In search of an optimal acid-base indicator for examining surfactant micelles: Spectrophotometric studies and molecular dynamics simulations

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GRAPHICAL ABSTRACT
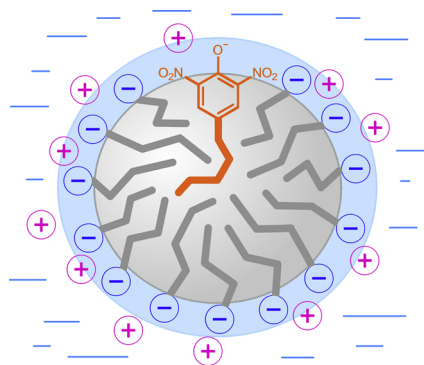
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ABSTRACT

We report on combined experimental and theoretical investigations of the water/micelle interface of cationic, anionic, zwitterionic, and non-ionic surfactants using a new hydrophobic acid-base indicator 2,6-dinitro-4-*n*-dodecylphenol. The indices of the so-called apparent ionization constant, pK_a^{app}, of the indicator fixed in the micellar pseudophase are determined by the spectrophotometric method. The data allows estimating the Stern layer's electrostatic potential of the ionic micelles Ψ. Molecular Dynamics modeling was used to locate the dye molecule and, in particular, its ionizing group OH→O⁻ within the micelles of the studied surfactants. The comparison of the Ψ values estimated using 2,6-dinitro-4-*n*-dodecylphenol with both our computer simulation and literature experimental results reveals obstacles in monitoring electrical interfacial potentials. In particular, the Ψ values of the surfactant micelles with alkylammonium groups determined via 2,6-dinitro-4-*n*-dodecylphenol are overestimated. The reason is specific interactions of the indicator anion with the surfactant head groups. For anionic surfactants, however, this indicator is quite suitable, which is confirmed by the location of HA and A⁻ equilibrium forms in the pseudophase.

1. Introduction

Acid-base indicators can serve as a universal tool for examining versatile colloidal aggregates and interfaces [1–3]. They are widely used for studying surfactant micelles [1–3], drops of microemulsions [2,3], phospholipid bilayers [1], gelatin layers [4], polymers [5], etc. Not only their color transitions, but also the light emission of fluorescent indicators is often used for monitoring the properties of micelles [6,7]. Among them, the estimation of the electrostatic surface potential of micelles and related aggregates is of special interest because of crucial role of this parameter in the interfacial processes. However, the information derived using the acid-base indicators depends fundamentally on the positioning of these molecular probes within the micellar pseudophase. Nowadays, this probe's location can be studied quantitatively using Molecular Dynamics modeling of a micelle plus indicator complex immersed into aqueous environment. This, in turn, allows validating different indicators from the viewpoint of their usefulness for determination of the electrostatic surface potential. This paper presents a step in this direction.

For the ionization of an indicator acid, HA, completely fixed in a micellar pseudophase, the so-called apparent pK_a^{app} value can be obtained using the spectrophotometric procedure, Eq. (1).

$$pK_a^{app} = pH + \log \frac{[HA]}{[A^-]} \qquad (1)$$

The concentration ratio indicator : micelle in the solution should be around unity. Normally, the bulk pH value is determined potentiometrically with a glass electrode in a cell with liquid junction. The brackets denote the equilibrium concentrations of the corresponding forms. The pK_a^{app} value can be represented as shown in Eq. (2), which is sometimes called the Hartley–Mukherjee–Fromherz–Funasaki (HMFF) equation [8–13].

$$pK_a^{app} = pK_a^w + \log \frac{\gamma_{A^-}}{\gamma_{HA}} - \frac{\Psi F}{RT \ln 10} = pK_a^i - \frac{\Psi F}{RT \ln 10} \qquad (2)$$

Here K_a^w is the thermodynamic ionization constant in water, K_a^i is called 'intrinsic' constant, γ_{A^-} and γ_{HA} are the activity coefficients of the transfer of the indicator forms from water to the micellar pseudophase, Ψ stands for the electrostatic potential of the micellar surface of an ionic surfactant, that is the Stern layer, F, R, and T have their usual meanings. The spectroscopic method gives the ratio of the equilibrium concentrations of HA and A$^-$ forms. Contrary to the pK_a^{app} value, direct determination of pK_a^i is challenging, however, some indirect methods were developed [1–3,9,11–15]. Clearly, from the pK_a^{app} and pK_a^i values, it is possible to estimate the Ψ value for the given ionic micelle, Eq. (3).

$$\Psi = \frac{RT \ln 10}{F} (pK_a^i - pK_a^{app}) \qquad (3)$$

This approach can also be used for droplets of microemulsions [3], phospholipid liposomes [16,17], monolayers [10,18], etc; see ref [1–3,14,15,19–22]. for details.

However, using different indicators for these measurements provides different Ψ values for the same system [2,3,23]. Therefore, some criteria should be established to minimize the variability. Such 'best' indicators should be firmly fixed in the pseudophase and its ionizing group should be located in the Stern layer. Though some disturbances of the microenvironment by the indicator molecule are inevitable, they should be as small as possible. Hence, the size of the molecule should be not too large. Finally, as the K_a^i value is usually modeled by the ionization constant either in nonionic micelles or in water–organic mixtures, the location of the acidic and basic forms of the indicator in the micellar pseudophase should be similar. After the publications by Fromherz et al. [10,11], the coumarin indicators with long hydrophobic hydrocarbon tails were often used for these purposes [15,16]. Also, the solvatochromic betaine dye, the so-called Reichardt's dye, which is also an acid-base indicator, was utilized [2,14]. Some other hydrophobic,

especially long-tailed indicators were examined [20]. A hydrophobic dye *N,N'*-di-*n*-octadecylrhodamine was also proposed for Ψ estimation [2,21]. Though the molecule of this dye is rather bulky, and the ionization of the COOH group displays only a small spectral effect, the *N,N'*-di-*n*-octadecylrhodamine was proposed because the change of the pK_a values of rhodamines in going from water to water-organic mixtures [24] and the micelles of nonionic surfactants [2,21] is small. This is because the acid-base couple is of cation/zwitterion type. Therefore, it can minimize the errors in modeling the pK_a^i values in ionic micelles by those in nonionic ones.

NMR spectroscopy was often used for revealing the location of the indicators within the micellar pseudophases [20,25,26], together with theoretical approaches applied to the same or similar systems [27–31].

We performed several Molecular Dynamics (MD) simulations of Reichardt's betaines in their cationic and zwitterionic forms in micelles of various surfactants [32–34]. In a special paper [22], we applied MD modeling to the first acid-base indicator used in 1940 by Hartley and Roe for estimating the electric potential of micelles [8] and discovered some peculiarities in location of this dye molecule and its anion in cationic and anionic micelles.

In the present paper, we propose a new indicator, 2,6-dinitro-4-*n*-dodecylphenol (DDP), as a possible suitable tool for examining the micellar surfaces. The rationale is as follows. (i) The dodecyl chain ensures the fixation of the indicator in the micelles of surfactants of any types. (ii) The aromatic moiety is not very large. (iii) Based on our previous studies [22,32–34], the HA and A$^-$ forms are expected to have similar orientation in the interfacial micellar layer. (iv) The pK_a values of nitrophenols undergo rather small changes in going from water to water-organic mixed solvents [35–37]. Therefore, we expected that the variations of the pK_a^i value in going from nonionic to ionic micelles will be caused mainly by the Ψ values of the latter.

Various alkyl derivatives of nitro- and dinitrophenols were often used in biophysical research [38,39]. Hence, the indicator considered in the present study may be useful in examining biological objects.

This indicator was synthesized and its pK_a^{app} value was determined in the micellar solutions of *N*- cetylpyridinium chloride (CPC), cetyltrimethylammonium bromide (CTAB), cetyldimethylammonium propanesulfonate (CDAPS), Triton X 100 (TX 100), and sodium *n*-dodecylsulfate (SDS). MD modeling was carried out for the HA molecule and the A$^-$ anion in micelles of ionic surfactants. The molecular structures of the indicator and the surfactants are shown in Scheme 1.[1]

We show that this indicator can be used for reliable measuring the Ψ values of anionic surfactant micelles, while for surfactants possessing alkylammonium head groups, the Ψ values obtained this way are biased. We suggest a molecular explanation for this effect.

2. Materials and methods

2.1. Chemicals

Hydrochloric, hydrobromic, sulfuric, and acetic acids, sodium and potassium chlorides were of analytical grade. The aqueous solution of NaOH was prepared from a saturated solution using CO$_2$-free water and it was kept protected from the atmosphere. Standard buffers with pH 1.68 (oxalate); 4.01 (*o*-phthalate); 6.86 (phosphate); and 9.18 (borate) at 25 °C were used for pH standardization. CPC (× 1 H$_2$O, Merck, 99%), CTAB (Sigma, 99%), CDAPS (Fluka, > 99%), SDS, (Vekton, Russia), TX 100 (Sigma) were used as received.

2.2. Synthesis of 2,6-dinitro-4-n-dodecylphenol and its sodium salt

The sample of 4-*n*-dodecylphenol was prepared as described in the

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[1] In our previous paper [33], a type error was occurred in the structural formula of *n*-dodecylsulfate.
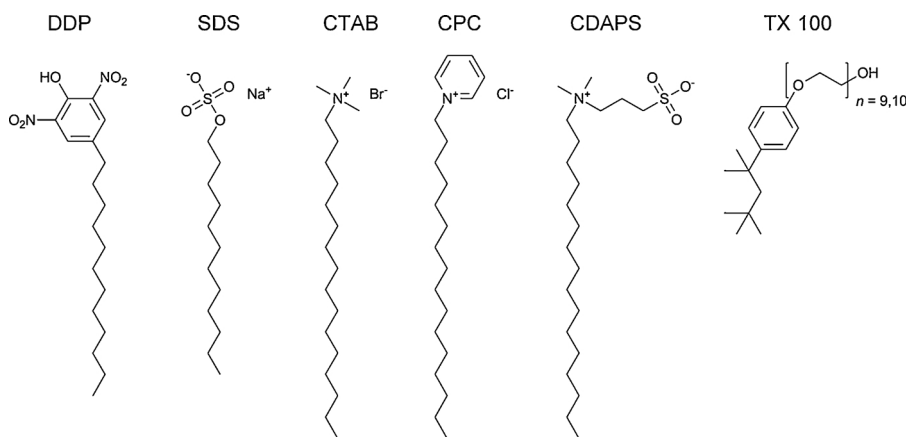
Scheme 1. Molecular structures of the studied dye (DDP) and surfactants.

literature [40,41]. To the solution of 0.262 g of 4-*n*-dodecylphenol in 1.5 mL of glacial acetic acid 0.3 g 99% nitric acid was added under stirring. After 1 h, the reaction mass was poured on the mixture of 5 g ice and 1 mL of 10% aqueous ammonia. The deposited precipitate was extracted with several 2 mL-portions of dichloromethane. The extract was evaporated in vacuum, and thus obtained substance was three times re-crystallized from ethanol containing an excess of aqueous ammonia. The orange ammonium salt of 2,6-dinitro-4-*n*-dodecylphenol was heated for 1.5 h at 160 °C and 60 mm Hg. After the quantitative decomposition of the salt, 2,6-dinitro-4-*n*-dodecylphenol was obtained; m.p. 60.0–60.5 °C. The compound was diluted on heating in 10 mL of ethanol containing 0.04 g of NaOH. After cooling, the red crystals of sodium 2,6-dinitro-4-*n*-dodecylphenolate were deposited. The product was twice re-crystallized from 50% aqueous ethanol. The yield was 0.13 g. ^{1}H NMR of 2,6-dinitro-4-*n*-dodecylphenol in CDCl$_3$: ^{1}H NMR (CDCl$_3$, δ ppm): 11.26 (1 H, s), 8.11 (2 H, s), 2.66 (2 H, t, J = 7.9 Hz), 1.63 (2 H, m), 1.36-1.18 (18 H, m), 0.86 (3, t, J = 6.1 Hz).

2.3. Preparation of indicator + surfactant systems

Weight amounts of the indicator and the surfactant were pounded and transferred into a 25 or 50 mL volumetric flask. A small amount of water was added and the mixture was heated on a water bath. After eight-minute sonication it was placed in a thermostat. After making up to the required volume and careful mixing, the working solutions were prepared by diluting an aliquot (1 or 2 mL) of the initial solution with a buffer mixture and a salt solution and topping up to 10 mL. The indicator concentration in the working solutions in different surfactant systems was $(3–8) \times 10^{-5}$ M.[2] The preparation of the solutions, the pH and spectra measurements have been carried out at 25 °C.

2.4. Spectrophotometric determination of the apparent ionization constants

The absorption spectra were measured with the Hitachi U-2000 spectrophotometer against solvent blanks, at 25.0 ± 0.1 °C. The pH values were determined using the R 37-01 potentiometer and pH-121 pH-meter (Russia) with an ESL-43-07 glass electrode (Gomel, Belarus) in a cell with liquid junction (3.0 M KCl). An Ag|AgCl electrode was used as a reference electrode. The glass electrode was calibrated with standard buffer solutions (pH 1.68, 4.01, 6.86, and 9.18 at 25 °C). The particle size distribution and zeta-potentials were determined by dynamic light scattering (DLS) using Zetasizer Nano ZS Malvern Instruments.

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[2] Hereafter, 1 M = 1 mol dm^{-3}.

2.5. Experimental procedure

The concentration of CTAB in the working solutions was 0.003 M, the pH values were adjusted using either HBr, with NaBr addition (ionic strength 0.10 M) or HCl, with KCl addition (ionic strength 4.00); the spectra of HA and A$^-$ were measured in 0.66–1.00 M HBr and 0.09 M HCl solution and in borate and phosphate buffer solutions, at pH 9.2 and 6.9, respectively. The concentration of other surfactants in the working solutions was 0.01 M. In CPC and CDAPS solutions, the pH values were adjusted using HCl, the ionic strength 0.10 M was maintained by adding NaCl. The spectra of HA and A$^-$ were measured in 4.5 M H$_2$SO$_4$ and 1.0 M HCl, respectively. In the solutions of TX 100, the acetate buffers (CH$_3$COOH + NaOH mixtures) were used, whereas in the SDS solutions, besides acetate, several phosphate buffers were also used. The ionic strength of 0.10 M was maintained by NaCl additions. In these two surfactant systems, the spectra of the HA form were measured in 0.05 M HCl solutions. The spectra of A$^-$ were measured in borate and phosphate buffer solutions.

The ratio of the equilibrium concentrations of the acidic and basic forms was determined spectrophotometrically using the standard procedure. For each system, around 8 solutions with different pH values were normally used. As analytical positions, ca. 20 wavelengths with 1 nm-interval around λ_{max} of A$^-$ were used.

2.6. Simulation protocol

The computational part of the work was done using GROMACS 5 software package [42] The simulations were carried out at standard conditions (the temperature of 298 K; the pressure of 1 bar), which were maintained by the Berendsen algorithms with the thermostat time constant of 1 ps and the barostat time constant of 1.5 ps. 3D periodic boundary conditions were imposed. The time step equaled 2 fs for SDS or 1.6 fs for CTAB and CDAPS. The constraints were put on all bonds, the particle mesh Ewald method was used for electrostatics, and van der Waals interactions were cut at 1 nm.

For each system, the initial configuration was a water box containing a micelle with a dye molecule placed inside. The length of the box and the number of monomers in the micelle was equal to 8 nm and 60 for SDS or 9.7 nm and 80 for CTAB and CDAPS, respectively. 60 and 80 were the aggregation numbers of the first two surfactants [43], while for CDAPS, the value equal to CTAB was taken to facilitate the comparison of computed characteristics between CTAB and CDAPS. As we have revealed for Reichardt's dye in CTAB micelles [34], the aggregation number value does not considerably affect the computed state of the indicator molecule. Three initial configurations were prepared for each particular system. They were qualitatively similar and differed in the location of the dye molecule inside the micelle only. The initial configurations were subject to a 10 ns equilibration after which 30 ns

productive runs were performed. During the 10 ns period the dye molecule relocated from the micelle interior to the micelle surface, and the rest of the run resided there. Reaching equilibrium was estimated by computing orientation of the molecule and hydration of the hydroxyl O atom (as described in sections 3.4, 3.5) by 0–5 ns, 5–10 ns, 10–15 ns, and 10–40 ns intervals and comparing them. The 5–10 ns, 10–15 ns, and 10–40 ns averages were generally close to one another while 0–5 ns usually outstood indicating 10 ns is enough for equilibration of such systems. For each system, the characteristics computed using each of the three runs, were averaged.

The simulations were performed using the well known OPLS-AA force field [44]. The models for SDS and CTAB were taken from our previous works [45,46], while the one for CDAPS was prepared as follows. In the CTAB potential model, one methyl group was replaced with the ethyl group, represented with the standard OPLS-AA parameters. Then, the $CH_2–SO_3^-$ group extracted from our potential model for sodium dodecyl sulfonate [22] was attached to the ethyl group.

The dye was parameterized in accordance with the standard OPLS-AA methodology in order to keep the mutual compatibility of all used potential models. Even though the force field contained the values of the atomic point charges for the hydroxyl, nitro, and methyl groups, bonded to a benzene ring, we decided to recalculate these charges for the DDP molecule because the built-in charges were obtained for single-substituted benzene derivatives, while in the case of DDP the interactions between the substituents lead to redistribution of the electronic density. At the first stage, quantum-chemical geometry optimization of the molecule at the RHF level of theory using the 6–31 G(d) basis set was performed. Then, fitting the distribution of the electrostatic potential around the molecule with a system of atom-centered point charges using the CHELPG algorithm [47] was done.

We used the RED server [48] linked to Gaussian 09.E to perform the procedure [49]. The point charges were computed for the 2,6-dinitro-4-methylphenol molecule, while for the rest of the hydrocarbon tail they were taken from the force field. This is justified because the inductive effect of the benzene ring on the hydrocarbon chain quickly diminishes.

We also prepared the potential models for two other dyes, 2,6-dinitro-4-pentylphenol (PDP) and 2-nitro-4-nonylphenol (NNP). For deriving the potential model of the latter compound, quantum-chemical computations were performed for the 2-nitro-4-methylphenol molecule.

The counter-ion for the anionic forms was Na^+, and water was represented by the SPC model.

3. Results and discussion

3.1. Experimental determination of ionization constants in micelles

The absorption spectra of 2,6-dinitro-4-*n*-dodecylphenol in micellar media at different pH values are presented in Figs. 1–3. The maximal

molar absorptivities of the HA molecule and the A^- ion in various micellar systems are around 4.9×10^3 M^{-1} cm^{-1} and 9.1×10^3 M^{-1} cm^{-1}, respectively. The isosbestic point is unambiguous, except the CDAPS and CTAB + 4.00 M KCl systems. For CDAPS, the working solutions were stable only for 10 min, after which some sediment was deposited. They were restored via slight heating.

Taking into account that the aggregation number of the surfactants in all systems is of the order of 10^2, the dye : micelle ratio was around unity or somewhat higher. The DLS study demonstrates that the micellar size with and without the indicator is approximately equal.

The dependences of the ionization degree of the indicator on pH are shown in Fig. 4. The solid lines correspond to the ionization degrees calculated using the pK_a^{app} values.

The pK_a^{app} and λ_{max} values are collected in Table 1. The data qualitatively agree with the data published for nitrophenols in micellar media [37,50,51]. The pK_a^{app} value in CPC micelles is lower than in CTAB ones (Table 1). This is in line with the data for a number of nitrophenols [50] and other dyes [2,3]. Also, the pK_a^{app} of a given indicator is as a rule lower in a cationic micelle with Cl^- counterion as compared with that with Br^-, everything else being equal [2,3]. The results for 2,6-dinitro-4-dodecylphenol obtained in the present study should be compared with those published in our previous paper devoted to nitrophenols, including 2,6-dinitrophenol in cationic and zwitterionic micelles [52].

It is also interesting to compare the λ_{max} values with those for 2,6-dinitrophenol [52]. In CDAPS and CTAB micelles, $\lambda_{max}(A^-)$ for 2,6-dinitrophenol is 450 and 455 nm, respectively. These are higher than in water (430 nm) but lower than those for the hydrophobic analogue in the same micelles, which are around 470 nm (Table 1). This gives evidence for deeper penetration into the micellar pseudophase of the 2,6-dinitro-4-dodecylphenolate as compared with the less hydrophobic analog.

The pK_a^{app} values of the hydrophilic dinitrophenol are always higher than for the hydrophobic dye in the above micelles. In CDAPS, at 0.05 M Cl^-, pK_a^{app} = 2.53 ± 0.02 at the maximal surfactant concentration (0.005 M) [52], whereas the extrapolation to complete binding of HA and A^- by the micelles results in pK_a^{app} = 2.76 ± 0.02 [52]. For 2,6-dinitro-4-dodecylphenol in CDAPS micelles, pK_a^{app} = 2.00 ± 0.02 (Table 1). In 0.01 M CTAB solution at 4.00 M KCl, pK_a^{app} of 2,6-dinitrophenol is 2.51 ± 0.02 [52], which is also substantially higher than pK_a^{app} = 2.20 ± 0.02 of the hydrophobic indicator (Table 1). Finally, in CTAB at 0.05 M Br^-, the pK_a^{app} value of 2,6-dinitrophenol is 1.31 ± 0.01 [52]. The extrapolation to 0.1 M Br^- using the well-known approaches [2] leads to a value of 1.5–1.6, which is also higher than 1.35 ± 0.05 in Table 1. Concluding, in all cases the pK_a^{app} of 2,6-dinitro-4-dodecylphenol in cationic and zwitterionic micelles is lower than for the indicator without the $C_{12}H_{25}$ tail. A possible explanation is that the hydrophobic dye penetrates deeper into the micellar pseudophase in
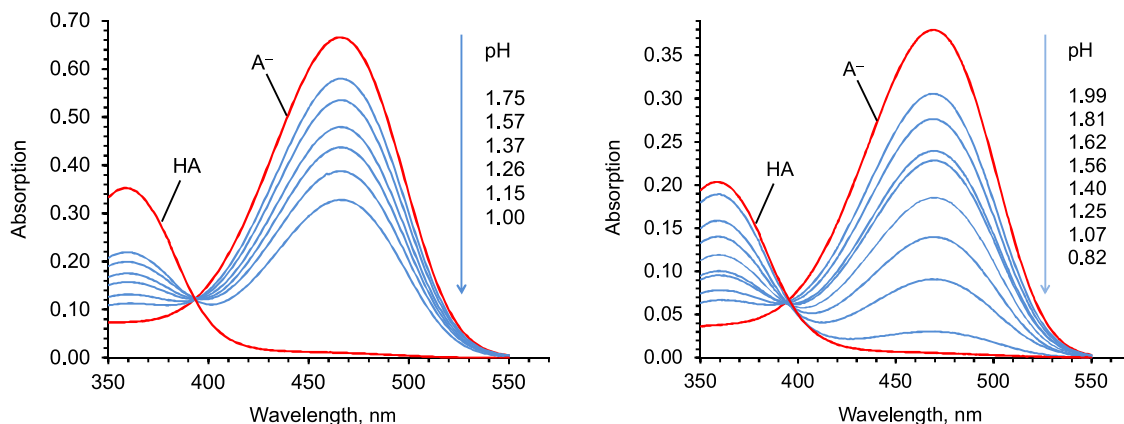

Fig. 1. Absorption spectra of 2,6-dinitro-4-*n*-dodecylphenol in 0.01 M CPC solutions, 0.10 M NaCl (a) and 0.003 M CTAB solutions, 0.10 M NaBr (b).
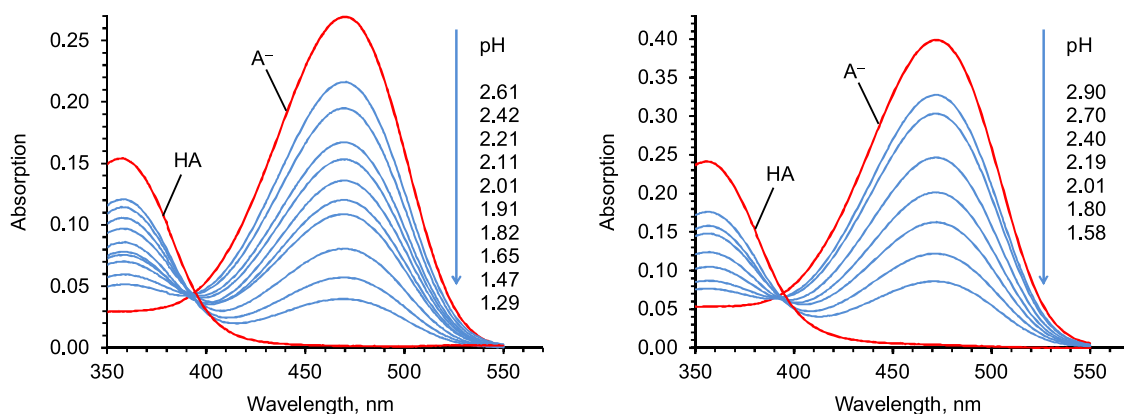
Fig. 2. Absorption spectra of 2,6-dinitro-4-*n*-dodecylphenol in 0.01 M CDAPS solutions, 0.10 M NaCl (a) and 0.003 M CTAB solutions, 4.00 M KCl (b).
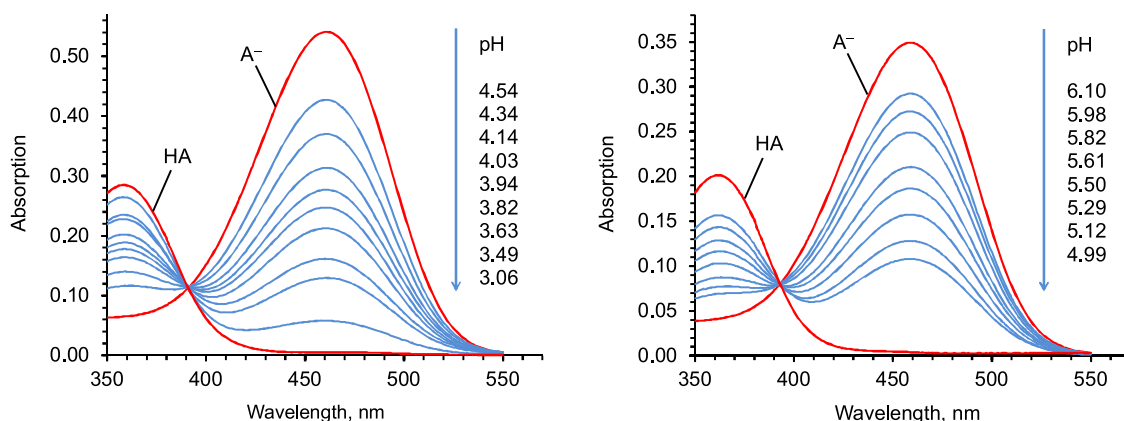

Fig. 3. Absorption spectra of 2,6-dinitro-4-*n*-dodecylphenol in 0.01 M TX 100 solution, 0.10 M NaCl (a) and 0.01 M SDS solution, 0.10 NaCl (b).

accordance with the λ_{max} values (see above).

Another problem is that the thermodynamic pK_a^w value of 2,6-di-nitro-4-dodecylphenol in water is unavailable experimentally. For 2,6-dinitrophenol $pK_a^w = 3.71$. Using the Hammett's $\sigma = 0.15$ and $\rho = 2.1$ constants for 4-alkyl radical and phenol in water the $pK_a^w = 4.02$ value can be predicted. However, the nitro groups in 2- and 6-positions can influence the electronic effect of the alkyl chain. For 4-methyl-2,6-

Fig. 4. Dependence of ionization degree of 2,6-dinitro-4-*n*-dodecylphenol fixed in micelles vs pH of the bulk (aqueous) phase in micellar solutions of CPC (1); CTAB (2,4); CDAPS (3); TX 100 (5); SDS (6). Surfactant concentrations: 0.01 M (CPC, CDAPS, TX 100, SDS) and 0.003 M (CTAB); ionic strength of the bulk phase for (2) and (4): 0.10 M NaBr and 4.00 M KCl, respectively; in all other cases: 0.10 M (NaCl); 25 °C.

dinitrophenol, an experimental value of 4.35 is available [53], whereas for 4-isobutyl-, 4-isoamyl-, and 4-isooctyl- derivatives of 2,6-dini-trophenol, the values of 4.3, 4.1, and 4.1, respectively were determined [38]. In any case, the difference between the pK_a^{app} in TX 100 and pK_a^w is small, thus confirming the choice of the indicator.

3.2. Micellar effects and estimation the electrostatic surface potential

The values of $\Delta pK_a^{app} = pK_a^{app} - pK_a^w$ calculated using the pK_a^w value of 4.1 are shown in Table 1. The sign of the effects is predictable: in-creasing pK_a^{app} in SDS micelles and decreasing in cationic ones. An important detail is a substantial pK_a^{app} decrease in the zwitterionic micelles and in the case of cationic surfactants under the condition of strong shielding of the micellar surface charge via 4.00 M KCl.

The calculation of the Ψ values using Eq. (3) was done following one of the most recognized procedures. Namely, the pK_a^i value in ionic (including zwitterionic) micelles was equated to the pK_a^{app} value in nonionic micelles (= 4.02, Table 1). First of all, with such approach the screening of the surface charge even by 4 M KCl is far from being complete. Also, the Ψ value in micelles of the zwitterionic surfactant is surprisingly high (Table 1). This should be attributed to the local electrostatic potentials in the interfacial layer. Finally, the $|\Psi|$ value in anionic micelles in the presence of 0.1 M NaCl is approximately two times lower than in the cationic micelles at the same ionic strength. Similar proportion was observed with *N,N'*-di-*n*-octadecylrhodamine as indicator [2,21], but the absolute values are markedly lower.

These conclusions rest on the assumption of the equality of pK_a^i in all kinds of micelles. This, in turn, is true at least if the location and hydration of the indicator and especially of its ionizing group is similar in different pseudophases. We used MD modeling to clarify these issues.
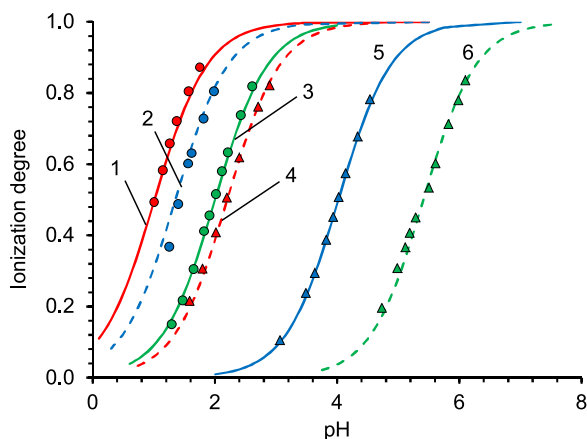
Table 1
Indices of apparent ionization constants of 2,6-dinitro-4-dodecylphenol and related parameters[a].

Surfactant, conc.	Salt background, M	$\lambda_{\max}$(HA), nm	$\lambda_{\max}$(A⁻), nm	pK_a^{app}	ΔpK_a^{app} [d]	Ψ, mV
None[b]	0	345	430	3.71[c]	—	—
SDS, 0.01 M	0.10	362	459	5.41±0.02	+1.3	–82
TX 100, 0.01 M	0.10	358	462	4.02±0.01	–0.1	0
CDAPS, 0.01 M	0.10	358	469	2.00±0.02	–2.1	+120
CTAB, 0.003 M	4.00 (KCl)	356	472	2.20±0.02	–1.9	+108
CTAB, 0.003 M	0.10 (Br–)	359	469	1.35±0.05	–2.8	+158
CPC, 0.01 M	0.10	359	465	1.01±0.02	–3.1	+178

[a] Ionic strength 0.10 M (buffer + NaCl), if not otherwise specified.
[b] Data for 2,6-dinitrophenol, ref. [52].
[c] Thermodynamic value for 2,6-dinitrophenol, pK_a^w; in ref. [35], pK_a^w = 3.70.
[d] For ΔpK_a^{app} calculation, a value of pK_a^w = 4.1 was used, see the text.

3.3. Molecular dynamics modeling of indicator localization

Using the MD simulations the location of the phenolic moiety of the dye molecule in the micelles was estimated by the analysis of the distribution functions of the distances (DFDs) between the micelle center of mass (COM) and the chosen atoms of the dye. We selected two atoms: i) the O atom of the dissociating hydroxyl group (it will be further denoted O_{OH}) and ii) the C atom of the hydrocarbon tail bonded to the benzene ring (denoted C_α). The graphs are shown in Fig. 5. The peaks on these DFDs indicate the preferable region of the micelle where the particular atom is located. For comparison, DFDs between the micelle COM and the atoms S or N of the surfactant ions are calculated, as well, because they indicate the location of the micelle surface layer.

The results show that the hydroxyl group is situated in the surface layer and it is not immersed into the micelle, while the C_α atom is situated much deeper in it. Importantly, the difference between the average location of the neutral and anionic forms is very small, the corresponding peaks almost coincide. A notable difference is observed for the C_α atom in CDAPS micelles only.

3.4. Modeling of indicator orientation

Deeper understanding of the dye molecule location in the micelle is provided by its orientation with respect to the micelle surface. To quantify it, we introduced the pitch angle θ defined as $\angle$ (the micelle COM, the C_α atom of DDP, the O_{OH} atom of DDP). Its distribution functions shows how the molecule is aligned. The definition of the angle and the results of calculations are shown in Fig. 6.

For the anionic form, the θ values around 160° are typical for all micelles. This corresponds to the orientation that is roughly parallel to the micelle radius with the hydroxyl group pushed towards the bulk phase. A similar picture is observed for the neutral form in SDS micelles, but the maximum is at 140° and the peak is wider that means a stronger inclination of the molecule. In CTAB and CDAPS micelles this effect is even more pronounced: the high probability of the values 80–120° means that the orientation with the molecule lying roughly

parallel to the micelle surface is populated, too.

3.5. Modeling of indicator microenvironment

Apart from the location of the dye molecule the composition of the medium where it resides (i.e., its microenvironment) is important as it ultimately determines the pK_a^i shift upon binding by the micellar pseudophase. We employed the same approach for its description as in our previous works devoted to the Reichardt's solvatochromic indicators and the azo dye [22,32–34]. The atoms of the solution that surround the phenolic moiety of the DDP molecule (i.e. which are located within 0.4 nm of at least one of its atoms) were classified into three categories: the atoms of water molecules, the atoms of surfactant head groups, and the atoms of surfactant hydrocarbon tails. The average numbers of atoms in these categories characterize the microenvironment of the dye molecule. The results are shown in Fig. 7.

In the SDS micelles, the dye is much better hydrated than in the CTAB and CDAPS ones. The difference between CTAB and CDAPS is quite small (10–15%). Moreover, in CDAPS micelles only the positively charged $[CH_2–N(CH_3)_2–CH_2]^+$ fragments contribute to the microenvironment of the hydroxyl group, while there are no contacts with the negatively charged SO_3^- fragments. The contact of the whole dye molecule with the SO_3^- fragments is non-zero but very small. Therefore, the dye should be considered as situated in the electric field with positive potential despite the surfactant zwitter-ions as a whole are neutral. This should have consequences related to the value of pK_a^{app} in these micelles.

Importantly, for both the whole molecule and its individual hydroxyl group the microenvironment remains almost unchanged upon going from the neutral form to the anionic one in all micelles. The differences are 2.9 atoms in SDS, 0.9 atoms in CTAB, and 1.0 atom in CDAPS, which are less than for the other dyes that we studied previously, the Reichardt's betaines [32–34] and the azo dye [22]. This fact together with the similarity of the location of these two forms provides microscopic justification of the application of the proposed dye as a suitable probe of the micelle electrostatic potential.
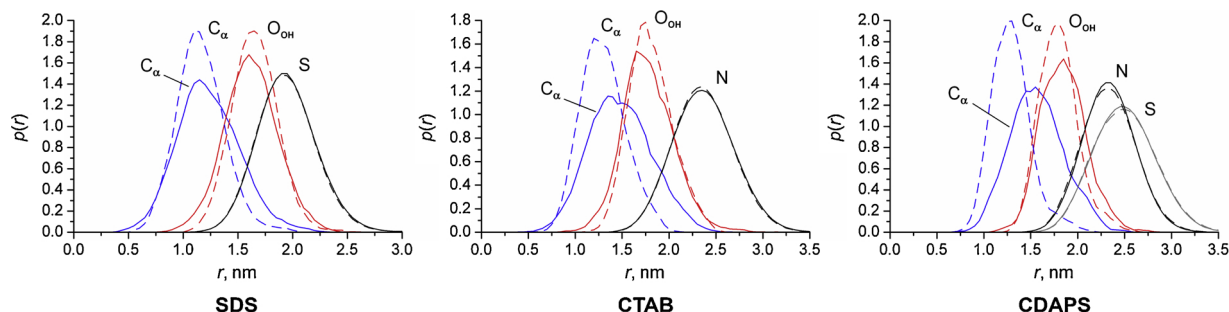

Fig. 5. Distribution functions of the distances between the micelle COM and the C_α, O_{OH} atoms of DDP or S (N) atoms of the surfactant ions; solid curves are for the neutral form, dashed curves are for the anionic form.
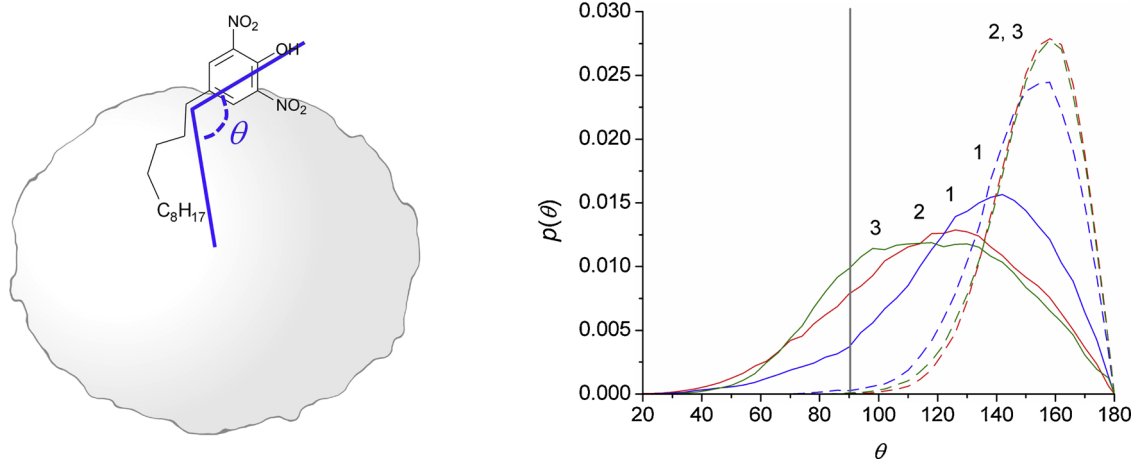
Fig. 6. Left: the definition of the angle θ (gray zone depicts the micelle hydrocarbon core); right: the distribution functions of θ. 1 — SDS solution, 2 — CTAB solution, 3 — CDAPS solution; solid curves are for the neutral form, dashed curves are for the anionic form.
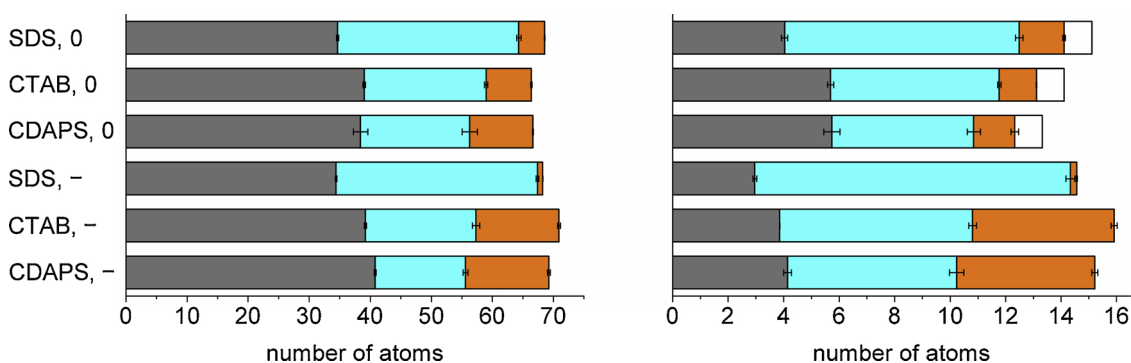

Fig. 7. Numbers of atoms of various kinds in the microenvironment of the phenolic moiety of the DDP molecule (left) and of the hydroxyl O atom (right); gray: atoms of hydrocarbon tails, blue: atoms of water molecules, orange: atoms of surfactant head groups, white: the H atom in the hydroxyl group. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

In order to elucidate the role of the hydrocarbon tail length, a dye with C_5H_{11} group, 2,6-dinitro-4-*n*-pentylphenol, or PDP, was examined. The location of PDP in SDS micelles is shown in Supporting Information, Fig. S1. In general, both forms of PDP are situated 0.1 – 0.2 nm closer to water phase than DDP, which shows that the length of the hydrocarbon radical does affect, albeit weakly, the dye location in the micelles.

3.6. Comparing with data obtained using other indicators

Most experimental data obtained in the present study refer to the ionic strength 0.10 M. This is because of the low pK_a^{app} values in cationic micelles, which requires using relatively high HCl and HBr concentrations. However, the obtained pK_a^{app} values can be re-calculated to the ionic strength (in this case it is the counterion concentration) of 0.05 M using the well known slopes of the pK_a^{app} vs logarithm of counterion concentration dependences [2,3,21], Eqs. (4) and (5) for cationic and anionic micelles, respectively.

$$\left(\frac{\partial pK_a^{app}}{\partial \log[Br_w^-]}\right)_T = \beta \qquad (4)$$

$$\left(\frac{\partial pK_a^{app}}{\partial \log[Na_w^+]}\right)_T = -\beta \qquad (5)$$

Here, β is the degree of counterion binding [2,3]. It means that the $|\Psi|$ values in SDS, CTAB, and CPC micelles as obtained via Eq. (3) should be increased by 13 mV, using the $\beta = 0.75$ value. For example, Ψ is equal to -95 mV for SDS and to $+171$ mV for CTAB micelles at counter-ions

Na$^+$ or Br$^-$ concentration of 0.05 M.

In Table 2 and 3, the Ψ values estimated obtained with 2,6-dinitro-4-*n*-dodecylphenol are compared with the data obtained with other indicators, most often applied for Ψ determination, first of all the hydrophobic hydroxycoumarins.

Table 2
The values of the electrostatic potential of SDS micelles determined by various methods.

Indicator	Ψ, mV 0.05 M Na$^+$
2,6-Dinitro-4-*n*-dodecylphenol, this work	-95[a]
4-Heptadecyl-7-hydroxycoumarin	-114[b]
4-Octadecyloxy-1-naphthoic acid	-87[c]
Standard Reichardt's dye[d,e]	-95
n-Decylfluorescein[e]	$-110\ (-144)$[f]
N,N'-Di-*n*-octadecylrhodamine[e]	-59
Calculation via Ohshima–Healy–White equation, ref. [55]	-66[g]

[a] At 0.10 M Na$^+$, $\Psi = -82$ mV, this work.
[b] At 0.10 M Na$^+$, $\Psi = -95$ mV, ref. [15].
[c] From the value -93 mV in ref. [20] recalculated to Na$^+$ concentration of 0.05 M.
[d] 4-(2,4,6-triphenylpyridinium-1-yl)-2,6-diphenyl phenolate.
[e] Ref. [2,3].
[f] The values in parenthesis are determined using the constants of two-step equilibria of *n*-decylfluorescein.
[g] Calculated using the values of micellar radius, molecular area of the ionic head group, and degree of counterions binding 2.0 nm, 0.60 nm^2, and 0.75, respectively.

Table 3
The values of the electrostatic potential of CTAB and CDAPS micelles determined by various methods.

Indicator	Ψ, mV		
	CTAB micelles		CDAPS micelles
Ionic strength =	0.05 M	4.0 M KCl	0.05–0.10 M
2,6-Dinitro 4-*n*-dodecylphenol, this work	+171	+108	+120
4-Heptadecyl 7-hydroxycoumarin, 4-undecyl-7-hydroxycoumarin, and 4-octadecyloxy-1-naphthoic acid [a]	+118 [b]	— [c]	—
Standard Reichardt's dye [d]	+99 (+117) [e]	+30	+65
n-Decylfluorescein [d]	+122 (+103) [f]	+23 (+15) [f]	+55 (+46) [f]
N,N′-Di-*n*-octadecylrhodamine [d]	+99	+16	+36
Calculation via Ohshima–Healy–White equation, ref. [55] [g]	+88	—	—

[a] Average values from ref. [11,14,20,54] recalculated to Br⁻ concentration of 0.05 M via Eq. (4), see also ref. [21].

[b] At NaBr concentration of 0.05 M the value ca. + 90 mV was given in Fig. 6 in ref. [11].

[c] For *n*-dodecyltrimethylammonium chloride micelles in 4.0 M NaCl solution, Ψ = +43 mV with 4-heptadecyl-7-hydroxycoumarin, ref. [54].

[d] Ref. [2,3].

[e] Recalculated via Eq. (4) from the value +141 mV determined at low ionic strength published in ref. [14].

[f] The values in parenthesis are determined using the constants of two-step equilibria of *n*-decylfluorescein.

[g] Calculated using the values of micellar radius, molecular area of the ionic head group, and degree of counterions binding 2.6 nm, 0.474 nm², and 0.73, respectively.

With 4-heptadecyl-7-hydroxycoumarin, the values Ψ = –122, –110, and −95 mV were obtained in SDS micellar solutions with ionic strength (NaCl) 0.025, 0.065, and 0.102 M, respectively [15]. Fernandez and Fromherz [11] and Drummond and Grieser [54] reported Ψ values obtained with 4-undecyl- and 4-heptadecyl-7-hydroxycoumarins, respectively; these data agree with those published by Hartland et al. [15] and are considered in ref. [21]. The 4-octadecyloxy-1-naphthoic acid was also used [20]. As the ionic strength in these studies [11,20,54] was substantially lower compared to our experiments, the corresponding corrections would make the difference smaller. Only these recalculated values are compiled in Table 3. However, the electrostatic potential estimated with the coumarin indicators [11,15,54] shows somewhat more negative Ψ values than were estimated with 2,6-dinitro-4-dodecylphenol.

It should be stated that, in the case of SDS micelles, the proposed indicator 2,6-dinitro-4-dodecylphenol provides the Ψ values agreeing roughly with other estimates (Table 2). Further *pro et contra* for using just this indicator should be followed from the results of MD modeling, see above. This is not the case for the CTAB micelles at 0.05 M Br⁻ (Table 3).

For CTAB micellar solutions, the Ψ values were obtained by several authors with the hydrophobic coumarins at ionic strengths < 0.05 M [11,14,20,54]. In Table 3, these and some other values are re-calculated to [Br⁻_w] = 0.05 M using Eq. (4). In addition, we obtained some values using the Reichardt's betaine dye, *n*-decylfluorescein, and *N,N′*-di-*n*-octadecylrhodamine [2,3,21]. They are also compiled in Table 3.

The inspection of Table 3 allows stating that the indicator 2,6-dinitro-4-dodecylphenol shows substantially more positive Ψ values in cationic micelles: in the case of CTAB micelles at 0.05 M Br⁻, the results obtained with the new indicator are evidently different (Table 3).

The overestimate of the Ψ values obtained with 2,6-dinitro-4-dodecylphenol may also be proven using the Ohshima–Healy–White equation [55], which allows calculating the electrostatic potential values for well-defined surfactant micelles [2,21], although these results depend to some degree on the values of the molecular area of the head groups and β. This equation for spherical micelles is given below, Eq. (6).

$$\frac{1-\beta}{s_i} = \frac{2\varepsilon\varepsilon_o \kappa RT}{F} \sinh(Y/2)\left(1 + \frac{2}{\kappa r \cosh^2(Y/4)} + \frac{8\ln[\cosh(Y/4)]}{(\kappa r)^2 \sinh^2(Y/2)}\right)^{\frac{1}{2}}. \quad (6)$$

Here, s_i is the area of charged head group (molecular area), $Y = \Psi F/RT$, κ is the reciprocal Debye length, $\varepsilon_o = 8.854 \times 10^{-12}$ F m⁻¹, $\varepsilon_o = 78.5$ at $T = 298.15$ K. Actually, the left hand side in Eq. (6) is the surface charge density.

Eq. (6) may also be used for verifying the experimentally estimated value Ψ = +171 mV for CTAB micelles. At [Br⁻] = 0.05 M this value corresponds to a micellar surface charge density value of 2.45 elementary charges per nm², if the micellar radius is 2.6 nm. If β = 0.75, the molecular area of the head group is 0.10 nm², which is impossible taking the vanderWaals value of 0.38 nm² [56]. Even for β = 0.60, s_i is also as low as 0.16 nm². So, this also confirms the overestimated Ψ value for cationic surfactant micelles obtained with the 2,6-dinitro-4-dodecylphenol. Indeed, if, for instance, Ψ equals to 100 mV, the surface charge density is 0.762, and the molecular area at β = 0.75 and 0.60 is 0.328 and 0.525 nm², respectively.

Furthermore, for CTAB micelles in 4.0 M KCl solution, Ψ = +16 mV and + 30 mV as obtained with *N,N′*-di-*n*-octadecylrhodamine and Reichardt's dye, respectively [2], while the value of +108 mV was obtained for CTAB with 4.00 M KCl with the hydrophobic dinitrophenol in the present study (under these conditions, the CTAB micelles convert into the CTAC ones).

Moreover, whereas for the zwitterionic CDAPS micelles, the Ψ value obtained with *N,N′*-di-*n*-octadecylrhodamine and Reichardt's dye equal to + 36 and + 65 mV, respectively [2], the application of 2,6-dinitro-4-dodecylphenol leads to Ψ = +120 mV (Tables 1,3).

The differences between the Ψ values determined by the 2,6-dinitro-4-dodecylphenol and an averaged value obtained by other approaches are 64 mV for CTAB micelles at ionic strength 0.05 M, 85 mV for ionic strength 4.00 M, and 68 mV for CDAPS.

As one of possible explanations it can be assumed that the strong decrease in the pK_a^{app} value of 2,6-dinitro-4-dodecylphenol reflects only the local electrostatic potentials at the location of the ionizing group of the indicator. However, the simulations in comparison with another phenolic indicator, cation of the Reichardt's dye [32–34], does not support such explanation, as it is seen in Table 3. Also, the orientation of the 2,6-dinitro-4-dodecylphenolate, A⁻, in CTAB, CDAPS, and SDS micelles is similar, but the negative Ψ value in SDS is certainly not overestimated.

A probable reason may be some specific interaction in the micelles with alkylammonium moiety. Indeed, the contacts of the phenolate oxygen of A⁻ with the cationic headgroups of surfactants are evident (Fig. 7). The same refers to the nitro groups, which favor the delocalization of the negative charge in the indicator anion, thus stabilizing it and decreasing the pK_a^i value. This, in turn, leads to overestimating the Ψ value, if such specific effect is not taken into account.

The strong delocalization of the negative charge in nitrophenolates is known to reduce the pK_a increase in going from water to polar non hydrogen bond-donor solvents. For example, in dimethylsulfoxide

Table 4
Average distances of the C_α and O atoms of DDP to the micelle COM (nm).

micelles	C_α atom			O_{OH} atom		
	HA	A^-	delta	HA	A^-	delta
SDS	1.23	1.16	−0.07	1.62	1.66	0.04
CTAB	1.48	1.30	−0.18	1.78	1.81	0.03
CDAPS	1.57	1.30	−0.27	1.85	1.80	− 0.05

Table 5
Average distances of the C_α and O atoms of PDP and NNP to the micelle COM (nm).

dye	micelles	C_α atom		O_{OH} atom	
		HA	A^-	HA	A^-
DDP	SDS	1.42	1.27	1.68	1.73
NNP	CTAB	1.31	1.40	1.64	1.85

(DMSO), the rise of pK_a is 6.4 units for phenol [57], 3.8 for 2-nitrophenol [57], 1.66 for 2,5-dinitrophenol [58], 1.2 for 2,6-dinitrophenol [57], and 0.9 for 2,4-dinitrophenol [58]. For the last-named indicator, the pK_a even drops from 4.11 in water to 3.56 in 65 vol. % aqueous DMSO [59]. In our case, the mechanism of the additional stabilization of the anion is somewhat different from that in DMSO, and probably consists in further shifting the electron density from the phenolate oxygen caused by the interaction of the electrophilic electronically unsaturated NO_2 substituents with the tetraalkylammonium groups.

To support this hypothesis we used the data reported by Seguchi [50]. In his work, the pK_a^{app} = 2.40 value of 2,4-dinitrophenol in CTAB solutions (in the presence of 3% ethanol, 30 °C) [50] corresponds to the same value (2.37 in 0.016 M CTAB, 0.05 M KBr, 25 °C) of this indicator obtained in our laboratory [52]. Therefore, the value pK_a^{app} = 5.86, reported by Seguchi for the 2-nitro-4-n-nonylphenol in CTAB micellar solutions, can be attributed to the Br^- concentration of ca. 0.05 M. In Brij 35 micellar solutions, pK_a^{app} = 8.52 for the same indicator [50], which allows estimating the Ψ value in CTAB micelles as +157 mV. Though it is again somewhat lower compared to the +171 mV value obtained with 2,6-dinitro-4-dodecylphenol, but still overestimated. Indeed, by Eq. (6) the s_i = 0.130 and 0.209 nm^2 values can be estimated for β = 0.75 and 0.60, respectively. These molecular areas of the head groups are again unlikely small, although the indicator used bears only one nitro group.

Note, that for the anionic surfactant, the data with 2-nitro-4-n-nonylphenol [50] gives the Ψ value around −90 mV, which is close to that obtained with 2,6-dinitro-4-dodecylphenol (−95 mV, see above). This supports the hypothesis of specific interactions between our indicator and ionic head groups only in the case of cationic and zwitterionic surfactants.

Accordingly, it may be concluded that the excessive polarizability of the electrophilic NO_2 groups may cause a substantial change in the intrinsic value, pK_a^i, of corresponding indicators in Stern layer of micelles with alkylammonium groups. This results in overestimation of the Ψ value. According to this explanation, the indicators with electron-withdrawing groups less polarizable than nitro groups, e.g. 2,6-trifluoromethyl-4-n-dodecylphenol or 2,6-cyano-4-n-dodecylphenol, or even unsubstituted 4-n-dodecylphenol may be likely well-suited for cationic micelles.

In contrast, 2,6-dinitro-4-dodecylphenol is quite suitable for examining micelles of anionic surfactants.

Therefore, we performed MD simulations for 2-nitro-4-n-nonylphenol (NNP). The location of NNP in CTAB micelles is shown in Supporting Information, Fig. S2. The difference between the locations of NNP and DDP is of the same magnitude, despite the absence of one

nitro group.

In order to make these comparisons clearer, the average distances of the C_α and O atoms to the micelle COM were computed for each case. The values for DDP are collected in Table 4, while the results for other dyes are listed in Table 5. The difference of the quantities between anionic and neutral forms can easily be calculated, which are also listed in Table 4 (the 'delta' values).

The microenvironment of NNP is shown in Fig. S3. Interestingly, removing one nitro group causes different shifts in hydrations of the neutral and anionic forms. As a result, the difference between the hydrations of these forms increases in comparison with DDP and becomes 4.0 atoms in CTAB micelles.

4. Conclusions

In search of an optimal acid-base indicator for examining micelles of ionic surfactants, 2,6-dinitro-4-n-dodecylphenol was synthesized and the indices of the apparent ionization constants, pK_a^{app}, were obtained by the spectrophotometric method supplemented by potentiometric pH determination. Molecular Dynamics simulations demonstrate that in micelles of any kind, the location of the HA and A^- forms is quite similar. Additionally, simulations were made for two other hydrophobic nitrophenols and their anions in micelles.

The values of the electrostatic interfacial potential of the micelles, that is the potential of the Stern layer, Ψ, were determined by the standard procedure, using the pK_a^{app} value of the indicator in nonionic micelles as the indices of the intrinsic ionization constant pK_a^i in ionic micelles. Thus obtained Ψ values in the micelles of surfactants bearing alkylammonium and alkylpyridinium groups appeared to be much higher than those either estimated using other indicators or calculated by the Ohshima–Healy–White equation. This was explained in terms of the specific interactions between the nitro groups of the indicator with alkylammonium or pyridinium groups in the Stern layer of the micelles: these interactions additionally stabilize the A^- form of the indicator, thus decreasing the pK_a^i value. The latter is therefore difficult to predict. On the other hand, the indicator 2,6-dinitro-4-n-dodecylphenol is suitable for examining anionic micelles. So, the Ψ value for the SDS micelles is −95 mV (at ionic strength 0.05 M).

Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.colsurfa.2018.12.048.

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