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Electrochemical oxidative aromatization of 9-substituted 9,10-dihydroacridines: cleavage of C–H *vs* C–X bond

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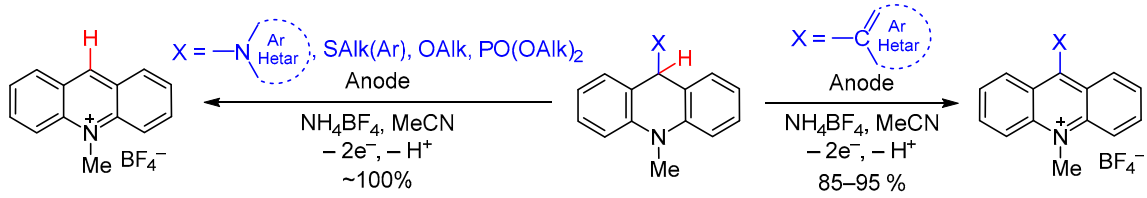


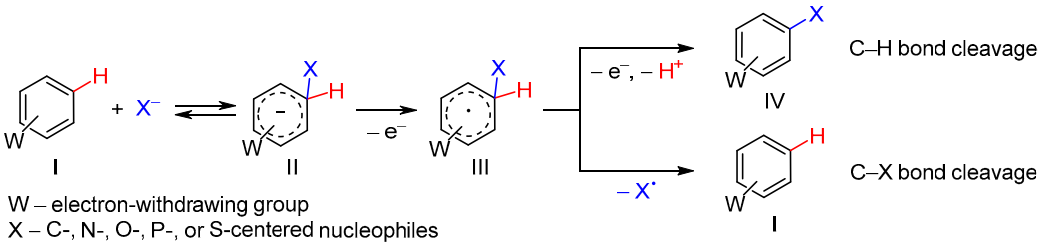
Reactivity of dihydroacridines bearing a C–X fragment at the geminal C-9 atom (where X = C, N, O, P, S) on anode has been investigated by means of electrochemical oxidation and thermodynamic and quantum-chemical calculations. The electrochemical oxidation results either in the formation of the 9-substituted acridines or in the cleavage of the C–X bond. This dual behavior of dihydroazines is analogous to processes reported in literature that take place upon treatment with chemical oxidants.

Keywords: acridines, dihydroacridines, bond dissociation energy, C–H functionalization, electrochemical oxidation, S_N^H reactions, thermodynamic studies.

Nitrogen-containing heteroaromatic ring systems are building blocks for a wide range of compounds with pharmaceutical and technical applications.[1,2] Acridines, a class of nitrogen heterocycles, are actively used as photoredox catalysts,[3] molecular machines,[4] sensors,[5] and transistors.[6] Besides, acridine derivatives are especially attractive due to their various biological activity.[7,8] Inhibitors of acetylcholinesterase,[9] substances with antitumor,[10,11] antiviral,[12] antimalarial,[13] antiprion,[14] analgesic[15] properties have recently been found among these compounds. Importantly, the 9-substituted acridines are applied as NAD^+ coenzyme models for the study of hydride transfer reaction.[16,17] However, effective methods of their functionalization are limited and usually based on cross-coupling reactions with transition metals.[18,19] The most common ways of the synthesis of 9-substituted acridines are still the methods of building the acridine scaffold from prefunctionalized ring systems[20–23] and substituting easily leaving groups, mainly chlorine.[24]

At the same time there are methods of direct C–H functionalization without metallocatalysis, including reactions of the nucleophilic aromatic substitution of hydrogen (S_N^HAr reactions).[25–29] According to the generally accepted mechanism of the S_N^HAr reactions, these processes take place following a two-stage scheme. In the first stage, electron-rich compound (nucleophile X^-) interacts with electron-deficient aromatic substrate **I**, most often in a reversible way, which results in the formation of the intermediate **II**, the so-called σ^H-adduct. The oxidative aromatization of the σ^H-adduct **II** with the formal elimination of hydride ion ($H^- = 2e^- + H^+$) is taking place in the second stage using an oxidizing agent which can be either the initial substrate **I** or an external oxidant (Scheme 1).

Scheme 1



Studies show that the oxidation stage consists of elementary acts of electron transfer with the formation of the radical species **III** and further oxidative aromatization by removal of a proton and an electron, which is equivalent to elimination of a hydride ion. However, the reaction can proceed along a different pathway with the cleavage of C–X bond and the elimination of the nucleophilic fragment as a radical (Scheme 1).[30–32]

Questions about the direction of the oxidative aromatization of σ^H-adducts have been raised earlier in the literature. Thus, the results of mass spectrometric study of the processes of dihydroazine aromatization have been compared with the experimental data on their chemical oxidation.[30] The well-known Fukuzumi research group has studied in detail the phenomenon of the cleavage of C–H and C–C bonds in the one-electron oxidation of 9-alkyl-10-methyl-9,10-dihydroacridines, including the effect of size and structure of the alkyl substituent. Using kinetic and ESR measurements, fast cyclic voltammetry, and theoretical calculations, it was shown that the cleavage of C–C bond becomes dominant in the case of bulky tertiary alkyl substituents.[31] Gallardo and Guirado have carried out the thermodynamic studies for a series of the nitroaromatic σ^H-adducts containing heteroatom nucleophile residues (OH, OR, SR, F).[32] They have shown that under electrochemical oxidation conditions one-electron oxidation occurs followed by homolytic elimination of the nucleophilic group and the subsequent recovery of the initial substrate. The authors have also showed that the dissociation energies of bonds at the geminal carbon atom are the determining factors in the direction of aromatization.

The analysis of the literature on the C–H functionalization, not catalyzed by transition metals, of both aromatic and heteroaromatic π-deficient compounds reveals a interesting feature: about 70% of studies are devoted to the formation of C–C bonds and only about 12% to C–N bonds. The remaining 18% of publications are associated with the formation of C–O, C–S, C–P, and C–Si bonds. It is not excluded that a noticeably smaller share of the products of C–X substitution in comparison with the products of C–C coupling can be explained by the decay of σ^H-adducts to the initial compounds.[33] In general, the direction of the process depends on the nature of the nucleophile: in the case of C-nucleophiles, the cleavage of C–H bond is observed, while for heteroatom (N, S, P, O) nucleophiles the cleavage of C–X bond is more often encountered.

One can assume that the observed patterns in the behavior of σ^H-adducts are of a similar nature, and attempts to investigate, explain, and predict the direction of aromatization can have a general character for the chemistry of arenes and heteroarenes. So far, such work has been carried out only on the example of nitroarenes.[32] On the other hand, there have been no similar studies in respect to the heterocyclic σ^H-adducts of type **II**, although they are much more convenient due to the higher stability, in some cases even with the possibility of carrying out X-ray diffraction analysis.[34]

The present paper is devoted to the study of the electrochemical oxidative aromatization of dihydroacridines with a C–X fragment at the geminal C-9 atom (where X = C, N, O, P, S) and the identification of a general pattern for the direction of the above process, using X-ray diffraction, thermodynamic and quantum-chemical calculations, also taking into account the possibility of decay of the radical intermediates **III** (Scheme 1). Previously,[35,36] we have developed methods of the direct C–H functionalization of the *N*-methylacridinium cations using C-, N-, S-, P-, and O-nucleophiles, which allowed to afford a wide range of σ^H-adducts **1**–**34** (Fig. 1).

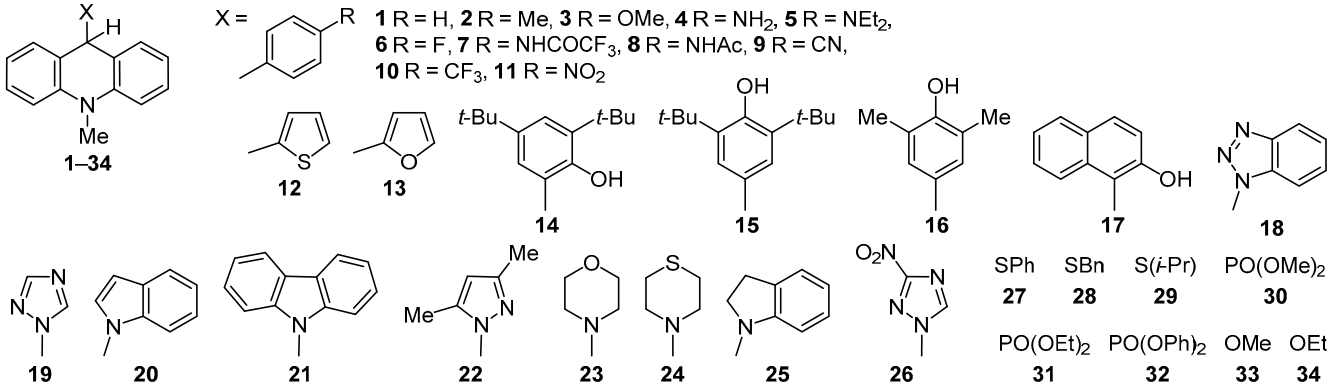
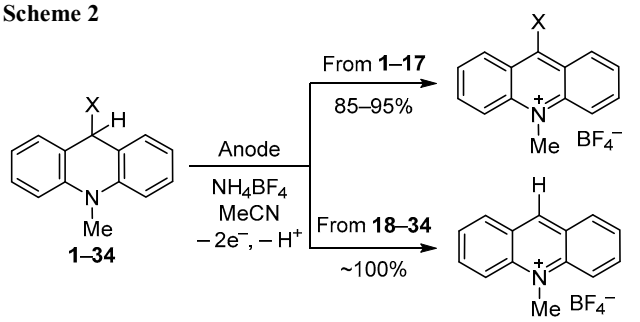


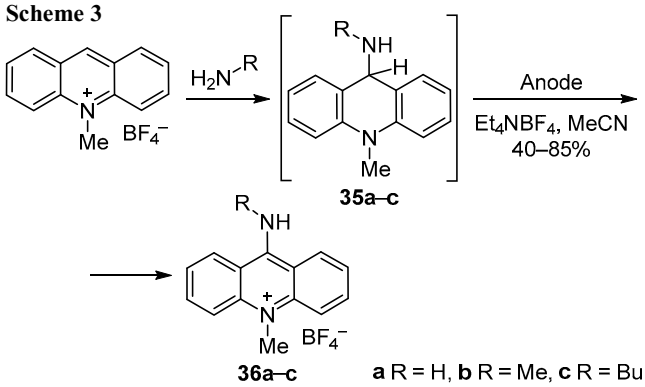
Figure 1. Investigated range of σ^H-adducts **1**–**34**.

The studied dihydroacridines **1**–**34** were subjected to preparative electrochemical oxidation. Two paths of aromatization were observed: either the formation of the S_N^H product or the destructive oxidation to the initial acridinium cation. The direction of the process depends on the nature of the nucleophile: in the case of C-nucleophiles (compounds **1**–**17**) the yield of the target S_N^H products was close to quantitative.[35] With regards to anodic aromatization of the σ^H-adducts with heteroatomic nucleophiles **18**–**34**, only the initial acridinium salt was isolated in quantitive yield (Scheme 2). At the same time, under analogous conditions of electrochemical oxidation the amination of acridinium with primary amines was realized with good yields (40–85%) of 9-aminoacridines **36a**–**c** (Scheme 3). Intermediates **35a**–**c** could not be isolated.[37]

Scheme 2



Scheme 3



It is possible that the cleavage of C–H or C–X bond is associated with the steric properties of dihydroacridines. Such studies had not previously been carried out, therefore we performed an analysis of the X-ray diffraction data for compounds **1**, **4**, **10**, **11**, **18**–**21**, **23**, **24**, **27**, and **31**. All investigated dihydroacridines have a pseudo-boat conformation of the central heteroatomic ring of the acridine moiety (Fig. 2). The nucleophilic fragment and the electron pair of the sp^3-nitrogen atom of the dihydroazine ring are located pseudoaxially, the proton of the sp^3-carbon atom is in the pseudoequatorial position. As can be seen from the data presented in Table 1, the deviation from planarity φ of the acridine ring system due to formation of a dihedral angle between the phenylene moieties varies from 6.66° (compound **21**) to 35.24° (compound **1**). In this case, molecular packing has a very significant effect on the size of the dihedral angle, for the same structure, the difference in φ value for the molecules in two layers of the same crystal packing can reach ten degrees (compound **18**). This peculiarity does not allow us to establish correlation between the experimental angles and the calculated quantum-mechanical characteristics.

Table 1. Selected crystal characteristics of dihydroacridines from X-ray diffraction data analysis

Dihydroacridine	φ*, deg	Σ_N**, deg
1	35.24	355.2(3)
4	23.42	358.0(3)
10	33.99	355.8(3)
	34.03	355.8(3)
11	34.84	355.6(1)
	27.60	358.8(1)
18	21.95	358.4
	30.18	357.6
19	21.74	358.8(3)
20	28.36	358.1(3)
21	6.66	359.94(47)
23	29.67	357.4(3)
24	24.14	358.3(9)
27	32.44	355.5(9)
	34.97	356.1(9)
31	27.91	357.6(7)

* Deviation from planarity in the acridine moiety (180° minus dihedral angle between phenylene fragments).
** Sum of the valence angles at the endocyclic nitrogen atom of the acridine moiety.

The sum of the valence angles of the endocyclic nitrogen atom (N–CH_3 group) correlates well with the value of the dihedral angle. Its reduction with increasing angle is easily explained by a decrease in the conjugation effect between the phenylene moieties and by a change of the planar configuration of nitrogen atom to the trigonal-pyramidal one (from sp^2 to sp^3 state). Thus, the X-ray diffraction data indicate, that all the test compounds have similar molecular geometry. The absence of fundamental differences between them does not allow us to explain the observed different behavior under conditions of the electrochemical oxidation.

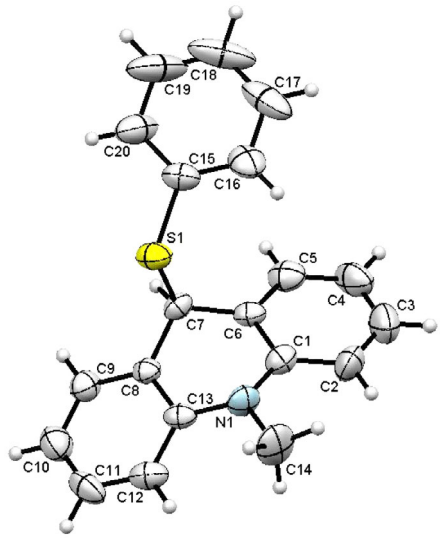
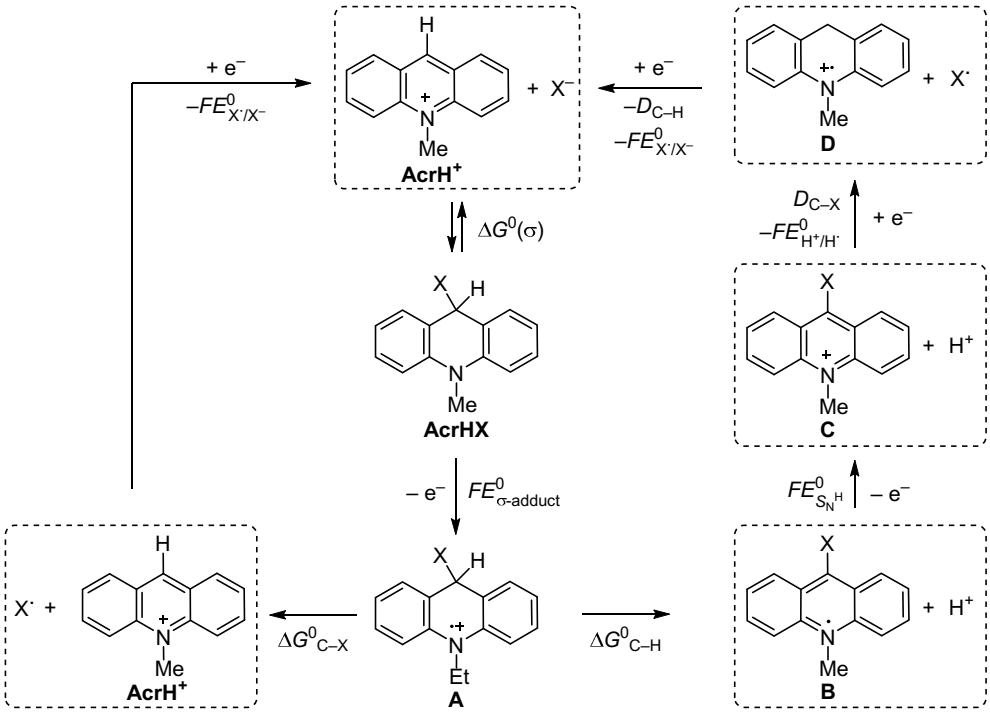


Figure 2. Molecular structure of compound **27** with atoms represented as thermal vibration ellipsoids of 50% probability.

Scheme 4



As already mentioned, the difference between dissociation energies of C–H and C–X bonds at the geminal site (C-9) is a determining factor in the transformation of the σ^H-adducts of nitroarene derivatives.[32,38] We assumed that the approach proposed for nitroarenes can be used for heterocyclic intermediates. In order to relate the Gibbs standard chemical reaction energy (ΔG^0), the Gibbs standard electrochemical energy ($-FE^0$) for a one electron transfer, and the bond dissociation energy (D) we have used a thermodynamic cycle (Scheme 4) described earlier.[32,38–40]

The radical and radical cation intermediates shown in Scheme 4 have been observed experimentally.[41,42] The thermodynamic cycle begins with the formation of a bond between the 1-methylacridinium cation (**AcrH**$^+$) and a nucleophile ($\Delta G^0(\sigma)$) to afford the σ^H-adduct **AcrHX**. The next step involves one-electron oxidation of the intermediate ($-FE^0_{\sigma H\text{-adduct}}$) and formation of the key radical cation **A**. It can undergo dissociation of either the C–H (ΔG^0_{C-H}) or the C–X bond (ΔG^0_{C-X}), which leads to the radical of $S_N{}^H$ product **B** or to the initial acridinium cation **AcrH**$^+$, respectively. Radical **B**, generated by a proton elimination, is oxidized to the $S_N{}^H$ product **C** ($-FE^0_{S_N{}^H}$). The latter is transformed through the homolytic cleavage of the C–X bond (D_{C-X} into the radical cation **D**, which may recombine with a hydrogen atom. To close the thermodynamic cycle, protons are reduced to hydrogen ($-FE^0_{H^+/H\cdot}$), and a nucleophilic radical X$^\bullet$ is transformed into anion X$^-$ ($-FE^0_{X\cdot/X^-}$). In the case of the C–X bond dissociation, reduction of X$^\bullet$ into X$^-$ is also necessary to close the cycle.

In accordance with the thermodynamic cycle, the values of ΔG^0_{C-H} and ΔG^0_{C-X} are related by equations (1) and (2).

$$\Delta G^0_{C-H} = -\Delta G^0_{\sigma} + D_{C-H} - D_{C-X} + FE^0_{X\cdot/X^-} - FE^0_{\sigma H\text{-adduct}} - FE^0_{S_N{}^H} + FE^0_{H^+/H\cdot} \quad (1)$$

$$\Delta G^0_{C-X} = -\Delta G^0(\sigma) + FE^0_{X\cdot/X^-} - FE^0_{\sigma H\text{-adduct}} \quad (2)$$

The combination of the latter gives equation (3).

$$\Delta G^0_{C-H} - \Delta G^0_{C-X} = D_{C-H} - D_{C-X} - FE^0_{S_N{}^H} + FE^0_{H^+/H\cdot} \quad (3)$$

For a favorable implementation of the $S_N{}^H$ process, the condition (4) must be met, which gives inequality (5).

$$\Delta G^0_{C-H} < \Delta G^0_{C-X} \quad (4)$$

$$\Delta G^0_{C-H} - \Delta G^0_{C-X} < 0 \quad (5)$$

The difference between ΔG^0_{C-H} and ΔG^0_{C-X} depends only on the bond dissociation energies and the standard reaction potentials $E^0_{S_N{}^H}$ and $E^0_{H^+/H}$, which allows to avoid the difficult experimental measurement of $\Delta G^0(\sigma)$, $E^0_{X\cdot/X^-}$, and $E^0_{\sigma H\text{-adduct}}$ values. The literature values of potentials $E^0_{S_N{}^H}$ and $E^0_{H^+/H\cdot}$ are –0.46 and –1.53 V, respectively.[38,43,44] Transforming expressions (3) and (5) gives inequality (6), and by substituting known values, we get the conditions necessary for the $S_N{}^H$ process (7).

$$D_{C-H} - D_{C-X} < FE^0_{S_N{}^H} + FE^0_{H^+/H\cdot} \quad (6)$$

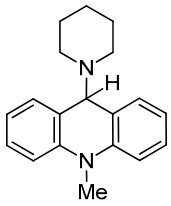
$$D_{C-H} - D_{C-X} < 24.67 \text{ kcal/mol} \quad (7)$$

It should be noted that the value of D_{C-H} for 10-methyl-9,10-dihydroacridine has been determined and reported to be 80[45] or 72 kcal/mol.[44] Since there are no values of the dissociation energies of C(9)–X bonds of 10-methyl-9,10-dihydroacridine in the literature, we decided to carry out quantum-chemical calculations of these values for some model compounds. Table 3 shows the calculated values of bond dissociation energies for various substituents.

According to the data of thermodynamic calculations and bond dissociation energy (BDE) calculations, the σ^H-adduct obtained from C-nucleophile **1** undergoes oxidation by the $S_N{}^H$ mechanism, i.e., by the cleavage of

Table 3. C(9)–X bond dissociation energies of selected 10-methyl-9,10-dihydroacridines, calculated by DFT/B3LYP 6-31G(d) and DFT 6-31G(d,p) methods[46]

Dihydroacridine	D_{C-H}, kcal/mol	D_{C-X}, kcal/mol	$D_{C-H} - D_{C-X}$, kcal/mol
1	66.81	63.66	3.15
27	71.22	37.30	33.92
31	71.68	48.43	23.25
35a	64.17	51.31	12.86
35c	67.41	45.43	21.98
37	66.77	35.65	31.12
38	66.03	32.30	33.73



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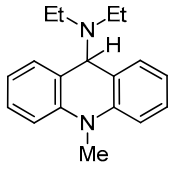

38

the C–H bond and the retention of the C-substituent (Ph) in the structure. Adducts **35a**,**c**, obtained by the interaction of **AcrH**$^+$ with primary amines, behave similarly. For the intermediates with secondary amines **37**, **38** and sulfur derivative **27**, $D_{C-H} - D_{C-X} > 24.67$ kcal/mol, so the oxidative process passes destructively with cleavage of the C–X bond. According to the calculations, the P-centered compound **31** is in the boundary region, and this makes cleavage of the C–H bond unlikely or highly ineffective, as we have observed experimentally. Thus, the previously proposed prognostic approach[32,39] can be extended to the field of heterocyclic chemistry, which makes it possible to estimate in advance the direction of the aromatization reaction.

However, the process of constructing a complete thermodynamic cycle involving all the intermediates, the search for or the calculation of all the necessary parameters for predicting the aromatization pathway of the σ^H-adducts is rather labor-intensive, and, in some cases, is completely incapable of implementation. So, we have attempted to find a more accessible and simple method to evaluate the possibility of the direct C–H functionalization. We calculated the enthalpy for formal oxidation reactions (1) and (2) (Scheme 5) for a number of compounds by the PM3 method, the parameterization of which is based on thermochemical data. The results of the calculations are shown in Table 4.

Scheme 5

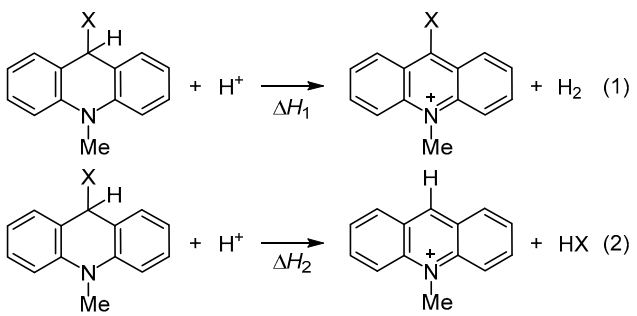

Table 4. Enthalpies ΔH_1 and ΔH_2 of formal oxidation reactions (1) and (2), respectively, of 9-substituted 10-methyl-9,10-dihydroacridines calculated by semiempirical method PM3

X	Compound	ΔH_1, kcal/mol	ΔH_2, kcal/mol	$\Delta H_1 - \Delta H_2$, kcal/mol
H		–199.20	–199.20	0.00
C	**1**	–205.52	–193.74	–11.78
C	**2**	–206.26	–193.74	–12.52
C	**3**	–206.55	–193.71	–12.84
C	**4**	–207.54	–193.72	–13.82
C	**5**	–208.82	–193.70	–15.12
C	**6**	–203.11	–193.66	–9.45
C	**7**	–202.62	–193.67	–8.95
C	**8**	–206.68	–193.88	–12.80
C	**9**	–200.80	–193.48	–7.32
C	**10**	–200.27	–193.43	–6.84
C	**11**	–197.49	–193.19	–4.30
C	**12**	–203.82	–195.88	–7.94
C	**13**	–202.18	–194.08	–8.10
C	**14**	–204.90	–195.25	–9.65
C	**15**	–207.71	–193.71	–14.00
C	**16**	–206.93	–193.77	–13.16
C	**17**	–203.65	–195.64	–8.01
N	**18**	–196.55	–198.26	+1.71
N	**19**	–191.02	–196.85	+5.83
N	**20**	–198.04	–199.38	+1.34
N	**21**	–202.64	–200.52	–2.12
N	**22**	–198.01	–200.10	+2.09
N	**23**	–202.56	–197.95	–4.61
N	**24**	–201.23	–198.61	–2.62
N	**25**	–205.81	–199.76	–6.05
S	**27**	–200.42	–200.09	–0.33
S	**28**	–200.13	–198.01	–2.12
P	**30**	–198.23	–214.86	+16.63
P	**31**	–198.63	–215.03	+16.40
O	**33**	–202.10	–204.61	+2.51
NH	**35a**	–217.62	–197.04	–20.58
NH	**35b**	–210.83	–195.70	–15.13
NH	**35c**	–212.29	–195.67	–16.62

The results of the present calculations, involving a complete optimization of the molecule geometries, indicate a correlation between the nature of the nucleophilic substituent and the type of oxidation reaction of the adduct. In the case of σ^H-adducts with a substituent derived from a C-nucleophile or from a primary amines, the oxidation is accompanied by the cleavage of C–H bond and the retention of the substituent, as evidenced by the negative value of $\Delta H_1 - \Delta H_2$. Anodic aromatization of the σ^H-adducts derived from heteroatom nucleophiles (secondary amines, N-heterocycles, thiols, alcohols, phosphites) proceeds destructively with the cleavage of C–heteroatom bond and the recovery of the initial substrate, as evidenced by the mainly positive value of $\Delta H_1 - \Delta H_2$.

Thus, it was demonstrated that in the electrochemical oxidative aromatization of σ^H-adducts, the nature of the nucleophile is the determining factor for the reaction pathway. The thermodynamic approach proposed earlier

for nitroarenes was successfully extended to the field of heterocyclic chemistry. Thermodynamic studies can explain the difference in the mechanism of σ^H-adducts oxidation from the standpoint of BDE values. In addition, the enthalpies of the studied reactions, obtained by the semiempirical PM3 method, are in good agreement with the experimental results on the intermediates oxidation. Thus, the proposed calculation methods can be used for the primary evaluation and prediction of the direction of aromatization of the key S_N^H intermediates.

Experimental

^{1}H and ^{13}C NMR spectra were recorded on a Bruker Avance 500 instrument (500 and 126 MHz, respectively) in DMSO-d_6 with TMS as internal standard. Elemental analysis of carbon, hydrogen, and nitrogen was carried on an Eurovector EA 3000 automatic analyzer. The determination of the mass fraction of fluorine was carried out by spectrophotometric method on a SPECORD 200 instrument. Melting points were determined on Boetius combined heating stages and were not corrected.

All starting reagents and solvents were obtained from commercial sources and dried by standard procedures before use. Compounds **1**–**26**, **30**–**32**, **36a**–**c** were synthesized according to the known procedures.[35–37,47,48] Structures **37** and **38** were used as theoretical models and have not been synthesized. The electrochemical oxidation of the studied compounds was carried out in accordance with previously described methods.[35,49]

10-Methyl-9-(3-nitro-1,2,4-triazol-1-yl)-9,10-dihydroacridine (26). Yield 143 mg (75%). Yellow crystalline powder. Mp 154–155°C. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 8.54 (1H, s, H triazole); 7.57 (2H, d, *J* = 7.4, H Ar); 7.46 (2H, t, *J* = 7.5, H Ar); 7.31 (2H, d, *J* = 8.3, H Ar); 7.23 (1H, s, 9-CH); 7.07 (2H, t, *J* = 7.3, H Ar); 3.54 (3H, s, NCH_3). Found, %: C 62.41; H 4.33; N 22.85. $C_{16}H_{13}N_5O_2$. Calculated, %: C 62.53; H 4.26; N 22.79.

9-(Methylamino)-10-methylacridinium tetrafluoroborate (36b). Yield 200 mg (65%). Yellow crystals. Mp 202–204°C (decomp.). ^{1}H NMR spectrum, δ, ppm: 10.46 (1H, s, NH); 8.50–8.47 (2H, m, H Ar); 8.09–8.04 (4H, m, H Ar); 7.60–7.58 (2H, m, H Ar); 4.11 (3H, s, NCH_3); 3.64 (3H, s, NCH_3). ^{13}C NMR spectrum, δ, ppm: 159.0; 140.8; 136.4; 125.2; 123.8; 116.9; 112.5; 36.2; 35.8. Found, %: C 57.99; H 4.81; N 8.94; F 24.61. $C_{15}H_{15}BF_4N_2$. Calculated, %: C 58.10; H 4.88; N 9.03; F 24.51.

Synthesis of 9,10-dihydroacridines 27–29 (General method). A solution of KOH (38 mg, 0.685 mmol) in EtOH (3 ml) and the appropriate thiol (0.685 mmol) were added to a suspension of 10-methylacridinium iodide (200 mg, 0.623 mmol) in EtOH (3 ml). The reaction mixture was stirred at room temperature for 40–50 min, then diluted with H_2O (15 ml). A precipitate formed which was filtered off, washed with H_2O, and recrystallized from EtOH.

10-Methyl-9-(phenylsulfanyl)-9,10-dihydroacridine (27). Yield 164 mg (87%). Colorless crystals. Mp 141–143°C (mp 139–141°C[50]). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 7.31–7.19 (5H, m, H Ar); 7.12–7.06 (4H, m, H Ar); 7.01 (2H, d, *J* = 8.2, H Ar); 6.85 (2H, t, *J* = 7.2, H Ar); 5.82 (1H, s, 9-CH); 3.27 (3H, s, NCH_3). ^{13}C NMR spectrum: δ, ppm: 141.9; 134.8; 132.9; 128.5; 128.2; 128.1; 128.0; 121.8; 120.4; 112.5; 51.7; 32.9. Found, %: C 78.99; H 5.66; N 4.83. $C_{20}H_{17}NS$. Calculated, %: C 79.17; H 5.65; N 4.62.

9-(Benzylsulfanyl)-10-methyl-9,10-dihydroacridine (28). Yield 166 mg (84%). Colorless crystals. Mp 133°C. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 7.32–7.26 (4H, m, H Ar); 7.25–7.20 (5H, m, H Ar); 7.09 (2H, d, *J* = 8.1, H Ar); 6.99–6.96 (2H, m, H Ar); 5.35 (1H, s, 9-CH); 3.57 (2H, s, CH_2); 3.41 (3H, s, NCH_3). ^{13}C NMR spectrum, δ, ppm: 142.0; 137.9; 128.7; 128.4; 128.1; 128.0; 126.7; 122.3; 120.3; 112.7; 46.4; 34.8; 32.9. Found, %: C 79.45; H 6.12; N 4.57. $C_{21}H_{19}NS$. Calculated, %: C 79.45; H 6.03; N 4.41.

9-(Isopropylsulfanyl)-10-methyl-9,10-dihydroacridine (29). Yield 132 mg (79%). Colorless crystals. Mp 89°C. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 7.29–7.23 (4H, m, H Ar); 7.09–7.05 (2H, m, H Ar); 6.97–6.94 (2H, m, H Ar); 5.44 (1H, s, 9-CH); 3.40 (3H, s, NCH_3); 2.66–2.58 (1H, m, $C\underline{H}(CH_3)_2$); 1.13 (6H, d, *J* = 6.7, $CH(C\underline{H}_3)_2$). ^{13}C NMR spectrum, δ, ppm: 142.0; 127.9; 127.8; 122.8; 120.2; 112.7; 44.9; 33.5; 32.9; 23.3. Found, %: C 75.68; H 7.15; N 5.31. $C_{17}H_{19}NS$. Calculated, %: C 75.79; H 7.11; N 5.20.

Synthesis of 9,10-dihydroacridines 33, 34 (General method). 10-Methylacridinium iodide (200 mg, 0.623 mmol) was added to a solution of MeONa (0.685 mmol) in MeOH (10 ml) or EtONa (0.685 mmol) in EtOH (10 ml) for the synthesis of compound **33** and **34**, respectively. The reaction mixture was stirred at room temperature until a colorless solution formed. The solvent then was evaporated, and the residue was suspended in H_2O. The product was extracted with CH_2Cl_2, and the extract was dried over Na_2SO_4. The solvent was evaporated, and the product was recrystallized from MeOH (for compound **33**) or EtOH (for compound **34**).

9-Methoxy-10-methyl-9,10-dihydroacridine (33). Yield 108 mg (77%). Colorless crystals. Mp 81–82°C (mp 76–77°C[51]). ^{1}H NMR spectrum, δ, ppm: 7.49–7.35 (4H, m, H Ar); 7.23–7.21 (2H, m, H Ar); 7.06–7.02 (2H, m, H Ar); 5.31 (1H, s, 9-CH); 3.48 (3H, s, NCH_3); 2.97 (3H, s, OCH_3). ^{13}C NMR spectrum, δ, ppm: 141.4; 130.0; 128.8; 120.8; 119.7; 112.9; 75.9; 52.9; 32.8. Found, %: C 79.92; H 6.85; N 6.27. $C_{15}H_{15}NO$. Calculated, %: C 79.97; H 6.71; N 6.22.

9-Ethoxy-10-methyl-9,10-dihydroacridine (34). Yield 113 mg (76%). Colorless crystals. Mp 60–61°C. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 7.45–7.43 (2H, m, H Ar); 7.40–7.36 (2H, m, H Ar); 7.21–7.19 (2H, m, H Ar); 7.04–7.00 (2H, m, H Ar); 5.40 (1H, s, 9-CH); 3.47 (3H, s, NCH_3); 3.32–3.22 (2H, m, OCH_2); 0.94 (3H, t, *J* = 7.0, $CH_2C\underline{H}_3$). ^{13}C NMR spectrum, δ, ppm: 141.5; 129.8; 128.7; 121.4; 119.7; 112.9; 74.5; 60.7; 32.8; 15.1. Found, %: C 80.19; H 7.22; N 5.98. $C_{16}H_{17}NO$. Calculated, %: C 80.30; H 7.16; N 5.85.

X-ray structural investigation of compounds 1, 4, 10, 11, 18–21, 23, 24, 27, and 31. Crystals were obtained by slow evaporation of MeCN solution. X-ray diffraction experiments were carried out on an automated diffractometer Xcalibur S with CCD detector following the standard procedure (graphite monochromator, MoKα radiation,

λ 0.71069 Å, ω-scanning with step 1°). The unit cell parameters were refined using all collected spots after the integration process. The data were not corrected for absorption.

Structures **1**, **4**, **10**, **11**, **18**–**21**, **23**, **24**, **27**, and **31** were solved by direct methods with the SHELX97 program package.[52] Structure **11** was solved using Olex2 with the Superflip structure solution program by charge flipping.[53] All the structures were refined by full-matrix least squares on F^2 using ShelXL97. All the non-hydrogen atoms were refined with anisotropic temperature factors. The H atoms at the C(sp^3)-9 atoms in the dihydroazine rings were solved and refined independently in isotropic approximation. All other H atoms were calculated with AFIX and were included in the refinement at "riding" model with a common isotropic temperature factor. Crystallographic data of the investigated compounds have been deposited at the Cambridge Crystallographic Data Center (deposits CCDC 1479454 for compound **1**, CCDC 1479456 for compound **4**, CCDC 1479453 for compound **10**, CCDC 1896716 for compound **11**, CCDC 165508 for compound **18**, CCDC 929423 for compound **19**, CCDC 929424 for compound **20**, CCDC 929426 for compound **21**, CCDC 929427 for compound **23**, CCDC 929428 for compound **24**, CCDC 1896715 for compound **27**, CCDC 1896717 for compound **31**).

Thermodynamic and BDE calculations. All the calculations were carried out using the Gaussian 09 software.[54] Optimization of the structures (opt) was carried out until the first local energy minimum by a consecutive use of HF/3-21, HF/6-31G(d), DFT-B3LYP/6-31G(d) bases (for compounds containing sulfur and phosphorus, the last used basis was DFT-B3LYP/6-31G(d,p)). A check for the global minimum was not conducted. The calculation of the thermodynamic parameters (freq) was carried out either on DFT-B3LYP/6-31G(d) basis or on DFT-B3LYP/6-31G(d,p) one (for S- and P-containing compounds). The bases used for BDE calculations are assigned to the average accuracy calculations.

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