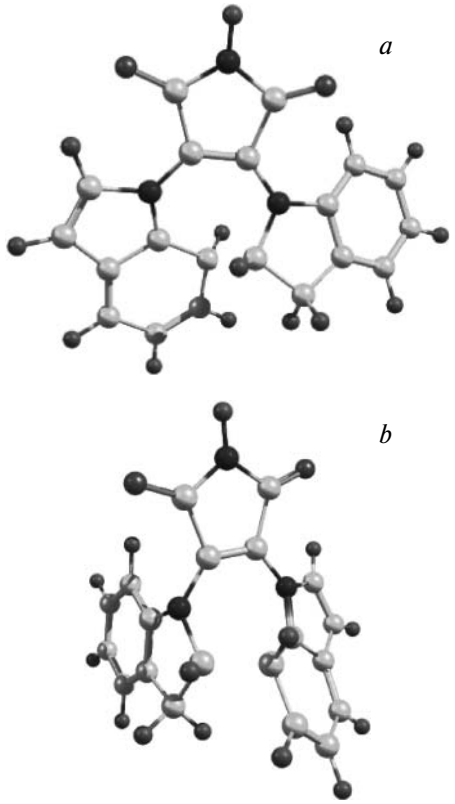


Fig. 4. Cyclization of system **3′**: intermediate for "spiral-like" *trans*-attack (*a*) and activated complex for "V-shaped" *cis*-attack (*b*).

ceed with a very low but non-zero potential barrier (2.74 kcal mol^{-1}) (Table 1).

The PES of system **2′** is also flattened, but the potential barriers are somewhat higher compared to system **3′** (9.33 and 7.72 kcal mol^{-1} for the 2—7′- and 2—2′-cyclization, respectively). In contrast to the cyclization of system **3′** in this case the potential barrier to 2—2′-cyclization is lower than the barrier to 2—4′-cyclization (see Table 1).

Table 1. Angle of attack of electrophilic center (φ), distance between reaction centers (R_{C-C}), energy difference between frontier orbitals (Δε), and activation barriers ($\Delta E^{\neq}$/kcal mol^{-1}) to 2—2′-, 2—4′-, and 2—7′-cyclizations of indoleninium systems **1′**—**3′** according to B3LYP/6-31G(d) calculations

Parameter	**1′**		**2′**		**3′**	
	2—4′	2—2′	2—4′	2—2′	2—7′	2—2′
φ/deg	138.04	127.36	131.24	106.23	115.97	109.45
R_{C-C}/Å	4.99	2.11	4.05	4.31	1.63	2.07
Δε/eV	2.6	2.6	2.5	2.5	2.3	2.3
$\Delta E^{\neq}$	10.52	29.47	9.33	7.72	0	2.74

Note. RHF/6-31G* calculated activation barrier to 2—7′-cyclization of system **3′** is 16.06 kcal mol^{-1} (31.63 kcal mol^{-1} for 2—2′-cyclization of system **1′**).

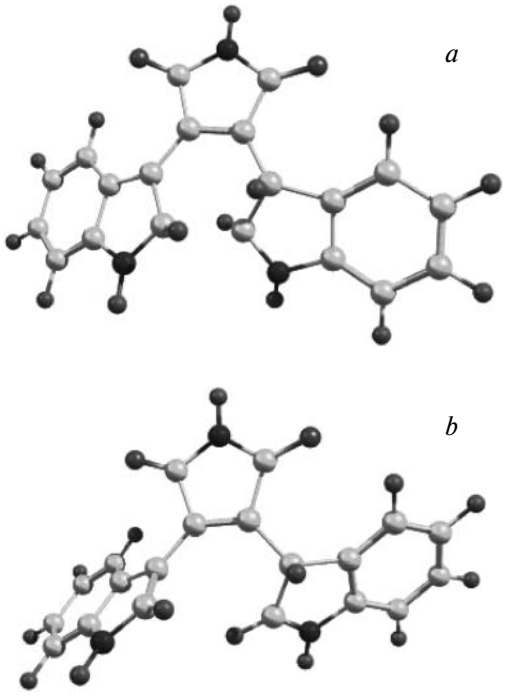


Fig. 5. Configurations of activated complexes for different types of cyclization of system **1′**: 2—2′- (*a*) and 2—7′-cyclization (*b*).

The largest difference in activation barriers was found for system **1′**. Here, the calculated potential barrier to 2—2′-cyclization (29.47 kcal mol^{-1}) is much higher than the calculated barrier to 2—7′-cyclization (10.52 kcal mol^{-1}) (see Table 1) despite a more favorable geometry (distance and angle of attack) in the former case (Fig. 5). Probably, this increase in energy is due to a structural feature of the activated complex for the 2—2′-cyclization (see Fig. 5, *a*), where hydrogen atoms in position 2 of the indole ring and in position 3 of the indoleninium ring eclipse each other. At the same time the experimentally observed 2—2′-cyclization of system **1′** probably indicates that steric strain (see above) in the formation of activated complex (see Fig. 5, *a*) is compensated by further facile proton removal from cyclic structure **5′** and subsequent opening of the five-membered ring in **5″** with the formation of **5‴** (see Scheme 2).

Indeed, B3LYP/6-31G(d) calculations showed that ring opening in indolocarbazole **5″** in an acid medium with the formation of aminophenylcarbazole **5‴** should proceed barrierlessly and be an exothermic process (ΔE = −45.48 kcal mol^{-1}). This can be explained by higher aromaticity of the newly formed aminophenylcarbazole **5‴** compared to the initial indolocarbazole **5″** (see Scheme 2).

The results of calculations of the 2—7′-, 2—4′-, and 2—2′-cyclizations of all indoleninium systems described above are listed in Table 1. We correlated the calculated activation barriers with the following parameters of the transition state: distances between the reaction centers,

the angle of attack of the intramolecular electrophile, and the energy gap ($\Delta\varepsilon$) as the energy difference between the frontier orbitals. The activation barriers are monotonous linear functions of the parameters mentioned above for the 2—7′- and 2—4′-cyclizations (see Table 1). This is consistent with experimental data, namely, system **3′** readily undergoes cyclization under mild conditions in the presence of CF_3COOH (this corresponds to calculations of a barrierless process); cyclization of system **2′** ($E^{\neq} = 9.33$ kcal mol^{-1}) requires the presence of a stronger acid ($MeSO_3H$) and a higher temperature. Note that we failed to isolate products of the 2—7′-cyclization of system **1′** under the experimental conditions, although in this case the calculated activation barrier ($E^{\neq} =$ 10.52 kcal mol^{-1}) is lower than the barrier to 2—2′-cyclization. 2—2′-Cyclization of system **2′** is characterized by a lower energy barrier compared to 2—4′-cyclization (7.72 *vs.* 9.33 kcal mol^{-1}, respectively), whereas the barriers to 2—2′-cyclizations of systems **3′** and **1′** are higher than the barrier to 2—7′-cyclization (see Table 1). Preferred formation of seven-membered ring under the action of acids on compound **2** (despite a high $E^{\neq}$ compared to the 2—2′-cyclization, see Table 1) seems to be due to the fact that azepine **7** (product of the cyclization of system **2′**) is insoluble and thus no longer involved in the reaction. This favors a shift of the equilibrium toward the 2—4′-cyclization despite the fact that the calculated activation barrier to 2—2′-cyclization is somewhat lower (see Table 1).

The results of our theoretical studies suggest the following. First, cyclization of protonated bisindolylmaleimides proceeds by pure ionic S_E-mechanism of electrophilic substitution in the aromatic nucleus (the radical ion and radical mechanisms were excluded in the course of our study). Second, cyclization of protonated bisindolylmaleimides obeys general trends established earlier for intramolecular cyclization reactions, namely, it requires a combination of optimum geometric parameters (angles and distances in the activated complex) and the smallest energy difference between the interacting frontier orbitals. Probably, a combination including a distance of about 2 Å, an angle of attack of 115°, and $\Delta E =$ 2.3 eV (see Table 1) is optimum for the 2—7′-cyclization of system **3′**, which is in agreement with experimental data (reaction proceeds barrierlessly).

Calculation Procedure

All structures of the intermediates and transition states of the intramolecular cyclization reactions under study were calculated using the density functional approach with the B3LYP functional and the 6-31G(d) basis set using the Gaussian-98 program package[10] with full geometry optimization.

Parameters of the frontier orbitals of the reacting species, in particular, their coefficients and energies were obtained from the results of the B3LYP calculations with the 6-31G(d) basis set.[10] Transition states were located using a conventional algorithm for search of saddle point using the QST3 procedure incorporated into the Gaussian-98 program package followed by calculating normal vibrational frequencies of the configurations of activated complexes using a Gaussian-98 standard procedure.

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