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QUANTUM-CHEMICAL STUDY OF NUCLEOPHILIC SUBSTITUTION IN PROTONATED TRISINDOLYLMETHANE*

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The total energies of reactants, products, and transition states of nucleophilic substitution reactions in protonated tris(indol-3-yl)methane have been assessed with the semiempirical AM1 method and the theory of functional density B3LYP/6-31(d) method. The results of calculations indicated that the reactions proceed by an S_N1-like mechanism, since the activation barrier for it is significantly lower than in the case of the S_N2-like mechanism.

Keywords: trisindolylmethane, quantum-chemical calculations, methods AM1, B3LYP/6-31G(d), nucleophilic substitution.

Tris(1-alkylindol-3-yl)methanes are the starting materials for obtaining tris(indol-3-yl)methylium salts possessing high cytotoxic activity. Tris(1-alkylindol-3-yl)methylium salts possess high cytotoxic activity and are inducers of apoptosis. The cytotoxic activity grows with increasing length of the alkyl substituent up to C(5) and then falls [1]. The properties of unsymmetrically N-substituted tris(1-alkylindol-3-yl)methylium salts have not been studied, since on synthesis of the initial unsymmetrical tris(1-alkylindol-3-yl)methanes by known methods mixtures of compounds are formed. Thus, on interacting 3-formyl-1-methylindole with 1-ethylindole in the presence of acid catalysts a mixture of tris(1-methylindol-3-yl)methane, tris(1-ethylindol-3-yl)methane, bis-(1-ethylindol-3-yl)(1-methyl-indol-3-yl)methane, and (1-ethylindol-3-yl)bis(1-methylindol-3-yl) methane is formed. The ratio of these products is determined by the reaction conditions and the means of separating the mixtures. Analogous mixtures are formed on interacting tris(1-alkylindol-3-yl)methane with 1-alkylindoles in the presence of acid catalysts (Lewis acids) (Scheme 1).

It may be proposed that under the action of Lewis acids an electrophilic center is induced in the trisindolylmethane molecule. This center is subject to attack by a nucleophile present in the reaction system (indole and its substituted derivatives). As quantum-chemical calculations of the partial Mulliken charges and Fukui indexes showed, the electron density on the C(3) atom of N-substituted derivatives of indole (possible

* Dedicated to the shining memory of A. N. Kost.

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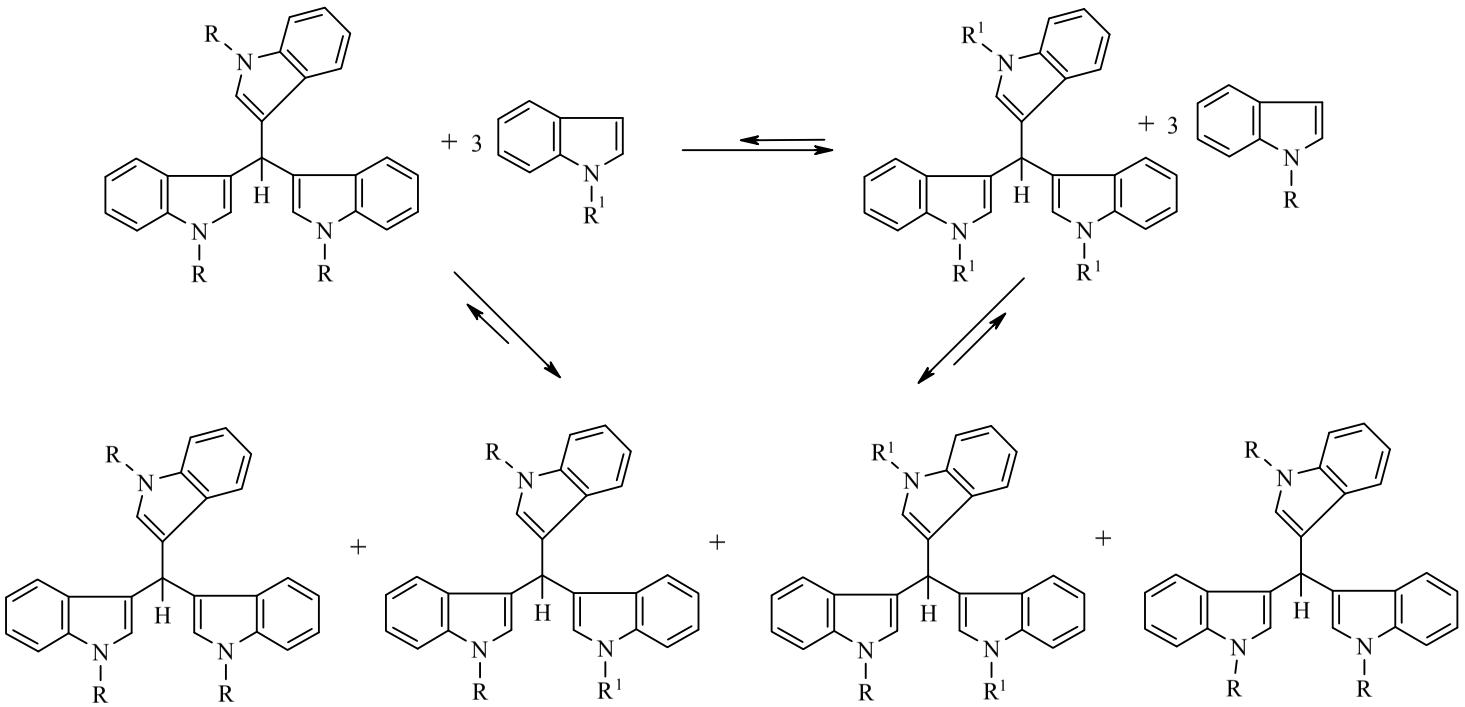
Scheme 1



R, R^1 = H, Me; Et , *n*-Pr; *n*-Bu, *n*-C_5H_{11}; *n*-C_6H_{13}, CH_2Ph; C_9H_{19}, $C_{10}H_{21}$

nucleophiles) is in fact unchanged in relation to the character of R and R^1 (Scheme 1) [1]. This indicates the possibility of carrying out a nucleophilic substitution according to an S_N1-like mechanism, the kinetics of which do not depend on the strength of the nucleophile (electron density at the nucleophilic center) [2, 3].

Further calculations showed that as a result of the action of the acids indicated above on trisindolylmethane (proton was used as model) structures are formed of the indolenium cation type (protonated trisindolylmethanes) (Fig. 1).

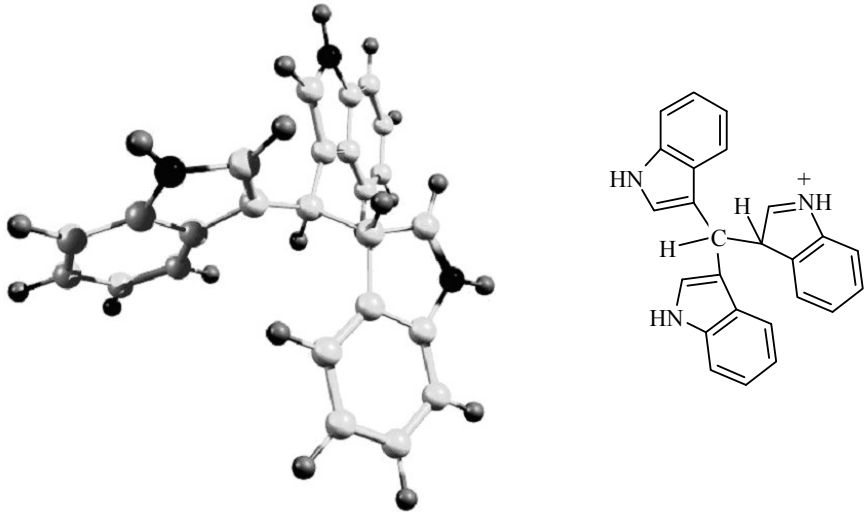
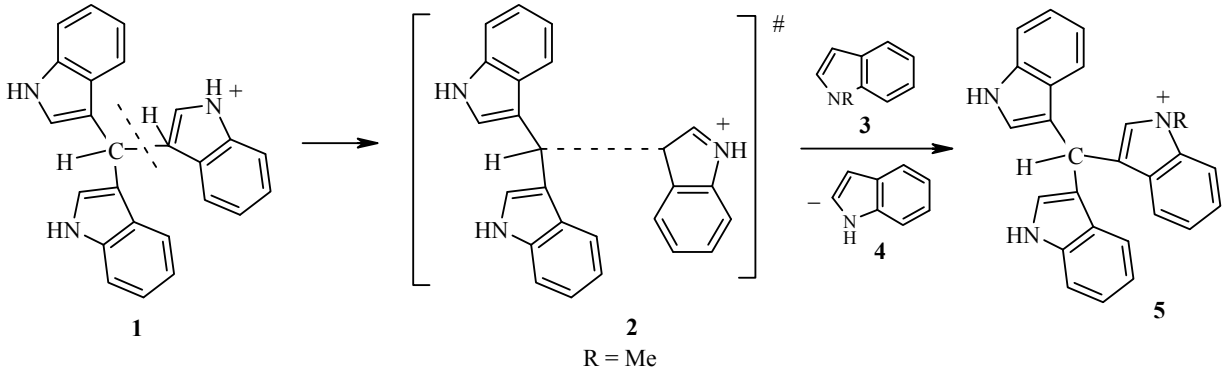


Fig. 1. 3D structure of protonated trisindolylmethane.

A special feature of the structure of protonated trisindolylmethane (Fig. 1) is the 'friability' of the C–C bond between the central carbon atom of trisindolylmethane and the carbon atom of the protonated indole ring. On protonation its length increases from 1.51 to 1.62 Å. This indicates the high probability of subsequent heterolytic cleavage of this bond in protonated trisindolylmethane.

We have investigated S_N1 (Scheme 2) and S_N2 variants (Scheme 3) of the mechanism of nucleophilic substitution in protonated trisindolylmethane.

Scheme 2

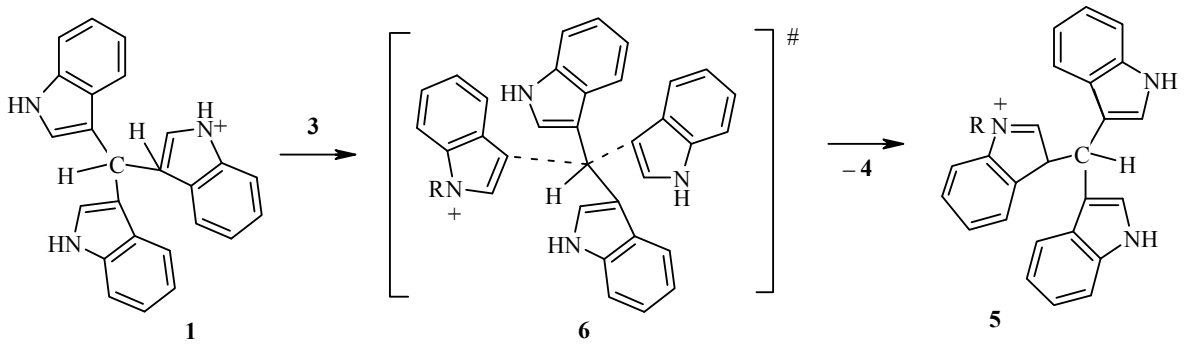


1 **2** **5**

R = Me

The hypothesis for the S_N1-like mechanism [2, 3] proposes heterolytic cleavage of the C–C bond in protonated trisindolylmethane **1**, after which the nascent cationic structure **2** attacks N-methylindole **3**, forming a new protonated derivative of trisindolylmethane **5**. The molecule of indole **4** is here a nucleophuge. We note

Scheme 3



1 **6** **5**

R = Me

that in the S_N1-like mechanism a transition state was proposed in which the C–C distance between the central carbon atom in trisindolylmethane and the carbon atom of the protonated indole ring is 2.01 Å, according to the calculation data. In the S_N2-like mechanism [2, 3] it was proposed that protonated trisindolylmethane **1** is attacked from the rear by a molecule of N-methylindole **3** and then product **5** is formed through transition state **6** with loss of nucleophuge **4**.

The quantum-chemical calculations of reactants, products, and transition states of reactions, carried out by the semiempirical AM1 method [4] and by the theory of functional density B3LYP/6-31G(d) [5] using the Gaussian 98 [6] and Spartan-08 [7] sets of programs, showed that in the gas phase the activation barriers $\Delta E^{\#}$ = 16.4 (AM1) and $\Delta E^{\#}$ = 16.1 kcal/mol (B3LYP/6-31G(d)) were more favorable for the reaction to proceed according to the S_N1-like mechanism (Scheme 2) than according to the S_N2-like mechanism (Scheme 3), for which (see Table 1) $\Delta E^{\#}$ = 51.8 (AM1) and $\Delta E^{\#}$ = 80.2 kcal/mol (B3LYP/6-31G(d)).

Such high activation barriers found in the calculations of the S_N2-like transition state are evidently explained by the distribution of electron density, as also by the stereoelectronic obstacles, arising from the rear approach of the bulky reactant (Scheme 3, Fig. 2*b*). According to the data of the AM1 and B3LYP/6-31G(d) methods, the charge on the central carbon atom in protonated trisindolylmethane was +0.040 (AM1) and -0.263 (B3LYP/6-31G(d)), in connection with which the possible subject of electrophilic attack may be considered to be not the central carbon atom, but atom C(2) of the protonated indole ring with a deficit of electrons, +0.067 (AM1) and +0.171 (B3LYL/6-31G(d)). For the S_N1-like mechanism (Scheme 2, Fig. 2a) such obstacles are absent.

It is interesting to note that the dissociation energy of protonated trisindolylmethane in the gas phase (Scheme 2) is comparatively small at -4.8 kcal/mol (B3LYP/6-31G(d)). The calculated effect of solvation in ethanol also indicates a preference for the S_N1-like mechanism. Within the framework of the PCM model [8] the

TABLE 1. Activation Barriers $\Delta E^{\#}$ Calculated by AM1 and B3LYP/6-31G(d) Methods for the Substitution Reaction of the Indole Residue of 1-Methylindole in Protonated Trisindolylmethane Proceeding according to an S_N1- or S_N2-like Mechanism

Mechanism	$\Delta E^{\#}$, kcal/mol				
	AM1		B3LYP/6-31G(d)		
	Gas phase	Water	Gas phase	Water (PCM)	EtOH (PCM)
S_N1	16.4	20.2	16.1	18.4	20.7
S_N2	51.8	59.9	80.2	—	—

dissociation energy of protonated trisindolylmethane (Scheme 2) on using the B3LYP/6-31G(d) method was -11.6 kcal/mol, i.e. less by 6.8 kcal/mol than in the gas phase.

According to the data of the calculations the formation of a mixture of N-alkylated trisindolylmethanes (Scheme 1) as a result of the reaction of N-alkylindoles with trisindolylmethanes in the presence of acid catalysts is explained by a predominance in the reaction mixture of particles of a cationic nature, corresponding to an S_N1-like mechanism [2, 3].

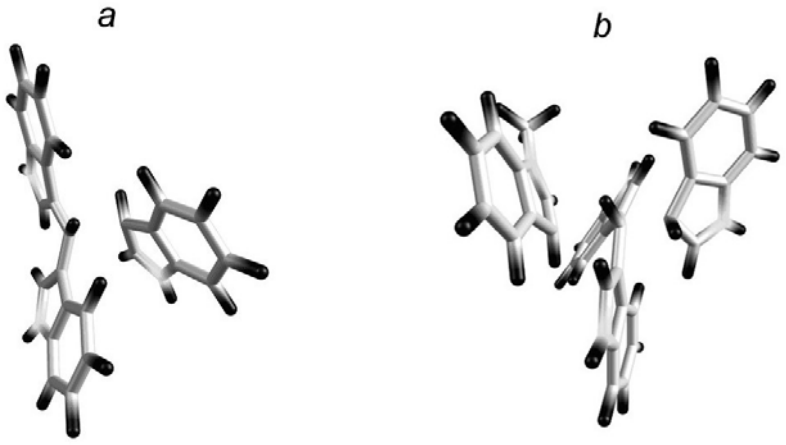


Fig. 2. 3D structures of the calculated transition states for *a*) S_N1- and *b*) S_N2-like mechanisms.

As already indicated above, the length of the N-alkyl substituent in tris(1-alkylindol-3yl)methanes does not affect the dissociation energy of protonated tris(1-alkylindol-3-yl)methanes.

When it was established by the calculations the nucleophilic substitution is more likely occur according to an S_N1-like mechanism (Scheme 2), the next problem was to study the effect of substituents of both donating and withdrawing type on the dissociation of protonated trisindolylmethane, being the limiting stage of the S_N1 mechanism [2, 3]. Quantum-chemical calculations by the AM1 and B3LYP/6-31G(d) methods showed that an electron-donating substituent in position 4 of the indole ring of protonated trisindolylmethane **1** reduces the energy of its dissociation according to Scheme 4 but an electron-withdrawing substituent in the same position increases this energy in comparison with that of the unsubstituted trisindolylmethane (Table 2).

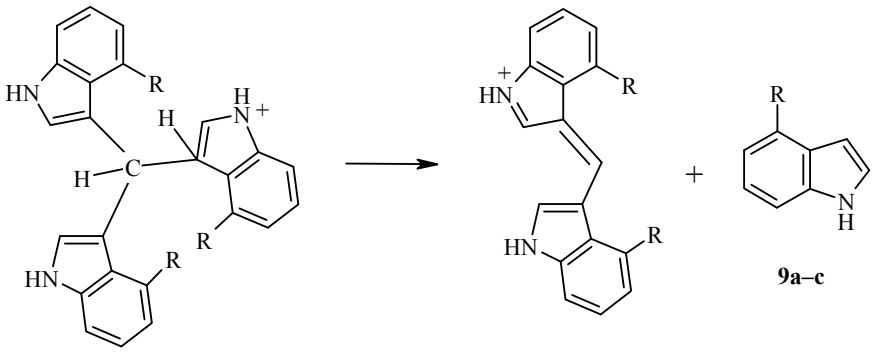
For the same substituents located in positions 5 and 6 of the indole nucleus, calculations of the dissociation energy of protonated derivatives of trisindolylmethane showed the absence of a correlation with the character of the substituent.

Consequently, based on the results of the calculations carried out there is a basis for assuming that the introduction of electron-donating substituents into position 4 of the indole nucleus will favor the course of nucleophilic substitution in protonated trisindolylmethane according to an S_N1-like mechanism as a result of stabilization of cation **8a-c** formed in the course of the reaction (Scheme 4).

TABLE 2. Dissociation Energies of Protonated Trisindolylmethanes **7**

Compound	Δ*E*, kcal/mol	
	AM1	B3LYP/6-31G(d)
7a	5.8	-6.5
7b	0.4	-15.2
7c	12.0	-3.1

Scheme 4



7–9 a R = H, **b** R = Me, **c** R = NO_2

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