Single-electron oxidation and nucleophilicity of aminomethylated calix[4]resorcinarenes

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The electrochemical oxidation of a number of aminomethylated calix[4]resorcinarenes (AMC) with different substituents at the nitrogen atom and the kinetics of nucleophilic substitution reactions of these compounds with *p*-nitrophenyl bis(chloromethyl)phosphinate were studied. The reactivity of the ionic associates of AMC in the nucleophilic substitution and the behavior of AMC in electrooxidation are determined by the same factors, namely, the amino-group basicity and the nature of the substituents at the nitrogen atom. These factors influence the ratio of the zwitter-ionic and anionic forms of AMC.

Key words: reversible single-electron electrochemical oxidation, nucleophilicity, kinetics, nucleophilic substitution, aminomethylated calix[4]resorcinarenes, esters of phosphorus acids.

In recent years, considerable attention of researchers has been attracted by macrocyclic polyphenols, calixarenes,[1—5] whose applications are related to their specific structure. Calixarenes act as receptors due to noncovalent interactions with diverse charged and neutral species (substrates), thus exhibiting catalytic and ionophoric activities, sensor properties,[1] and so on. Yet another interesting aspect of calixarene chemistry is the appearance of new properties upon functionalization. For example, we showed that the presence of pre-organized hydroxy and amino groups on the upper rim of the calix[4]resorcinarenes gives rise to clear-cut electron-donating properties. This feature of calix[4]resorcinarenes is clearly manifested in electron transfer[6—8] and nucleophilic substitution.[9] As molecular solutions in DMF or propan-2-ol, aminomethylated calix[4]resorcinarenes (AMC) **1** and **2**, unlike 2-aminomethylphenols (AMP), which represent their structural units, undergo reversible single-electron electrooxidation to give phenoxyl radicals.[6,7] A similar single-electron process is involved in the chemical oxidation by chloranil in DMF or by lead dioxide in toluene[7] and in the photoinduced oxidation by oxygen in DMF and in the sodium bis(2-ethylhexyl)sulfosuccinate—decane—water reverse micellar system.[8]

A search for efficient catalysts for cleavage of esters of phosphorus acids, which mainly occurs through transesterification, hydrolysis, and oxidation, is currently in progress. This problem is of interest in two aspects. On the one hand, the formation and cleavage of phosphoester bonds represent highly important biochemical reactions;[9] on the other hand, this is a way of detoxification (degradation) of organophosphorus neurotoxins,[10] for example, pesticides used in agriculture.

In water—alcohol media, AMC **1—4** are more reactive[11] than AMP as regards nucleophilic substitution in *p*-nitrophenyl esters of four-coordinate phosphorus acids (EPA). As in the case of AMP,[12] these reactions occur in two steps, the first one is phenolysis of EPA, *i.e.*, liberation of *p*-nitrophenolate upon transesterification and the formation of phosphorylated AMC (AMP) and the second step is hydrolysis of the latter product assisted by intramolecular catalysis by the aminomethyl group. The phenolysis and hydrolysis of EPA are known[13,14] to follow the S_N2(P) mechanism. For some charged and neutral nucleophiles, including phenols, the rate constants for the reactions with methyl iodide, which follow an S_N2 mechanism, obey a linear dependence on the oxidation potentials of nucleophiles.[15] Experimental determination of oxidation potentials is rather simple; this makes the electrochemical method quite attractive for evaluating the nucleophilicity of calix[4]resorcinarenes.

Nucleophilic substitution can be described in terms of a thermochemical cycle involving transfer of an electron from the nucleophile molecule (calixarene) to the electrophile (nitro group, C—Hal bond, phosphate or phosphonate groups, *etc.*) followed by recombination of the radical species thus formed. With such a description, the potentials of electrochemical oxidation of calixarenes and reduction of the corresponding groups become important. In order to estimate the reactivity of AMC to-

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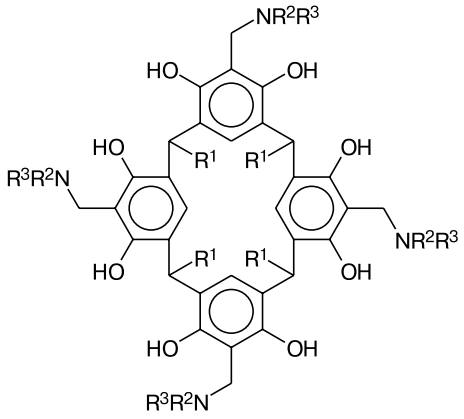
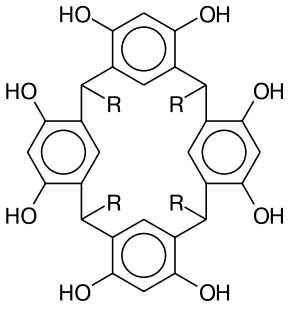
ward electron transfer and nucleophilic substitution of EPA and to elucidate the relationship between parameters characterizing the reactivity of AMC in these processes, we studied a number of AMC (**1—10**) with different substituents at the N atom and calix[4]resorcinarene (**11**) for comparison.



1—10

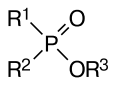
R^1 = Me, R^2R^3 = C_5H_{10} (**1**); R^1 = C_9H_{19}, R^2R^3 = C_5H_{10} (**2**);
R^1 = C_9H_{19}, R^2 = R^3 = Me (**3**); R^1 = R^2 = R^3 = Me (**4**);
R^1 = $C_{11}H_{23}$, R^2 = R^3 = Et (**5**); R^1 = Pr, R^2R^3 = C_4H_8NH (**6**);
R^1 = R^2 = Me, R^3 = $(CH_2)_2OH$ (**7**); R^1 = Me, R^2 = CH_2Ph,
R^3 = $(CH_2)_2NHCH_2Ph$ (**8**); R^1 = Me, R^2 = H, R^3 = Bu (**9**);
R^1 = Me, R^2 = H, R^3 = $(CH_2)_2NMe_2$ (**10**)



11

R = $C_{11}H_{23}$

As electrophiles, we took EPA differing in the type and the number of electrophilic centers: *p*-nitrophenyl bis(chloromethyl)phosphinate (**12**), *p*-nitrophenyl diphenyl phosphate (**13**), ethyl *p*-nitrophenyl chloromethylphosphonate (**14**), ethyl phenyl chloromethylphosphonate (**15**), triphenyl phosphate (**16**), and tris(pentafluorophenyl) phosphate.



12—16

R^1 = R^2 = CH_2Cl, R^3 = $C_6H_4NO_2$-*p* (**12**);
R^1 = R^2 = OPh, R^3 = $C_6H_4NO_2$-*p* (**13**);
R^1 = CH_2Cl, R^2 = OEt, R^3 = $C_6H_4NO_2$-*p* (**14**);
R^1 = CH_2Cl, R^2 = OEt, R^3 = Ph (**15**);
R^1 = R^2 = OPh, R^3 = Ph (**16**)

Experimental

Compounds **1—10** [16] and **11** [17] were synthesized by known procedures; the physicochemical characteristics of AMC **1—5** and calix[4]resorcinarene **11** were reported previously[6,11] and those for AMC **6—10** are given below. Esters **12—15** were prepared according to published methods,[18] the properties of triphenyl phosphate and tris(pentafluorophenyl) phosphate corresponded to the reported data.[19] ^{1}H NMR spectra were recorded on a Varian Unity-300 spectrometer (300 MHz) using $CDCl_3$ as the solvent and as the internal standard.

5,11,17,19-Tetra(piperazinomethyl)-2,8,14,20-tetrapropylpentacyclo[19.3.1.1^{3,7}.1^{9,13}.1^{15,19}]octacosa-1(25),3,5,7(28),9,11,13(27),15,17,19(26),21,23-dodecaen-4,6,10,12,16,18,22,24-octol (6). Yield 83%. Found (%): C, 69.16; H, 8.41; N, 10.61. $C_{60}H_{88}N_8O_8$. Calculated (%): C, 68.70; H, 8.39; N, 10.68. ^{1}H NMR, δ: 0.85—0.97 (t, 12 H, C$\underline{H}_3$—CH_2, ^3J = 7.0 Hz); 1.10—1.30 (m, 8 H, CH_3—C$\underline{H}_2$—CH_2); 2.12 (m, 8 H, CH_3—CH_2—C$\underline{H}_2$); 2.50—3.00 (m, 32 H, CH_2 piperazine ring); 3.72 (s, 8 H, C—CH_2—N); 4.25 (t, 4 H, C—C$\underline{H}$—CH_2, ^3J = 6.9 Hz); 7.40 (s, 4 H, H arom.); 7.90 (s, 8 H, OH).

5,11,17,19-Tetrakis[*N*-(2-hydroxyethyl)-*N*-methylaminomethyl]-2,8,14,20-tetramethylpentacyclo[19.3.1.1^{3,7}.1^{9,13}.1^{15,19}]octacosa-1(25),3,5,7(28),9,11,13(27),15,17,19(26),21,23-dodecaen-4,6,10,12,16,18,22,24-octol (7). Yield 82%. Found (%): C, 65.01; H, 7.97; N, 6.06. $C_{48}H_{68}N_4O_{12}$. Calculated (%): C, 64.57; H, 7.62; N, 6.27. ^{1}H NMR, δ: 1.74 (d, 12 H, C$\underline{H}_3$—CH, ^3J = 6.9 Hz); 2.42 (s, 12 H, NMe); 2.67 (m, 8 H, N—C$\underline{H}_2$—CH_2); 3.30 (m, 8 H, CH_2—C$\underline{H}_2$—OH); 3.71 (s, 8 H, C—CH_2—N); 4.21 (q, 4 H, MeC$\underline{H}$, ^3J = 6.9 Hz); 7.15 (s, 4 H, H arom.); 7.70 (s, 8 H, OH).

5,11,17,19-Tetrakis[*N*-(2-benzylaminoethyl)-*N*-benzylaminomethyl]-2,8,14,20-tetramethylpentacyclo[19.3.1.1^{3,7}.1^{9,13}.1^{15,19}]octacosa-1(25),3,5,7(28),9,11,13(27),15,17,19(26),21,23-dodecaen-4,6,10,12,16,18,22,24-octol (8). Yield 78%. Found (%): C, 77.70; H, 7.61; N, 7.59. $C_{100}H_{112}N_8O_8$. Calculated (%): C, 77.32; H, 7.21; N, 7.21. ^{1}H NMR, δ: 1.75 (d, 12 H, C$\underline{H}_3$—CH, ^3J = 6.9 Hz); 2.70 (m, 8 H, N—CH_2—C$\underline{H}_2$—NH); 2.87 (s, 8 H, NH—C$\underline{H}_2$—Ph); 3.60 (m, 8 H, N—C$\underline{H}_2$—CH_2—NH); 3.75 (s, 8 H, N—C$\underline{H}_2$—Ph); 3.80 (s, 8 H, C—CH_2—N); 4.52 (q, 4 H, MeC$\underline{H}$, ^3J = 6.9 Hz); 7.20 (m, 44 H, H arom.); 7.90 (s, 8 H, OH).

5,11,17,19-Tetra(butylaminomethyl)-2,8,14,20-tetramethylpentacyclo[19.3.1.1^{3,7}.1^{9,13}.1^{15,19}]octacosa-1(25),3,5,7(28),9,11,13(27),15,17,19(26),21,23-dodecaen-4,6,10,12,16,18,22,24-octol (9). Yield 70.3%. Found (%): C, 70.23; H, 9.30; N, 6.27. $C_{52}H_{76}N_8O_8$. Calculated (%): C, 70.59; H, 8.60; N, 6.33. ^{1}H NMR, δ: 0.92 (t, 12 H, C$\underline{H}_3$—CH_2, ^3J = 7.0 Hz); 1.35—1.51 (m, 16 H, C$\underline{H}_2$—C$\underline{H}_2$—Me); 1.73 (d, 12 H, C$\underline{H}_3$—CH, ^3J = 6.9 Hz); 2.64 (m, 8 H, CH_2—C$\underline{H}_2$—N); 3.95 (m, 8 H, CH_2—N); 4.58 (q, 4 H, C$\underline{H}$—Me, ^3J = 6.9 Hz); 6.00 (br.s, 4 H, NH); 7.20 (s, 4 H, H arom.); 7.88 (s, 8 H, OH).

5,11,17,19-Tetrakis[*N*-(2-dimethylaminoethyl)-*N*-aminomethyl]-2,8,14,20-tetramethylpentacyclo[19.3.1.1^{3,7}.1^{9,13}.1^{15,19}]octacosa-1(25),3,5,7(28),9,11,13(27),15,17,19(26),21,23-dodecaen-

4,6,10,12,16,18,22,24-octol (10). Yield 86%. Found (%): C, 65.46; H, 11.97; N, 12.09. $C_{52}H_{80}N_8O_8$. Calculated (%): C, 66.10; H, 8.47; N, 11.86. ^{1}H NMR, δ: 1.70 (d, 12 H, C<u>H</u>$_3$—CH, ^3J = 7.0 Hz); 2.12 (s, 24 H, NMe); 2.35 (t, 8 H, C<u>H</u>$_2$—NMe$_2$, ^3J = 7.2 Hz); 2.62—2.82 (m, 8 H, C<u>H</u>$_2$—CH$_2$—NMe$_2$); 4.01 (s, 8 H, C—CH$_2$—N); 4.50 (q, 4 H, MeC<u>H</u>, ^3J = 6.9 Hz); 5.80 (br.s, 4 H, NH); 7.35 (s, 4 H, H arom.); 8.06 (br.s, 8 H, OH).

The electrochemical oxidation of AMC **3**, **5—10** was studied[6] by cyclic voltammetry (CV) and ESR combined with electrolysis in DMF purified by the standard procedure. Compound **4** is poorly soluble in DMF; therefore, its electrochemical characteristics could not be obtained. A 0.1 *M* solution of Et_4NClO_4 was used as the supporting electrolyte. The voltammograms were recorded at 22 °C using a PI-50-1 potentiostat on an H 307/2 XY-recorder (potential sweep velocity 100 mV s^{-1}). A glassy-carbon disc electrode 2 mm in diameter embedded into fluoroplastic was used as the working electrode. Prior to each measurement, the electrode was mechanically polished. An Ag/AgNO$_3$ (0.01 mol L^{-1}) electrode in MeCN with a potential of +0.3 V *vs.* saturated calomel electrode was used as the reference electrode. The dissolved oxygen was removed by a flow of argon or nitrogen.

ESR studies combined with electrolysis *in situ* were carried out at 22 °C on a setup that comprised an SE/X-2544 ESR spectrometer, a potentiostat, and an electrochemical cell. This made it possible to perform the electrochemical process directly in the probe of the ESR spectrometer. A Pt helix served as the working electrode, a Pt wire was the auxiliary electrode, and an Ag wire was the reference electrode. The solutions were deaerated by three freezing—evacuation—thawing cycles.

The kinetics of reactions of compounds **7** and **9** with substrate **12** ($4 \cdot 10^{-5}$ mol L^{-1}) was studied by spectrophotometry under pseudo-unimolecular conditions by monitoring the increase in the optical density (λ = 400 nm) related to the *p*-nitrophenolate formed. This was done using a Specord UV-Vis spectrometer at 25 °C and pH 9.0 in a 80% (v/v) aqueous solution of propan-2-ol under conditions similar to those described previously.[9] The observed rate constants (k_{obs}) were calculated using a first-order equation. The substrate binding constants (K_{bind}), the critical aggregate concentration (CAC), and the rate constants for the reaction of the aggregates (k_m) were found from the known equation[20]

$$k_{obs} = (k_{H_2O} + k_m K_{bind} C_{Surf})/(1 + K_{bind} C_{Surf}), \qquad (1)$$

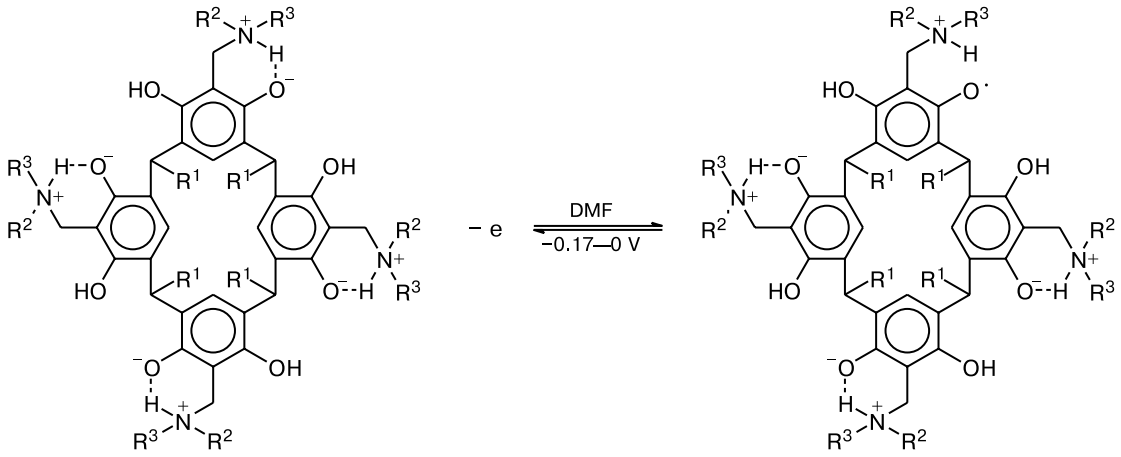
where k_{H_2O} is the reaction rate constant in aqueous propan-2-ol, C_{Surf} is the AMC concentration corrected for the CAC.

Results and Discussion

The AMC **3** and **5—10** are oxidized in two or three steps in nearly the same potentials region. The obtained oxidation peak potentials (E_p^{Ox}) and the N_{MeI} values (nucleophilicities of compounds with respect to MeI in MeOH) are summarized in Table 1. For comparison, the previously published data[6] for calix[4]resorcinarene **11** in the absence and in the presence of piperidine and tetraethylammonium hydroxide and for AMC **1** and **2** are listed. The first oxidation peak $E_p^{Ox,1}$ for compounds **1—3**, **5—10** with a peak current corresponding to the transfer of one electron is reversible (the difference between the potentials of the anodic and the corresponding cathodic peaks is 60 mV at 25 °C), while the subsequent peaks are irreversible. The potentials of the first peaks are markedly shifted to lower values relative to that of calix[4]resorcinarene **11** ($0.46\ V \le \Delta E_p^{Ox} \le 0.63\ V$). This fact, in combination with reversibility and the single-electron current of the peak are indicative of oxidation of zwitter-ions **1—3** and **5—10** to stable calix[4]resorcinarene radical cations (Scheme 1).

Phenoxyl-type radicals stable in DMF were detected by ESR for compounds **3** and **5—10** under electrooxidation conditions at the first-peak potentials directly

Scheme 1



1—3, 5—10

Table 1. Potentials of the oxidation peaks (E_p^{Ox}) of calix[4]resorcinarenes **1—11** on a glassy-carbon electrode in DMF[a]

Compound or mixture	$E_p^{Ox,1}$	$E_p^{Ox,2}$	$E_p^{Ox,3}$	N_{MeI}[b]
	V			
1	−0.10	0.14	0.35	7.92
2	−0.10	0.15	0.31	7.92
3	−0.06	0.40	—	7.77
5	−0.10	0.15	0.34	7.92
6	0	0.30	—	7.53
7	−0.11	0.30	0.78	7.96
8	−0.08	0.23	0.80	7.84
9	−0.14	0.30	—	8.08
10	−0.16	0.33	0.90	8.16
11	0.46	—	—	7.23
11 + piperidine (1 : 4)	−0.31	0.00	0.38	8.76
11 + Et_4NOH (1 : 10)	−0.53	−0.10	0.35	9.63

[a] Here and in Table 2, the potentials were measured *vs.* Ag/0.01 *M* solution of $AgNO_3$, $C = 1 \cdot 10^{-3}$ mol L^{-1}, 0.1 *M* solution of Et_4NClO_4 as the supporting electrolyte, potential sweep velocity 100 mV s^{-1}, $T = 22$ °C.

[b] N_{MeI} is the nucleophilicity of compounds with respect to MeI in MeOH.

in the probe of the ESR spectrometer. The ESR signals for all radical species are broadened due to dynamic processes related to conformation equilibria in solutions of compounds **3** and **5—10** and, probably, to the intramolecular delocalization caused by hopping of an electron over resorcinol fragments. The simplest spectrum was observed for the radical cation resulting from oxidation of AMC **8**. This was represented represented by a triplet of doublets. By analogy[6] with the radicals derived from AMC **1** and **2**, this can be interpreted as being due to the radical of substituted resorcinol with splitting from two equivalent methine protons ($a_{2H} = 3.6$ Oe) and from the proton in position 5 of the benzene ring ($a_H = 2$ Oe).

It was noted above that AMC are reversibly oxidized when exist in the zwitter-ionic form, which is equilibrated with the neutral form. In the zwitter-ionic form, the phenolate ion interacts with the proton of the ammonium ion. The energy of this interaction and the position of equilibrium are determined by the basicity of the amine. In the single-electron oxidation, the electron is transferred from one of the zwitter-ion fragments of the molecule with complete splitting of the O...H bond to give the phenoxyl radical (see Scheme 1). Therefore, the oxidation potential of AMC is a function of not only the ionization potential of the solvated molecule, but also of the equilibrium constants and the O...H bond energies and, hence, it is largely determined by the basicity of the amino group. The higher the basicity of the amine the higher the fraction of the zwitter-ionic form and the lower the bond energy and the oxidation potential of calix[4]resorcinarene. It follows from the data of Table 1 that the potentials of the first oxidation peaks of calix[4]resorcinarenes virtually do not depend on the length of the hydrocarbon radical R^1 (compounds **1**, **2**), but are determined by the nature of substituents at the N atom. Indeed, AMC **9** and **10** containing NHAlk groups are oxidized much more easily than AMC **3** and **5—8** with $NAlk_2$ groups. The elongation of the hydrocarbon chain in the amino group (see Table 1, compounds **3** and **5**) facilitates the electron abstraction. The results obtained are fully consistent with the change in the basicity of the amino group (secondary amines are stronger bases than tertiary amines, and an increase in the chain length enhances the basic properties of both secondary and tertiary amines[21]) and with the pK_a values for AMC **1—4** in aqueous propan-2-ol.[11]

Using published empirical dependences[22] of the nucleophilicity ($N_{MeI} = \log(k_N/k_{MeOH})$ in MeOH at 25 °C, where k_N and k_{MeOH} are the rate constants for the nucleophilic substitution reaction of MeI with the compound under study, a nucleophile, and MeOH, respectively) on the oxidation potentials for charged and noncharged nucleophiles, we determined the nucleophilicities of calix[4]resorcinarenes **1—3** and **5—11** (see Table 1). We considered AMC **1—3** and **5—10** and calix[4]resorcinarene **11** in the presence of piperidine or triethylammonium hydroxide (**11** − H) as anionic nucleophiles, whereas original calix[4]resorcinarene **11** was considered to be a noncharged nucleophile. Although in the study cited,[22] the potentials were measured in MeCN and in our study, in DMF, the values for AMC nucleophilicity that we obtained still appear to be trustworthy, because both solvents are aprotic and have similar dielectric constants. It can be seen from Table 1 that AMC are fairly efficient nucleophiles; their nucleophilicity is markedly higher than that for the phenoxide ion ($N_{MeI} = 6.43$) and is of the same order of magnitude or somewhat higher than the nucleophilicity of the iodide ion (7.4). Calix[4]resorcinarene **11** is characterized by the lowest nucleophilicity (7.22), which, however, becomes the highest in the presence of piperidine (8.76) or Et_4NOH (9.63).

According to the oxidation potentials, the calix[4]resorcinarenes studied can be arranged in the following sequence of increasing nucleophilicity: **11** $\ll$ **6** < **3** < **8** < **5** $\approx$ $\approx$ **7** $\approx$ **1** $\approx$ **2** < **9** $\approx$ **10** < (**11** − H).

The rate of nucleophilic substitution is known to depend on the reagent nucleophilicity and on the nature of the electrophilic center; in the case of EPA, the latter parameter can vary extensively by varying substituents at the phosphoryl group. Consideration of the influence of the nature of the electrophile on the reactions of AMC **1—3** and **5—10** and deprotonated calix[4]resorcinarene (**11** − H) with EPA in terms of the electron transfer using compounds **13** and **14** as examples shows that these substrates can react along two (compound **13**) or three (com-

Table 2. Potentials of the reduction peaks (E_p^{Red}) of compounds **13—16** at a glassy-carbon electrode in DMF

Compound	$-E_p^{Red,1}$	$-E_p^{Red,2}$	$-E_p^{Red,3}$
	V		
13	1.42	2.05	2.50
14	1.42	2.13	2.50
15	2.50	—	—
16	2.92	—	—

pound **14**) pathways, in conformity with the number of potential reaction centers.

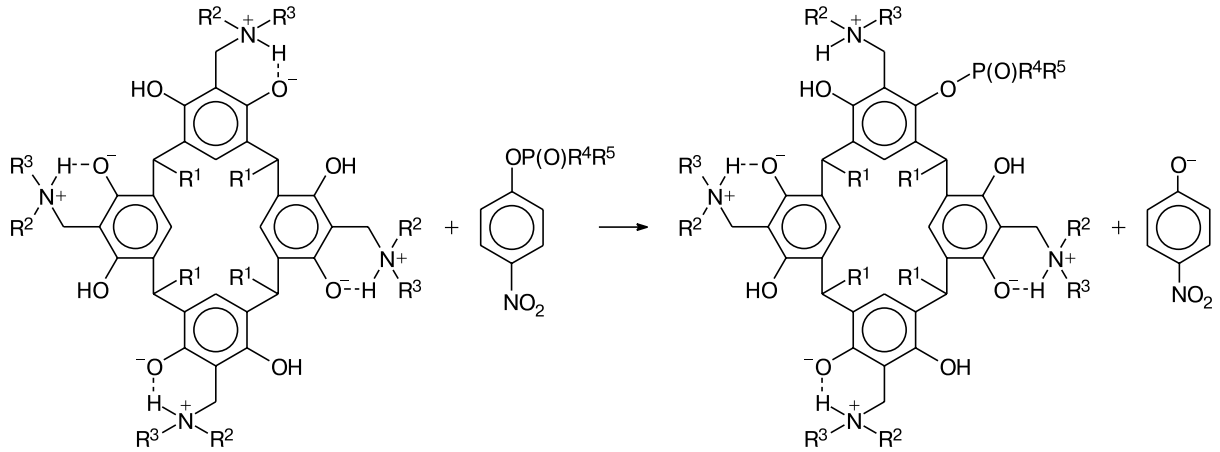
The nitro group is one of the potential reaction centers, as follows from the results of electrochemical reduction of EPA **13** and **14**. The voltammograms recorded for these compounds in DMF at the background of 0.1 *M* solution of Et_4NClO_4 are identical: they contain three reduction peaks, the first of them being reversible and the other peaks being irreversible. The single-electron level of the current in the first reversible step and the fact that the potentials (Table 2) are close to the reduction potentials of nitrobenzene ($E_p^{Red} = -1.41$ V) indicate that compounds **13** and **14** are reduced in the first step as typical nitroaromatic compounds to give stable radical anions. The difference between the oxidation potentials of calix[4]resorcinarenes **1—11** and the reduction potentials of EPA **13**, **14** is in the range of $1.25\ V \le \Delta E_p \le 1.42$ V. Oxidation of compounds **1—10**, **11** – H and reduction of EPA **13**, **14** are reversible processes; undoubtedly, with such potential gradient without compensation of the energy barrier ($1.25\ eV \le \Delta E \le 1.42$ eV), an outer-sphere electron transfer from calix[4]resorcinarene to the nitro group of compound **13** or **14** to give the phenoxyl radical and radical anion of **13** or **14** is impossible. The reaction products of calix[4]resorcinarenes with EPA could result only upon the inner-sphere electron transfer with synchronous formation of new energetically favorable bonds to yield a Meisenheimer complex[23] stabilized by elimination of easily leaving phosphate or phosphonate ions. Since the reduction potentials of phosphate **13** and phosphonate **14** are equal, the rates of nucleophilic substitution for these compounds should also be equal, all other factors being the same.

Dissociative electron transfer to an alkyl halide molecule is known[24] to induce cleavage of the C—Hal bond. Another possible route of the reaction between AMC and EPA includes electron transfer from calix[4]resorcinarenes to the C—Cl group of **14** with synchronous cleavage of the C—Cl bond, elimination of the Cl^- ion, and formation of the C—O—C bond (S_N2 mechanism). This reaction pathway is also probable, as the chloride ion is a rather good leaving group and the energy of the ether bond formed is of the same order as the energy of the P—O bond.[22]

It is known[25—28] that trialkyl and triaryl phosphates undergo irreversible electrochemical reduction with cleavage of the C—O or P—O single bonds. Then the third possible pathway in the reaction of calix[4]resorcinarenes **1—11** with EPA **13** and **14** includes electron transfer to the phosphoryl group with elimination of the best leaving *p*-nitrophenoxide ion and recombination of the phenoxyl and phosphorus radicals to give a new phosphate or phosphonate (Scheme 2). The electron transfer, the bond cleavage, and the formation of the new bond occur synchronously, which implies (in generally accepted terms) that the reaction follows the S_N2 mechanism.

Experimental determination of the reduction potentials of the phosphoryl group in compounds **13** and **14** is, in principle, impossible, because the electrochemical electron transfer is mainly directed on the nitro group. However, comparison of the potential of irreversible two-elec-

Scheme 2



tron reduction of triphenyl phosphate (**16**) (E_p^{Red} = −2.92 V),[18] tris(pentafluorophenyl) phosphate (E_p^{Red} = −2.34 V),[21] and ethyl phenyl chloromethylphosphonate (**15**) (E_p^{Red} = −2.50 V) provides the conclusion that the hypothetical reduction potential of the phosphoryl group in compounds **13** and **14** is ~1.0 V more negative than the reduction potential of the nitro group. Undoubtedly, in this case, the electron transfer from calix[4]resorcinarenes to the phosphoryl group is substantially (~1.0 eV) hampered compared to the transfer to the nitro group; however, this is compensated by the formation of the energetically favorable P—O bond (~3.7 eV).[14] It is noteworthy that phosphonate **15** is reduced much more easily than phosphate **16** (ΔE_p^{Red} = 0.42 V), which implies a higher rate of nucleophilic substitution for compound **15** compared to **16** or for phosphonate **14** compared to phosphate **13**.

Thus, as regards electron-transfer electrode reactions, there are no thermodynamic restrictions in principle that would preclude the existence of two (for compound **13**) or three (for compound **14**) pathways in the reaction with radicals derived from calix[4]resorcinarenes **1—11**. Evidence supporting a particular pathway cannot be deduced directly from electrochemical measurements; this requires integrated kinetic investigations based on monitoring of different parameters of the process.

Analysis of published data[13,14] and the results we obtained[11] in the kinetic studies of the reactions of AMC **4** with EPA **12** and **13** in 80% (v/v) aqueous propan-2-ol carried out by spectrophotometry and by ^{31}P NMR spectroscopy, *i.e.*, by monitoring the generation of *p*-nitrophenolate (spectrophotometry) upon cleavage of the substrate and the intermediate formation of the transesterification product followed by its hydrolysis to give the acid (^{31}P NMR), support the mechanism shown in Scheme 2. Thus, the reaction of AMC with EPA in 80% Pr^{i}OH follows the S_N2(P) mechanism.

A spectrophotometric study of the kinetics of reactions of AMC **1—4**, **7**, and **9**, containing different substituents at the N atom and hydrocarbon groups of different lengths on the lower rim of the hydrophobic cavity, with EPA **12** in 80% aqueous propan-2-ol at pH 9.0 (Fig. 1) using different AMC concentrations showed that the k_{obs}—$f(C_{AMC})$ curves reach a plateau, pointing to binding of substrate **12** by AMC aggregates.[11] It can be seen from Fig. 1 that the reactivities of these aggregates are determined by the nature of substituents at the N atom, which affects the basicity of the amino group and, as noted above, the proportions of the zwitter-ionic and monoanionic forms involved in the reaction, but do not depend on the length of the R^1 group. Thus, in 80% aqueous Pr^{i}OH, the hydrophobicity factor does not influence the reactivity of AMC, which probably form head-to-head aggregates in the medium used. These aggregates

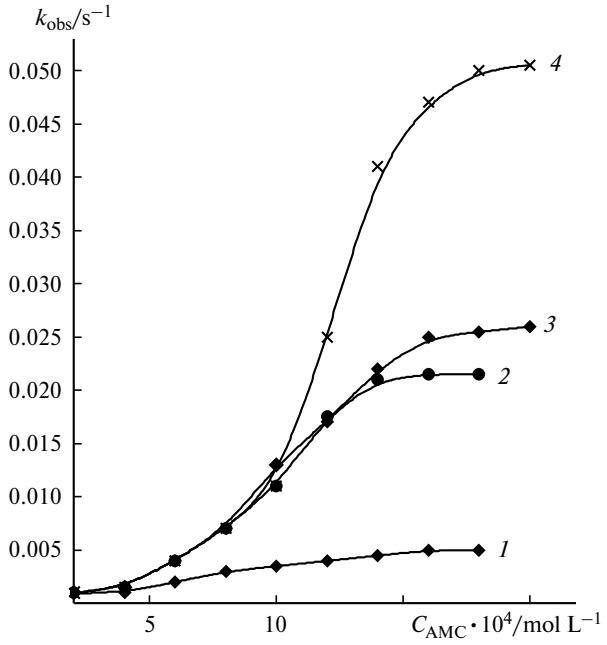


Fig. 1. Observed rate constants (k_{obs}) for the reactions of substrate **12** with AMC **1**, **2** (*1*), **3**, **4** (*2*), **7** (*3*), and **9** (*4*) *vs.* the concentration of AMC (C_{AMC}) in 80% aqueous propan-2-ol (pH 9.0, 25 °C).

are ionic associates existing due to electrostatic interactions and intermolecular hydrogen bonds, by analogy with the data reported previously.[1]

Table 3 lists the parameters of the reactions studied (CAC, k_m, and K_{bind}), which were determined by processing of the kinetic curves in terms of Eq. (1).

In the reaction series studied with the electrophile remaining the same (substrate **12**) and only the nature of the substituent in the nucleophile being varied (AMC **1**, **4**, **7**, **9**), the S_N2 reaction mechanism stipulates a linear

Table 3. Parameters for the reaction of substrate **12** with AMC **1—4**, **7**, and **9** in 80% (v/v) aqueous propan-2-ol at pH 9.0

AMC	CAC · 10^{-4} /mol L^{-1}	$k_m \cdot 10^{-2}$ /s^{-1}	K_{bind} /L mol^{-1}
1	1.3	3.7	235
2	1.5	3.8	250
3	1.7	2.3	470
4	1.6	2.3	485
7	6.1	6.4	620
9	7.2	14.0	514

Note. CAC is the critical aggregate concentration; k_m is the rate constant for AMC aggregation; K_{bind} is the rate constant for substrate binding.

dependence of AMC nucleophilicity on their oxidation potentials.

Analysis of the results obtained in a kinetic study of the reaction of the substrate **12** with AMC **1**, **4**, **7**, or **9** in 80% aqueous Pr^iOH and the study of the electrochemical behavior of these AMC in DMF (see Table 1) shows a correlation between the k_m and the nucleophilicities of the molecules that form aggregates, expressed by the equation

$$\log k_m = (-21.5\pm3.4) + (2.55\pm0.42)\cdot N_{MeI}, \quad (2)$$
$$n = 4,\ sd = 0.094,\ r = 0.98,$$

and between k_m and the potentials of reversible single-electron oxidation of AMC

$$\log k_m = (-2.28\pm0.19) - (9.8\pm1.8)\cdot E_p^{Ox,1}, \quad (3)$$
$$n = 4,\ sd = 0.10,\ r = 0.97.$$

The existence of correlations between these parameters suggests that ionic associates of macrocyclic AMC act as efficient nucleophilic reagents in the nucleophilic substitution reaction with EPA and that the reactivities of the ionic associates in these reactions and the reactivities of AMC molecules in electrochemical oxidation are determined by the same factors noted above, namely, by the basicity of the amino group and the nature of substituents at the N atom, which influence the ratio of the zwitterionic and monoanionic AMC forms.

In conclusion, note that the results of kinetic studies of the reactions of AMC with *p*-nitrophenyl esters of four-coordinate phosphorus acids attest in favor of the $S_N2(P)$ mechanism for the nucleophilic substitution. However, kinetic data do not rule out the possibility of other reaction pathways. Full and unambiguous description of the processes taking place in these systems requires additional investigations with monitoring of the reaction kinetics based on both the products and the starting compounds.

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