Quantum chemical study of the transformation of 2-(*N*-alkylamino)-3-(indol-1-yl)- and 2-(*N*-alkylamino)-3-(indol-3-yl)maleimides by protic acids: tandem hydride transfer/cyclization mechanism

E. E. Bykov, S. A. Lakatosh, and M. N. Preobrazhenskaya★

G. F. Gause Institute of New Antibiotics, Russian Academy of Medical Sciences,
11 ul. B. Pirogovskaya, 119021 Moscow, Russian Federation.
Fax: +7 (495) 245 0296. E-mail: mnp@space.ru

The geometric parameters, the charge distribution, and the energetics of *N*-methyl-2-(*N*-ethylanilino)-3-(indol-1-yl)- and *N*-methyl-2-(*N*-ethylanilino)-3-(indol-3-yl)maleimides and their conjugated acids were studied by density functional theory calculations at the B3LYP/6-31G(d) level. The mechanism of the tandem hydride transfer/cyclization sequence, which occurs after protonation of *N*-methyl-2-(*N*-ethylanilino)-3-(indol-1-yl)- and *N*-methyl-2-(*N*-ethylanilino)-3-(indol-3-yl)maleimides, was analyzed. The investigation of the potential energy surface for the tandem hydride transfer/cyclization of the iminium cation that formed upon protonation revealed that the hydride transfer followed by intramolecular cyclization at position 7 of the indole fragment in *N*-methyl-2-(*N*-ethylanilino)-3-(indol-1-yl)maleimide is the preferable process, unlike alternative intramolecular cyclization involving the cationic center at the C(2) atom of the indole fragment and the benzene ring of the *N*-ethylaniline fragment of the indoleninium cation in *N*-methyl-2-(*N*-ethylanilino)-3-(indol-3-yl)maleimide. A study of the key intermediates of the assumed reaction mechanism demonstrated that these intermediates are actually stationary points on the potential energy surface (minima and transition states).

Key words: quantum chemical calculations, *N*-methyl-2-(*N*-ethylanilino)-3-(indol-1-yl)maleimide, *N*-methyl-2-(*N*-ethylanilino)-3-(indol-3-yl)maleimide, protonation, cyclization, potential energy surface, hydride transfer, activated complex, indoleninium, iminium, intermediate, annulation.

It is of interest to study the chemical properties and reactivities of 2-(*N*-ethylanilino)-3-(indol-1-yl)- and 2-(*N*-ethylanilino)-3-(indol-3-yl)maleimides because some representatives of this series and related bis-indolylmaleimides were found to have valuable biological properties.[1,2] Earlier, it has been demonstrated[1,2] that under the action of protic acids, 2-(indol-1-yl)-3-(indol-3-yl)- and 2,3-bis(indol-1-yl)maleimides undergo 2—4´- or 2—7´-cyclization to form 8b,9b-dihydroindolo[4´,3´:3,4,5]pyrrolo[3´,4´:6,7][1,4]azepino[1,2-*a*]indole-1,3-diones or 9b,10-dihydroindolo[1´,7´:4,5,6]pyrrolo[3´,4´:2,3][1,4]diazepino[1,7-*a*]indole-1,3-diones, respectively.

Presumably, protonation followed by cyclization of *N*-methyl-2-(*N*-ethylanilino)-3-(indol-1-yl)maleimide (**1**), which can be considered as an "open" structure of 2,3-bis(indol-1-yl)maleimide studied earlier, will occur analogously, *i.e.*, through the formation of intermediate indoleninium cation **2**. The intramolecular electrophilic attack on the latter cation at the benzene ring of the ethylaniline group affords cation **3a** (Scheme 1). The mechanism of this reaction was confirmed[1] in the study of the transformation of *N*-benzyl-2-[(d_5-ethyl)anilino]-3-(indol-1-yl)maleimide (Scheme 2).

However, the reaction of compound **1** with TFA in CH_2Cl_2 or with $MeSO_3H$ in $PhCH_3$ gave annulation product **4** (see Scheme 1).[1] The assumed reaction mechanism involves the following three steps: 1) protonation of ethylanilinoindolylmaleimide **1** at position 3 of the indole fragment giving rise to indoleninium cation **2** with an electrophilic center at the C(2) atom of the indole bicyclic moiety; 2) the hydride shift from the C atom adjacent to the ethylaniline N atom to position 2 of the indole fragment to form iminium cation **3** (in this case, the indole moiety is, in fact, reduced to the indoline moiety); 3) intramolecular cyclization of iminium cation **3** to form protonated 1,4-diazepine **4** followed by proton abstraction to give diazepine **5**. It should be noted that cycliza-

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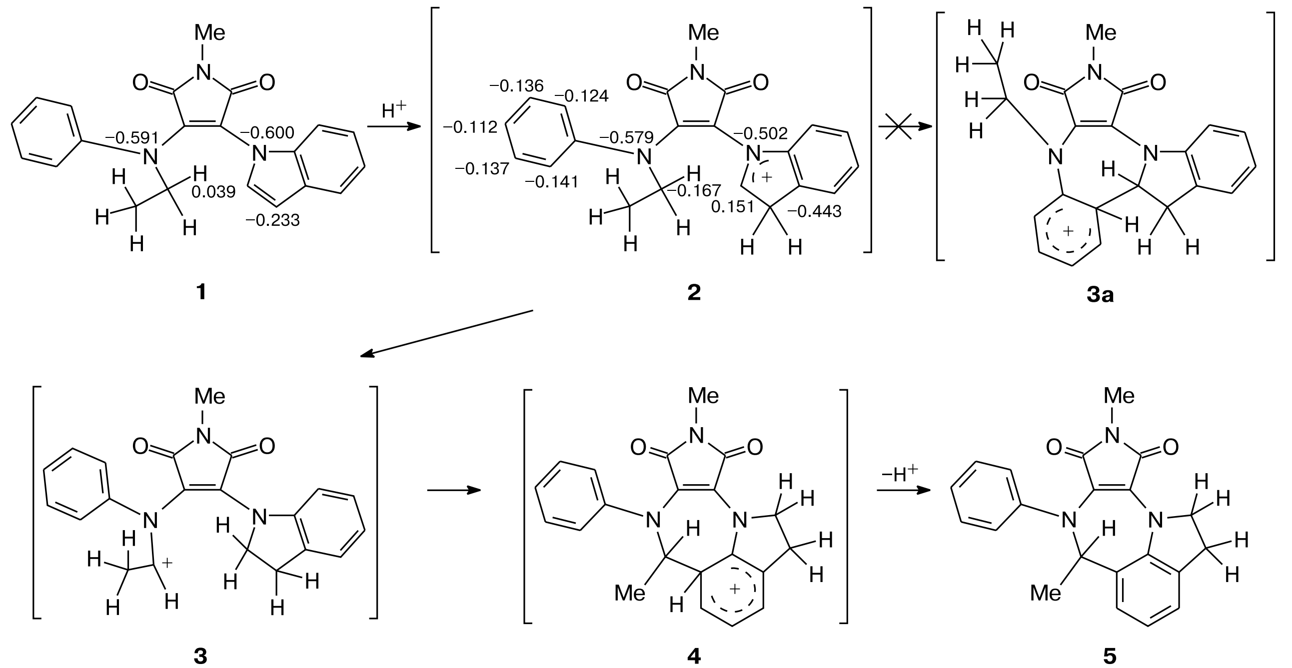
Scheme 1

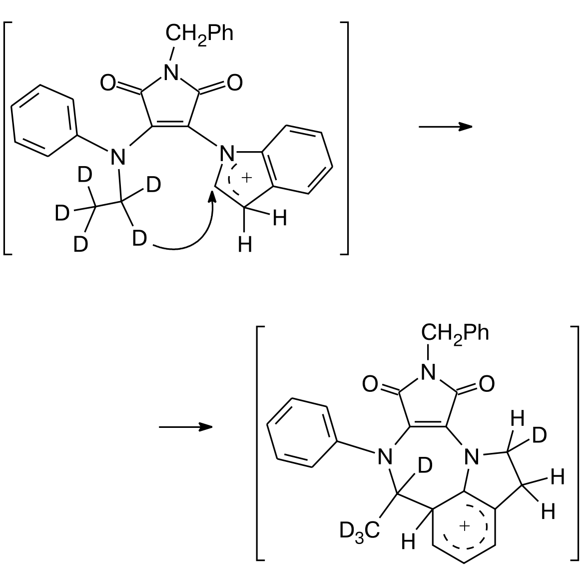


tion by the usual S_E mechanism of electrophilic substitution is preceded by rotation of the indoline ring about the C—N bond by ~270° (see Scheme 1).

The distribution of atoms D in the final product after the experiment with deuterium analog **1** (all H atoms in the ethyl group are replaced by deuterium)[2] confirmed our assumption about the hydride shift followed by cyclization of the iminium cation (see Scheme 2).

An analogous experiment with *N*-methyl-2-(*N*-ethylanilino)-3-(indol-3-yl)maleimide (**6**) demonstrated that the above-described hydride shift does not occur,[3] and the reaction proceeds through cation **7** involving the intramolecular electrophilic attack on the *N*-phenyl fragment of the ethylaniline group to give protonated azepine **8** (Scheme 3).

Scheme 2

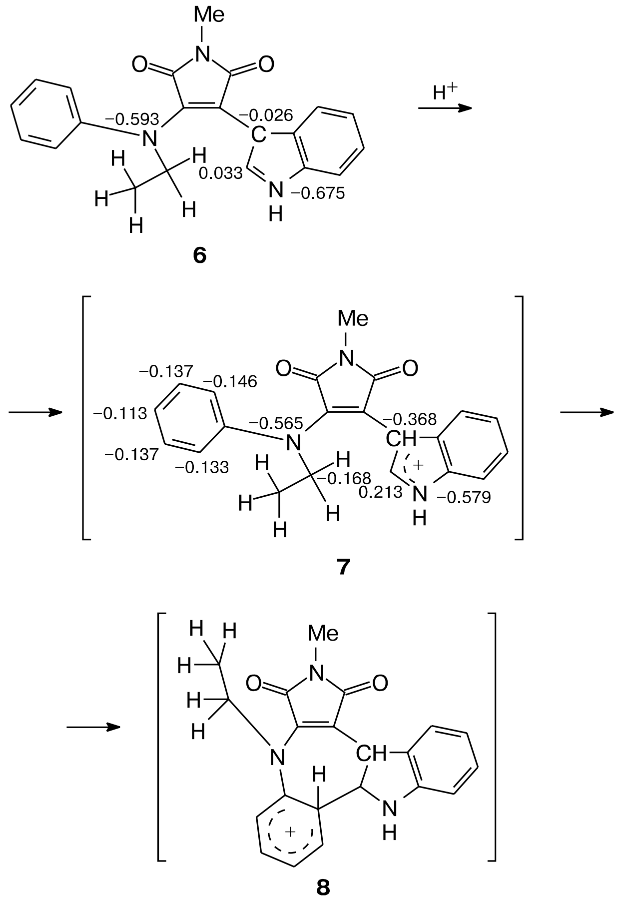


In view of the difference in the chemical behavior of isomers **1** and **6**, our aim was to study the factors responsible for the mechanism of the above-described transformations by quantum chemical calculations. As in the previous study,[4] the geometric structures of indolylmaleimides **1** and **6** and their conjugated acids **2** and **7**, as well as the energetics and the charge distribution on atoms, were investigated. The energy profiles of the tandem hydride transfer/cyclization sequence and the cyclization involving the attack on the phenyl group of the ethylaniline fragment were compared.

Direction of protonation of *N*-methyl-2-(*N*-ethylanilino)-3-(indol-1-yl)- and *N*-methyl-2-(*N*-ethylanilino)-3-(indol-3-yl)maleimides

To reveal the factors responsible for the direction of protonation of compounds **1** and **6**, we calculated their geometric parameters and the formal charges on atoms. Analogous calculations were carried out for the corresponding indoleninium cations **2** and **7** (see Schemes 1 and 3). The formal charges on the indole C(3) atom in compounds **1** and **6** (−0.233 and −0.026, respectively) are almost identical to those in bis-indolylmaleimides (see the previous publication[4]). This charge distribution is fa-

Scheme 3



vorable for protonation of compounds **1** and **6** at position 3 of the indole fragment. An analysis of the charge distribution in the corresponding indoleninium cations **2** and **7** (see Schemes 1 and 3) showed that the highest positive charges (+0.151 and +0.213, respectively) are accumulated on the C(2) atom of cations **2** and **7** of the indole moiety, which is consistent with the assumed location of the electrophilic center at this atom.

Analysis of the potential energy surface for tandem hydride transfer/cyclization of the intermediate iminium structure

Hydride transfer from the methylene group of the ethylaniline fragment to the positively charged C(2) atom of the protonated indole bicyclic moiety in indoleninium cation **2** is, in essence, the nucleophilic attack on the electron-deficient ring C atom. The approach of an internal nucleophile (the hydride ion) at an angle close to 120° can occur both below and above the plane of the indole ring. Hence, we calculated the activation energy and constructed the potential energy surface profile for each possible case. The overall view of the potential curve, like that in the study,[4] shows that the transformation of ethylanilinoindolylmaleimide **1** is a low-barrier reaction proceeding at the bottom of a valley of the potential energy surface (Fig. 1, *c*, *d*).

As can be seen from Fig. 1, the approach of a nucleophile below the plane of the indole ring (see Fig. 1, *a*) leads to the strained cyclic transition state TS_1 with $\Delta E^{\#}$ = 32.93 kcal mol^{-1}. The H atoms at the interacting reaction centers, which are in *syn* positions with respect to each other, are mutually eclipsed. The approach of the hydride ion above the plane of the indole ring (see Fig. 1, *b*) leads to the formation of the "open" unstrained transition state TS_2 (associated with structure **3**) with the *anti* orientation of the entering hydride ion relative to the H atom bound to the ring C(2) atom, $\Delta E^{\#}$ = 3.29 kcal mol^{-1}. Taking into account this ratio of the activation barriers, the target tandem hydride transfer/cyclization sequence proceeds apparently with higher probability through the iminium cation as the transition state (see Fig. 1, *b*).

This assumption is confirmed by the fact that the calculated potential barrier of the hypothetical alternative reaction ($\Delta E^{\#}$ = 22.93 kcal mol^{-1}), which is the usual S_E electrophilic attack on the phenyl ring of the *N*-ethylaniline fragment giving rise to protonated diazepine **3a** (see Scheme 1), is also substantially higher than that in the case of the unstrained transition state TS_2, *viz.*, the iminium cation ($\Delta E^{\#}$ = 3.29 kcal mol^{-1}).

An analysis of the geometry and the charge distribution in indoleninium cation **2** shows that the distance from the electrophilic center at position 2 of the indole fragment to the C atom of the phenyl group of the ethylaniline fragment (6.34 Å) is more than twice as long as that to the H atom of the ethyl group of the same fragment (2.75 Å). Consequently, for alternative cyclization at the phenyl ring of the *N*-ethylaniline fragment to occur, unhindered rotation of the *N*-ethylaniline group about the N—C bond is required for the achievement of the optimal distance and angle allowing the reaction centers to come into proximity. However, as opposed to the indole N atom, whose lone electron pair on the p orbital is conjugated with the aromatic indole π system, the lone electron pair on the p orbital of the N atom of the ethylaniline group is to a greater extent involved in the conjugation chain with the strongly electronegative maleimide ring (−M effect), which is manifested in an increase in the order of the C—N bond under consideration. The double bonding character of the C—N bond, at which the ethylaniline fragment is fused to the maleimide ring, is evidenced by its shorter length (1.34 Å) and the higher negative charge (−0.579) compared to those observed for the bond at which the indole N atom is fused to the maleimide moiety (1.41 Å and −0.502, respectively, see Scheme 1, Fig. 2).

Apparently, these factors make a substantial contribution to hindering of free rotation of the ethylaniline group about the C—N bond, which decreases the probability of

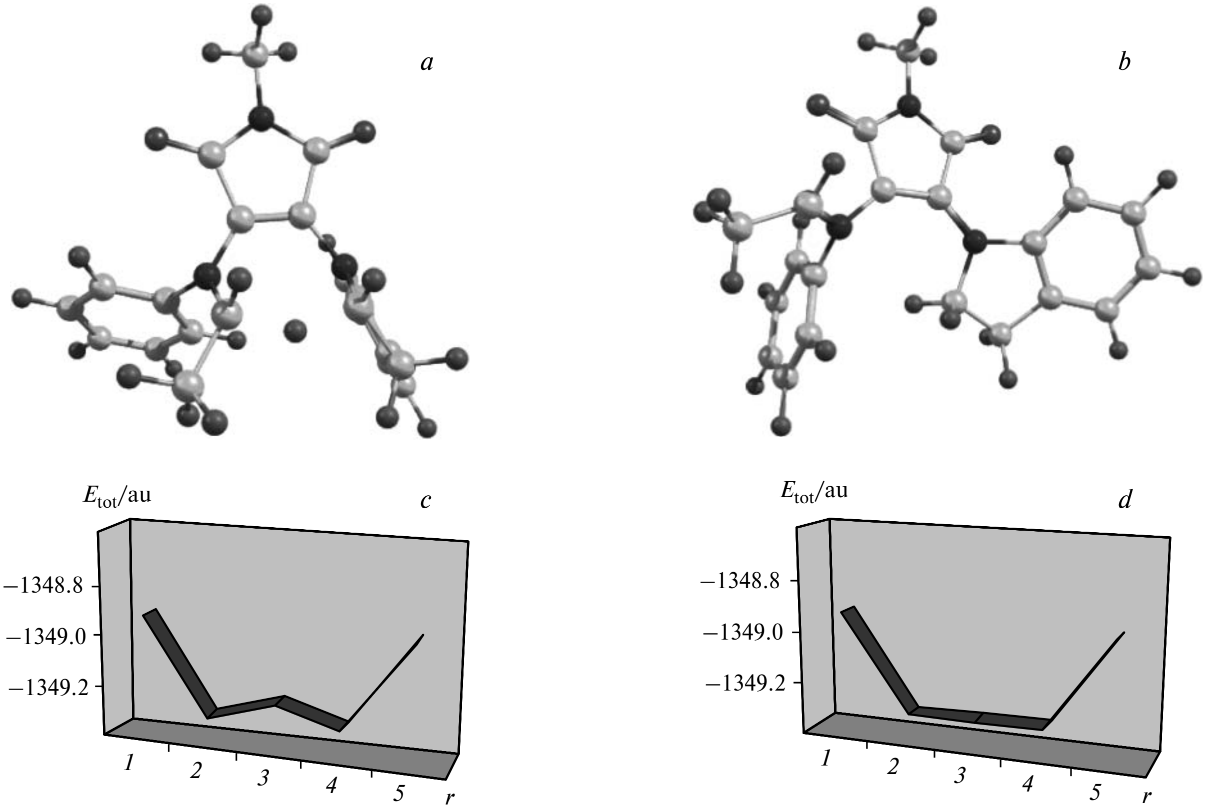


Fig. 1. Structures of the transition states TS_1 (*a*) and TS_2 (*b*) of compound **3** and the potential energy surface profiles (*c* and *d*, respectively) for the tandem hydride transfer/cyclization sequence: *1*, starting molecule **1**; *2*, indoleninium cation **2**; *3*, the transition state (the activated complex); *4*, protonated diazepine **4**; *5*, final diazepine molecule **5**; *r* is the reaction coordinate.

the spatial proximity between the phenyl ring and the electrophilic C(2) center of the indole fragment. Consequently, the spatial proximity between one of the H atoms of the methylene group of the ethylaniline fragment and the cationic center at the C(2) atom of the indole bicyclic fragment is the main factor determining the direction of the transformation of the indoleninium cation (see Fig. 2).

A study of *N*-methyl-2-(*N*-ethylanilino)-3-(indol-3-yl)maleimide (see Scheme 3) demonstrated that tandem hydride transfer/cyclization at the indole C(7) atom do not occur upon protonation of this compound. This fact can also be attributed to the influence of the steric factor. Thus the hydride ion in indoleninium cation **7** (Fig. 3) cannot approach the electrophilic center at the C(2) atom of the indole moiety at the necessary angle. The calculated activation energy for the hypothetical tandem hydride transfer/cyclization sequence for **7** is rather high ($E^{\#}$ = 38.29 kcal mol^{-1}) compared to that for the reaction

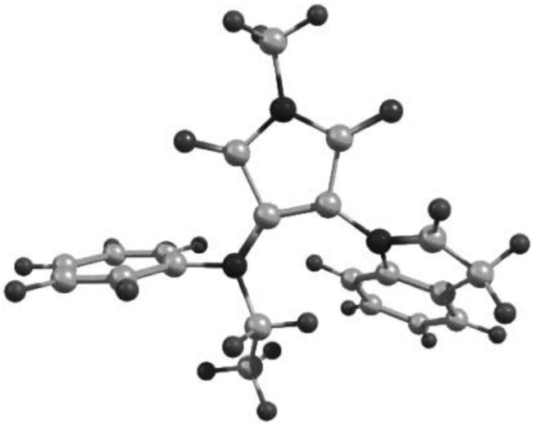


Fig. 2. Structure of indoleninium cation **2**.

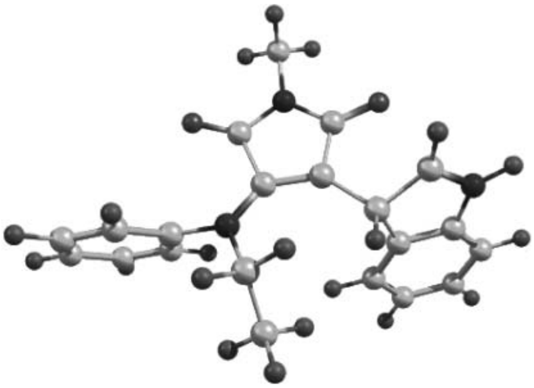


Fig. 3. Structure of indoleninium cation **7** related to 2-(*N*-ethylanilino)-3-(indol-3-yl)maleimide **6**.

of **2** proceeding through iminium transition state **3**. By contrast, $E^{\#}$ for cyclization of **7** at the phenyl group of the ethylaniline fragment is 13.09 kcal mol^{-1}. The rotation of the ethylaniline group about the C—N bond in cation **7**, which could provide a convenient conformation for the hydride transfer, is also apparently hindered due to an increase in the order of the C—N bond conjugated to the strongly electronegative maleimide ring, which is analogous to the situation observed for *N*-ethylanilinoindolylmaleimide (see above).

Based on the results of our calculations, as well as on the data reported in the study,[4] it can be concluded that "open" transition state **3**, *viz.*, the iminium cation, is preferable for the transformation of **1** involving the tandem hydride transfer/cyclization sequence due to the steric factors (the favorable geometric configuration of the indoleninium cation and its similarity to the configuration of the transition state). To the contrary, the transformation of **6** and its conjugated acid involves cyclization at the benzene ring without hydride transfer, which is in agreement with the experimental data.[3] We have also observed cyclization preceded by hydride transfer for *N*-methyl-2-diethylamino-3-(indol-1-yl)- and *N*-methyl-2-benzylamino-3-(indol-1-yl)maleimides.[1]

Calculation procedure

The structures of the reagents, the reaction products, the intermediates, and the transition states for all the reaction systems under consideration were calculated by the B3LYP density functional theory method with the 6-31G(d) basis set (the GAUSSIAN-98 program package[5]) and with full geometry optimization.

A search for the transition state was performed according to the standard algorithm using the QST3 procedure incorporated into the GAUSSIAN-98 program package (the saddle point determination) followed by calculations of the normal frequencies for the resulting configurations of the activated complexes according to the standard procedure incorporated into this program package.

The visualization of the geometric parameters of the calculated structures and the formal charges on atoms was carried out with the use of the Gauss View and ChemCraft program packages.

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