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Stable σ^H-adducts in the reactions of the acridinium cation with heterocyclic N-nucleophiles*

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A reaction of NH-heterocycles with the 10-methylacridinium cation in the presence of a base led to 9,10-dihydro-10-methyl-9-substituted acridines, which can be considered as stable intermediates in the aromatic nucleophilic substitution reaction of hydrogen. The structure of the intermediates was studied and their oxidation potentials were determined. Generally, the oxidation potential was found to symbatically change with the changes in the energy of HOMO.

Key words: aromatic nucleophilic substitution of hydrogen, σ^H-adducts, acridine, NH-heterocycles, cyclic voltammetry.

Classic methods for the functionalization of aromatic rings are based on electrophilic substitution reaction of hydrogen (S_E^H Ar) and nucleophilic substitution of groups readily leaving as anions (S_N^{ipso} Ar). The last decades are marked by the really triumphant development of the transition metal catalyzed cross-couplings at the C—X bond of arenes (X is the group readily leaving as an anion) with C- and heteroatomic nucleophiles (Negishi, Kumada, Suzuki, Buchwald reactions, *etc.*). At the same time, the contemporary requirements stimulate development of chemical science in agreement with the "green" chemistry principles and elaboration of environmentally friendly processes.[1] In the year 2005, the Green Chemistry Institute (GCI, USA) and global pharmaceutical corporations prioritized directions of the research and development in the field of chemistry.[2] Among other problems, a direct functionalization of the C—H bond in arenes was put on the first place.

One of the atom-saving variations of cross-coupling, which does not require the use of halides and transition metal catalysis, is the aromatic nucleophilic substitution reaction of hydrogen (S_N^H).[3,4] By the present moment, a vast body of data is accumulated on the S_N^H-coupling reactions leading to the formation of C—C, C—N, C—O, C—P, C—S, C—Si, and C—Hal bonds in various aromatic compounds of both carbo- and heterocyclic series.[5—8] The first step of the S_N^H-reaction includes a nucleophilic attack of the substrate with the formation of the intermediate σ^H-adduct (Scheme 1). Then follows the step of its aromatization, which is accompanied by the leaving of hydrogen and an electron pair (formally, the hydride ion) by the elimination (AE) or oxidation (AO) S_N^H-mechanism.

Rather frequently, the S_N^H AO reaction is carried out as a three-component synthesis, *i.e.*, an oxidant is added to the system simultaneously with the reaction participants. Obviously, it is necessary in this case to take into account the susceptibility of the reagents to oxidation: first of all of the nucleophile, and sometimes of the substrate **I**, too.

Thus, the choice of a proper oxidant is a crucial factor in accomplishing the S_N^H-conversions. At the present time, there are no clear-cut criteria of such choice, therefore, chemists at large are usually governed by their experience, intuition, and some empirical rules.[9,10] All of this does not stimulate development of S_N^H-reactions. An approach to the rational choice of the oxidation agent can be based on the measurement of oxidation potentials of σ^H-adducts **II** and on their structure. The studies of the behavior σ^H-intermediates on the anode is of sepa-

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* Dedicated to Academician of the Russian Academy of Sciences I. P. Beletskaya on the occasion of her anniversary.

Scheme 1
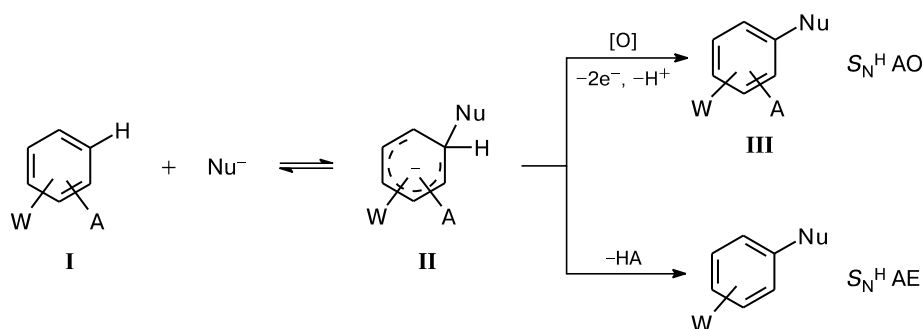
W is electron-withdrawing group. A is assisting group.

rate interest as an electrochemical version of $S_N{}^H$-reactions.

The choice of the acridinium cation as an object for this study was made based on the fact that it is a convenient model with only one electrophilic center. Besides, the acridines with substituents at position **9** are of interest because of their biological activity. Acridine derivatives are known to act as antiseptics.[11] In the last years, they were found to exhibit antitumor,[12,13] antiviral,[14,15] antimalarial,[16] antiprionic,[17] and analgesic properties.[18] Meanwhile, only a limited amount of works are devoted to the synthesis and studies of the properties of σ^H-adducts of acridine with N-nucleophiles. Thus, the synthesis of stable σ^H-adducts obtained by the attack of morpholine and piperidine on the acridinium cation was reported in the work.[19] Besides, the formation of unstable N-bound σ^H-adducts in the reaction of primary arylamines with 10-methylacridinium iodide (**1**) was detected by NMR and UV spectroscopy. Such adducts were shown to be unstable and to exist only in solutions at reduced temperatures.[20] The only example of this-type stable σ^H-adduct, which was characterized by X-ray crystallography, was obtained when 1,2,3-benzotriazole was used as the nucleophile.[21]

In the present work, we used a wide range of heterocyclic N-nucleophiles for the synthesis of 9,10-dihydro-10-methyl-9-substituted acridines. The reaction of 10-methylacridinium iodide (**1**) with NH-heterocycles gave the corresponding 9,10-dihydro-10-methyl-9-substituted acridines **2—9** in high yields (Scheme 2, Table 1). Physical and spectral characteristics of compounds **2** and **7** agree with the corresponding characteristics of compounds described earlier.[19,22]

The ^{1}H NMR spectra of dihydroacridines **2—9** obtained exhibit signals for the protons of the added heterocyclic moieties (Table 2), a singlet for the methyl group in the region δ 3.39—3.63 and characteristic signals in the region δ 6.90—7.80 corresponding to the aromatic protons of the acridine framework. The spectra of the N-adducts with the aromatic NH-heterocycles **2—6** are distinguished by the position of the signal for proton H(9) in the region

Scheme 2
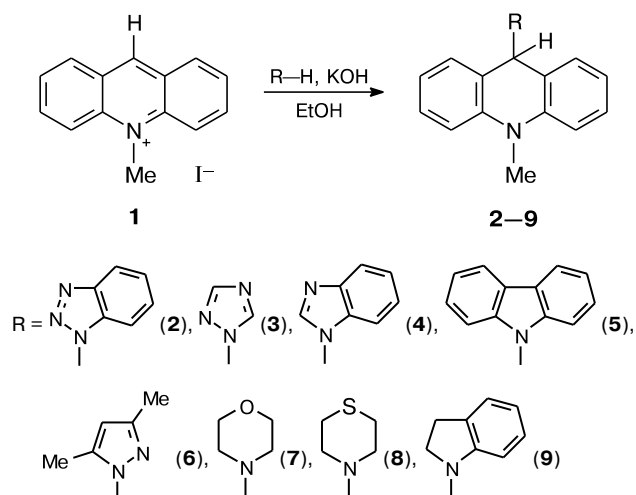
Table 1. Characteristics of compounds **2—9**

Com-pound	Molecular formula	Found Calculated (%)			M.p./°C	Yield (%)
		C	H	N		
2	$C_{20}H_{16}N_4$	<u>77.09</u> 76.90	<u>4.94</u> 5.16	<u>17.94</u> 17.94	169 (Pr^{i}OH)	74
3	$C_{16}H_{14}N_4$	<u>73.27</u> 73.26	<u>5.48</u> 5.38	<u>20.42</u> 21.36	182 (EtOH)	85
4	$C_{21}H_{17}N_3$	<u>80.73</u> 81.00	<u>5.63</u> 5.50	<u>13.22</u> 13.49	190 (EtOH)	83
5	$C_{26}H_{20}N_2$	<u>86.01</u> 86.64	<u>5.55</u> 5.59	<u>7.74</u> 7.77	196 (EtOH)	88
6	$C_{19}H_{19}N_3$	<u>78.87</u> 78.86	<u>6.80</u> 6.62	<u>14.59</u> 14.52	136 (MeOH)	79
7	$C_{18}H_{20}N_2O$	<u>77.06</u> 77.11	<u>7.33</u> 7.19	<u>9.93</u> 9.99	141 (EtOH)	91
8	$C_{18}H_{20}N_2S$	<u>73.15</u> 72.93	<u>6.95</u> 6.80	<u>9.37</u> 9.45	160 (EtOH)	88
9	$C_{22}H_{20}N_2$	<u>84.07</u> 84.58	<u>6.49</u> 6.45	<u>8.96</u> 8.97	129 (EtOH)	72

Table 2. ^{1}H NMR spectra of compounds **2**—**9** in solutions in DMSO-d$_6$

Compound	δ
2	3.63 (s, 3 H, NCH$_3$); 6.96 (s, 2 H, Ar); 7.29—7.55 (m, 9 H, Ar); 7.74 (s, 1 H, H(9)); 7.96 (m, 1 H, Ar)
3	3.50 (s, 3 H, NCH$_3$); 6.95 (s, 1 H, H(9)); 7.00—7.46 (m, 8 H, Ar); 7.80 (s, 1 H, H$_{Az}$); 8.14 (s, 1 H, H$_{Az}$)
4	3.60 (s, 3 H, NCH$_3$); 6.95 (m, 2 H, Ar); 7.14 (m, 2 H, Ar); 7.18 (s, 1 H, H(9)); 7.27 (m, 2 H, Ar); 7.36 (m, 4 H, Ar); 7.51 (m, 1 H, Ar); 7.60 (m, 1 H, Ar); 8.00 (s, 1 H, H$_{Az}$)
5	3.56 (s, 3 H, NCH$_3$); 6.58—6.69 (m, 4 H, Ar); 7.18—7.39 (m, 10 H, Ar); 7.54 (s, 1 H, H(9)); 8.20 (m, 2 H, Ar)
6	2.02 (s, 3 H, CH$_3$); 2.11 (s, 3 H, CH$_3$); 3.45 (s, 3 H, NCH$_3$); 5.8 (s, 1 H, H$_{Az}$); 6.73 (s, 1 H, H(9)); 6.92 (m, 4 H, Ar); 7.13 (m, 2 H, Ar); 7.30 (m, 2 H, Ar)
7	2.13 (m, 4 H, N(CH$_2$)$_2$); 3.35 (m, 4 H, O(CH$_2$)$_2$); 3.39 (s, 3 H, NCH$_3$); 4.64 (s, 1 H, H(9)); 7.00 (m, 2 H, Ar); 7.11 (m, 2 H, Ar); 7.30 (m, 4 H, Ar)
8	2.42 (s, 8 H, CH$_2$), 3.39 (s, 3 H, NCH$_3$), 4.78 (s, 1 H, H(9)), 6.99 (m, 2 H, Ar); 7.10 (m, 2 H, Ar); 7.29 (m, 4 H, Ar)
9	2.66 (m, 2 H, CH$_2$); 2.77 (m, 2 H, CH$_2$); 3.44 (s, 3 H, NCH$_3$); 6.13 (s, 1 H, H(9)); 6.51 (m, 1 H, Ar); 6.93 (m, 3 H, Ar); 7.03—7.12 (m, 4 H, Ar); 7.27—7.33 (m, 4 H, Ar)

δ 6.7—7.7, whereas for similar C-adducts, the signal for this proton is found in the region δ 5.0—5.5 (see Ref. 23), while in the case of addition of cycloalkylimines (compounds **7** and **8**), the signal for proton H(9) is in the region δ 4.64—4.78 (see Table 2).

The studies of geometric configuration of the geminal center at atom C(9) of the acridine fragment is important for the understanding of the transition state structure of both the addition step and the aromatization of adducts **2**—**9**. Single crystals of compound **3**—**5**, **7**, and **8** were studied by X-ray cristallography. The principal crystallographic parameters are given in Table 3. The molecular structures of compounds and the atom numbering scheme accepted in the structural experiments are given in Fig. 1.

Table 3. Principal crystallographic data and parameters of refinement for the structures of compounds **3**—**5**, **7**, and **8**

| Parameter	**3**	**4**	**5**	**7**	**8**
Formula	C$_{16}$H$_{14}$N$_4$	C$_{21}$H$_{17}$N$_3$	C$_{26}$H$_{20}$N$_2$	C$_{18}$H$_{20}$N$_2$O	C$_{18}$H$_{20}$N$_2$S
Temperature/K	295(2)	295(2)	295(2)	295(2)	
Crystal system	Monoclinic	Monoclinic	Orthorhombic	Tetragonal	Monoclinic
Space group	$P2_1/n$	$P2_1/c$	$Pbca$	P-42_1c	$P2_1/n$
a/Å	9.0097(3)	15.0541(13)	9.1049(8)	19.4503(12)	15.8091(10)
b/Å	10.4927(4)	10.4942(6)	17.6977(12)	19.4503(12)	5.6004(5)
c/Å	14.1909(5)	10.5119(7)	23.693(2)	7.8538(12)	17.701(2)
α/deg	90	90	90	90	90
β/deg	90.958(3)	103.436(7)	90	90	103.380(8)
γ/deg	90	90	90	90	90
V/Å^3	1341.36(8)	1615.2(2)	3817.8(6)	2971.2(5)	1524.7(2)
Z	4	4	8	8	4
d_{calc}/g cm^{-3}	1.299	1.280	1.254	1.253	1.291
μ/mm^{-1}	0.081	0.077	0.073	0.078	0.207
Region of measurements, θ/deg	2.70 < θ < 30.52	2.78 < θ < 26.34	2.66 < θ < 26.38	2.80 < θ < 26.34	3.12 < θ < 26.38
Number of observed reflections	9619	7255	16189	6812	5569
Number of independent reflections	4023	3217	3900	1642	2999
R_{int}	0.0168	0.0298	0.0398	0.0382	0.0323
Number of reflection with ($I > 2\sigma(I)$)	2137	1452	1809	927	1671
Completeness of reflection massif (%)	98.2%	97.3%	99.7%	95.8%	96.6%
Q-Factor F^2	1.001	1.005	1.004	1.001	1.008
R_1 ($I > 2\sigma(I)$)	0.0366	0.0356	0.0378	0.0309	0.0580
wR_2 ($I > 2\sigma(I)$)	0.0846	0.0758	0.0884	0.0792	0.1946
R_1 (on all the parameters)	0.0700	0.0893	0.0934	0.0660	0.0996
wR_2 (on all the parameters)	0.0889	0.0798	0.0943	0.0830	0.2047
Residual electron density (ρ_{max}/ρ_{min})/e Å^{-3}	0.137/−0.163	0.129/−0.150	0.167/−0.213	0.146/−0.146	0.412/−0.238
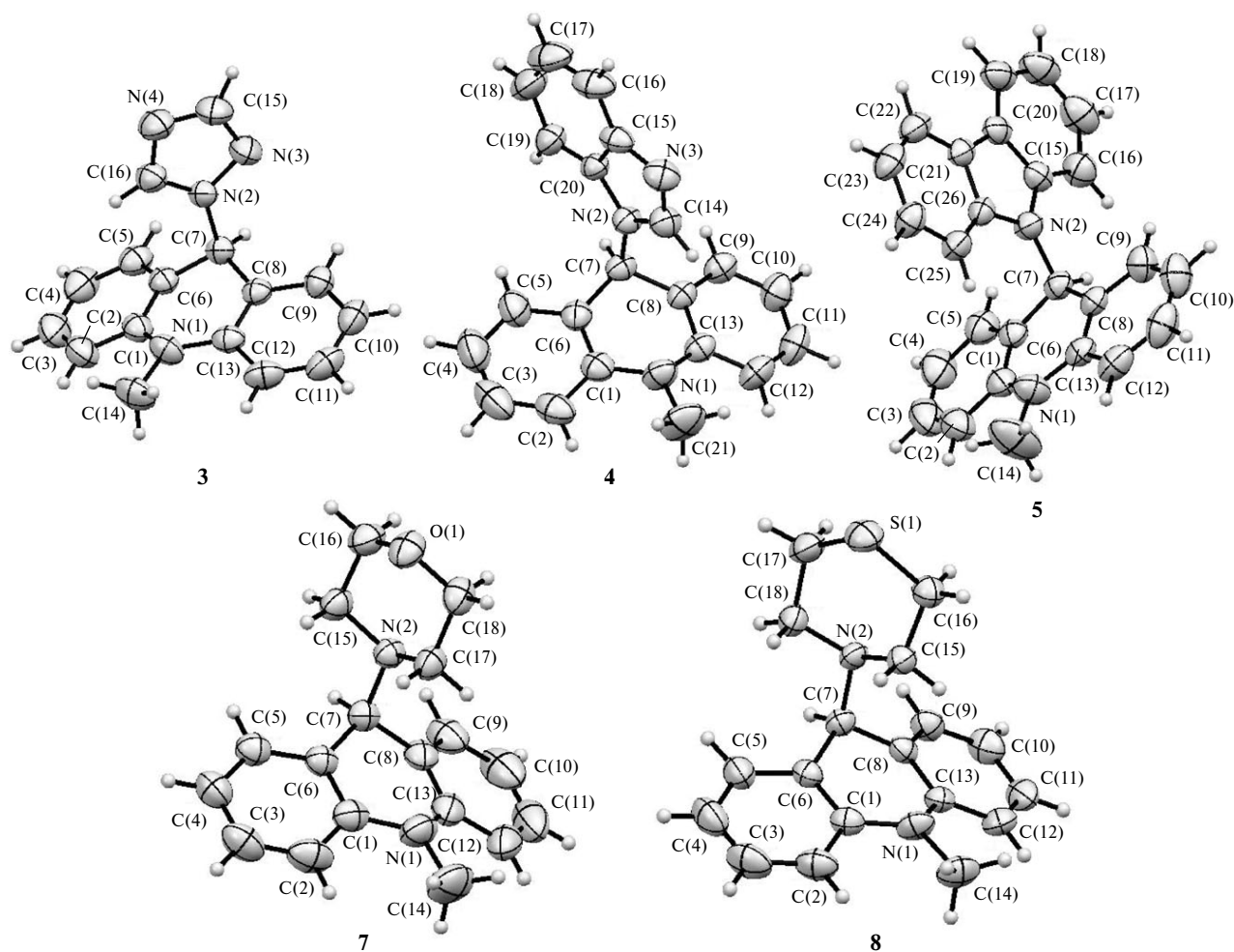
Fig. 1. Molecular structures of compounds **3**—**5**, **7**, and **8**.

The X-ray diffraction analysis data show that the compounds under study crystallize in the centrosymmetric space groups of symmetry. The molecular packing of the compounds is nonspecific, any essential shortened contacts are absent. As it was already mentioned, the sp³-hybridized atom at position 9 is the most important structural element of the molecule (in the structural experiment atom C(7)), which causes a distortion of the acridine system. The conformation of the dihydropyridine ring in compounds under consideration can be characterized as a pseudoboat, with atoms C(7) and N(1) deviating from the plane of the ring and the axial position of the added NH-heterocycle. As a result, the dihydropyridine ring experiences a bend along the axis N(1)—C(7), with the dihedral angle between the phenylene rings being able to reach a considerable value (29.67° for compound **7**, Table 4). The bond distances in the phenylene fragments are generally in good agreement with the standard values, the spread of the corresponding bond distances does not exceed 0.01 Å with respect to the average values. The length of the C(7)—N(2) bond increases in the sequence of compounds **5** < **8** < **4** < **7** < **3**, however, the difference between the maximal and the minimal bond distances is slightly more than 0.02 Å, which does not allow one to consider these changes as significant. At the same time, this value correlates well with the change in the dihedral angle between the plane of the N-nucleophilic fragment and the plane determined by atoms N(1)C(7)N(2) (see Table 4). Especially note that the dihedral angles between the phenylene rings correlate with the measured oxidation potentials (see Tables 4 and 5). Thus, as the distortion angle of the acridine system increases in the sequence of compounds **5**, **3**, **4**, **7**, their oxidation potentials decrease.

The oxidation potentials of 9,10-dihydro-10-methyl-9-substituted acridines **2**—**9** were determined by cyclic voltammetry (see Table 5).

Note that in the earlier works devoted to the study of electrochemical oxidation of dihydroacridines **A** on a platinum disk electrode with a ring, it was shown that the oxidation process included the electron transfer leading to the formation of radical cationic particles **B**, with their

Table 4. Selected bond distances, bond and dihedral angles for compounds **3—5**, **7**, and **8**

Parameter	3	4	5	7	8
Bond			d/Å		
C(7)—H(7)	0.970(9)	1.003(13)	0.969(13)	1.01(3)	0.92(4)
C(7)—N(2)	1.4929(11)	1.4860(19)	1.4701(19)	1.489(3)	1.479(4)
C(6)—C(7)	1.4951(13)	1.498(2)	1.500(2)	1.516(4)	1.509(4)
C(7)—C(8)	1.4974(12)	1.498(2)	1.495(2)	1.505(4)	1.495(5)
N(1)—C(1)	1.3979(12)	1.395(2)	1.390(2)	1.401(4)	1.396(4)
N(1)—C(13)	1.3956(12)	1.4015(19)	1.395(2)	1.405(5)	1.407(4)
N(1)—C(14)	1.4578(12)	1.465(2)	1.454(2)	1.465(4)	1.465(5)
C(1)—C(6)	1.4001(13)	1.399(2)	1.388(2)	1.393(4)	1.393(5)
C(8)—C(13)	1.4000(12)	1.395(2)	1.388(2)	1.388(4)	1.383(5)
C(3)—C(4)	1.3795(17)	1.368(3)	1.363(3)	1.365(4)	1.351(7)
C(10)—C(11)	1.3715(16)	1.382(3)	1.362(3)	1.382(6)	1.376(6)
Angle			ω/deg		
α^a	0.325	0.376	0.101	0.352	0.344
β^b	42.43	25.94	5.45	24.07	27.49
γ^c	21.74	28.36	6.66	29.67	24.14

[a] Angle α is the deviation of atom C(7) from the plane C(1)C(6)C(8)C(13).
[b] Angle β is the turn of the plane of N-nucleophile with respect to the plane N(1)C(7)N(2).
[c] Angle φ is the dihedral angle between the phenylene rings in dihydroacridines.

subsequent deprotonation and oxidation of radicals **C** to products **D** of the $S_N{}^H$-reaction (Scheme 3).[24,25]

It is obvious that the step of the single-electron transfer initiating this process should correlate with the HOMO energies of dihydroacridines. In fact, the calculations showed that the HOMO energies correlated well enough with the oxidation potentials of σ^H-adducts under studies. Quantum chemical calculations of the energies of HOMO, as the orbitals directly "involved" in the oxidation (see Table 5), were performed using the GAUSSIAN 09 software.[26] The correlation between the HOMO energy and the oxidation potential (Fig. 2) allows us to draw a con-

Scheme 3
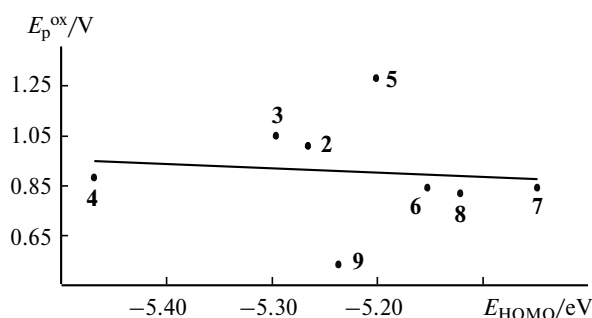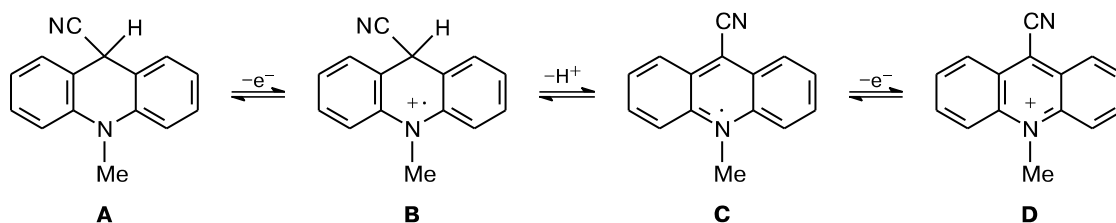
Fig. 2. The correlation dependence between the HOMO energies and the oxidation potentials $E_p{}^{ox}$ of compounds **2—9**.

Table 5. The calculated energies of HOMO and the experimentally found oxidation potentials

Compound	E_{HOMO}/eV	$E_p{}^{ox}$/V
2	−5.26540	1.01
3	−5.29615	1.05
4	−5.46894	0.88
5	−5.20091	1.28
6	−5.15248	0.84
7	−5.04771	0.84
8	−5.12064	0.82
9	−5.23656	0.53

clusion that the oxidation potentials of compounds, except **5** and **9**, change symbatically with the changes of the HOMO energies.

It can be suggested that the development of this approach will allow one to use quantum chemical calculations for the evaluation of stability of forming σ^H-adducts and their oxidation potentials, that, in turn, will suggest a more rational choice of synthetic methods and selection of oxidants for aromatization.

Experimental

Cyclic voltammograms were recorded on an Autolab PGSTAT128N instrument. The studies were carried out under inert gas argon in anhydrous acetonitrile with the additives of supporting electrolyte Bu_4NClO_4 (0.1 mol L^{-1}) at 17—18 °C in a three-electrode system. A platinum disk electrode ($d = 2$ mm) served as a working electrode, a glass graphite rod as a auxiliary electrode, Ag/AgCl was a reference electrode. The scanning rate 100 mV s^{-1}. The concentration of the samples 10^{-3} *M*. Elemental analysis was performed on a Carlo Erba 1108 automatic CHNO analyzer. ^{1}H NMR spectra were obtained on an AVANCE DRX-400 spectrometer (Bruker BioSpin) (solvent DMSO-d$_6$), using Me$_4$Si as an internal standard.

X-ray diffraction studies were performed on a Xcalibur 3 automatic four-circle diffractometer, using a standard procedure (Mo-Kα irradiation, graphite monochromator, 295(2)K, $\omega/2\theta$-scan technique). The structure was solved and refined using the SHELX software.[27] All the nonhydrogen atoms were refined in anisotropic approximation, some hydrogen atoms were placed into geometrically calculated positions and included into the refinement using the riding model with the dependent isotropic thermal parameters, some atoms (including all the protons at the sp^3-hybridized carbon atom of the dihydroacridine system) were solved and refined independently in isotropic approximation. The final parameters of refinement of the structure and some crystallographic parameters are given in Table 5. The results of the X-ray diffraction analysis were deposited with the Cambridge Structural Database (CCDC 929423, 929424, 929426—929428).

Acridine was commercially available from Aldrich. 10-Methylacridinium iodide was synthesized according to the known procedure.[28]

9,10-Dihydro-10-methyl-9-substituted acridines 2—9 (general procedure). An ethanolic solution (3 mL) of potassium hydroxide (38 mg, 0.685 mmol) and the corresponding NH-heterocycle (0.685 mmol) were added to a suspension of 10-methylacridinium iodide (**1**) (200 mg, 0.623 mmol) in ethanol (3 mL). The reaction mixture was stirred at room temperature for 40—50 min, then diluted with water (15 mL). A precipitate formed was filtered off, washed with water, and recrystallized from the corresponding solvent.

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