CHOOSING THE WAVELENGTH FOR SPECTROPHOTOMETRIC DETERMINATION OF THERMODYNAMIC DISSOCIATION CONSTANTS

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Abstract

Thermodynamic dissociation constant is of crucial importance for a wide range of utilitarian and research purposes, being a key physical and chemical parameter of a compound. Analytical wavelength is one of the parameters determined through the spectrophotometric determination of dissociation constants. The article offers an outline of the published approaches to the determination of the wavelength using the traditional method of spectrophotometric titration and introduces the new method of concentration spectrophotometry that measures this parameter with utmost accuracy.

Keywords: thermodynamic dissociation constant, wavelength, molar absorption coefficient, concentration spectrophotometry

Thermodynamic dissociation constant (pK_a^T) is used in various areas of research, being the key parameter in assessing the physical, chemical and biological properties of a compound [1]. It plays a major part in a number of analytical processes, e. g. chromatographic retention and pharmaceutical properties of organic acids and bases [2], acid-base titration [3], solvent extraction and complexing [4], structuring and interaction of the dissolved compound and the solvent. Dissociation constant is also used for determining stereochemical and conformational structures, the directions of nucleophile and electrophile attack, stability of intermediate compounds, in the correlational analysis involving the Hammett and Taft equations etc. Besides, thermodynamic dissociation constant is one of the vital parameters in drug developing. It can be used for the prognostication of the pharmacodynamic and pharmacokinetic properties of compounds: absorption, distribution, metabolism, elimination and toxicity, the so-called ADMET [5, 6]. The pK_a^T value is instrumental for understanding the transport of medical substances into the cells and through membranes.

Methods of UV/vis spectrophotometry used for analyzing the compounds with low solvency and low concentration are particularly important for obtaining the values of thermodynamic dissociation constants used in physical organic chemistry [7]. The samples must contain a UV-active chromophore, close enough to the area of the acid-base function in the molecule. Besides, the test sample should be free of alloys that might cause absorption in the UV/vis spectrum.

One of the key steps in determining the thermodynamic dissociation constant is the choice of analytical wavelength, i.e. the wavelength used for conducting the measurements that are subsequently analyzed. International literature doesn't seem to offer a universally recognized approach to choosing the analytical wavelength. Each researcher seems to base his or her choice on his/er own experience, classical procedures etc. This review summarizes the existing methods of choosing the wavelength for spectrophotometric determination of thermodynamic dissociation constants. Another method under consideration, apart from the well-known

approaches based on the traditional spectrophotometric titration, is concentration spectrophotometry method, that allows to unambiguously determine the analytical wavelength without using the concentrated solutions of strong acids and bases for determining the extreme prototropic forms.

Spetrophotometric titration method: choosing the wavelenght

Traditional spectrophotometric titration is one of the popular methods of determining the thermodynamic dissociation constants [8–10]. As the primary empirical data, it uses the dependences of absorbance (ionization ratio logarithm) on pH, obtained through registering the spectra of the test compound with the same concentration in a number of buffer solutions with various pH values at constant ionic force. For spectrophotometric titration, the analytical wavelength is chosen, as a rule, to correspond to the maximum difference between the absorbance of the solutions or of the molar absorption coefficients of the extreme prototropic forms with the changing of the pH of the solution [11–17]. In other words, the dissociated and non-dissociated forms are obtained by registering the spectra of the test compound at the same concentration, using the solutions of strong acids or bases. Apart from complicating the process of preparation and conducting of the experiment, this approach limits the usability of the method, since it's very hard to obtain the extreme forms for the compounds with poor resolution spectra.

It is sometimes impossible to choose just one wavelength where the changes of the absorbance and molar absorption coefficients of the protonated and non-protonated forms are at their highest. Then the researchers choose several wavelengths to conduct the measurements [18]. Thus, in [19] the measurements for various estrogen derivatives were conducted at several wavelengths. E. g., pK_a^T for 17α-estradiol was calculated at the following wavelengths: 240 nm, 248 nm, 295 nm, 300 nm (Fig. 1).
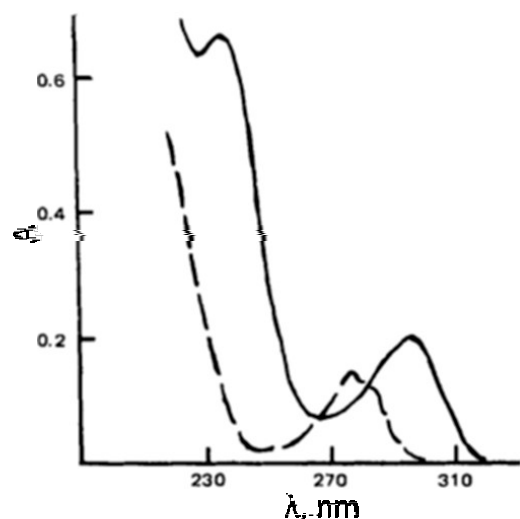
Fig. 1. UV spectra for 17α-estradiol at the concentration of $1.5 \cdot 10^{-5}$ M and cuvette length of 5 cm (— pH = 12.3; ···· pH = 3.6) [Wiley Online Library 66 (5): 624-627 (1977)].

     The chosen wavelengths might be so far apart due to the absorption maxima in the spectra of the prototropic forms of estrogens, registered in the strong acid or base solutions, and to their subsequent averaging for specific groups of estrogen derivatives. It's noteworthy that the values of estrogen's pK_a^{T} obtained at these lengths are in agreement with each other (Table 1).

Table 1.   Spectrophotometric Determination of pK_a^{T} for 17α-estradiol [Wiley Online Library 66 (5): 624-627 (1977)].

pH	240 nm		248 nm		295 nm		300 nm	
	A	pK_a^{T}	A	pK_a^{T}	A	pK_a^{T}	A	pK_a^{T}
12.3	0.670	-	0.423	-	0.200	-	0.192	-
3.6	0.0047	-	0.015	-	0.007	-	0.0	-
10.37	0.342	10.42	0.218	10.38	0.096	10.44	0.089	10.43
10.51	0.360	10.51	0.227	10.48	0.102	10.52	0.098	10.49
10.38	0.326	10.47	0.200	10.46	0.095	10.46	0.090	10.44
10.65	0.421	10.47	0.265	10.45	0.120	10.50	0.115	10.47
10.30	0.298	10.47	0.180	10.47	0.086	10.46	0.080	10.45
			$pK_a^{T} = 10.46 \pm 0.03$					

Apart from the abovementioned "classical" approaches to choosing the wavelength, there're some less trivial ones. Thus, the method of choosing the analytical wavelength presented in [20] relies on the form of the test compound. The neutral and the dianion forms of resorcin display the maximum absorption at 273.8 and 290.0 nm respectively (Fig. 2).
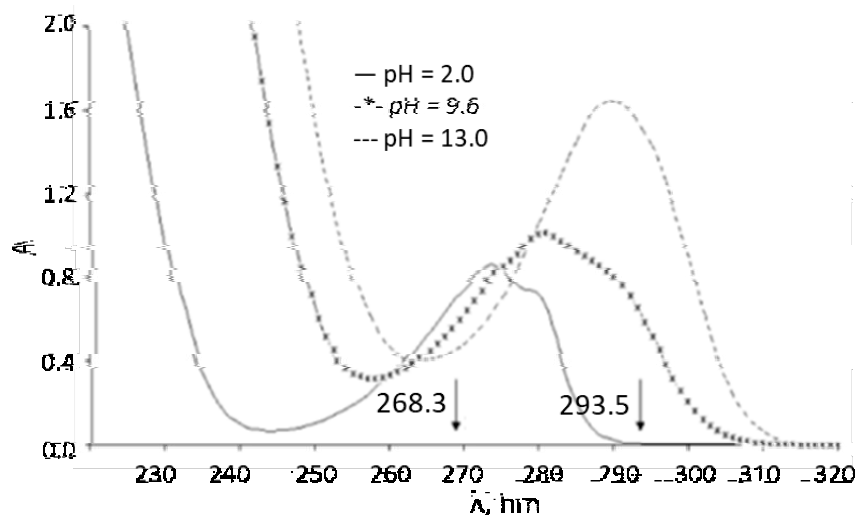

Fig. 2. Absorption Spectra of Resorcinol at Various pH Values. The arrows indicate the chosen wavelengths. [Spectrochimica Acta Part A 61: 93–102 (2005)].

The authors choose the analytical wavelength of 293.5 nm, the one where the absorption of dianion is at its maximum, while the absorption of the neutral resorcin is close to zero. In this range, resorcin monoanion displays the intermediate absorption between the two other types. Another chosen wavelength is 268.3 nm, where the neutral and monoanion forms are absorbed, while the absorption of dianion tends to the minimum. The obtained thermodynamic constants for resorcinol at the two different wavelengths are in agreement with each other (Table 2).

Table 2. Experimental Values of Resorcinol Thermodynamic Constants Determined by UV/vis Spectrophotometry [Spectrochimica Acta Part A 61: 93–102 (2005)].

λ (nm)	pK_{a1}^{T}	pK_{a2}^{T}
268.3	9.196 ± 0.005	10.904 ± 0.011
293.5	9.211 ± 0.011	10.901 ± 0.011

In [21], the spectra of 2,4-dinitrophenol reach the maximum absorption at 360 nm and 400 nm in the mixtures of 1-propanol-water with the ratios of 5, 10, 20, 30 и 40 and mas.%. The spectra of potassium sulphate of 2, 4-dinitrophenol reach their maximums at the same wavelengths. In the presence of a non-absorbing acid (HNO_3), the peak tends to shift to the short-wave range. Based on the measurements of spectra, the decision was taken to calculate pK_a^{T} at these wavelengths (Table 3). The proximity of dissociation constant values determined at various wavelengths seems fairly reliable.

Table 3. Thermodynamic Dissociation Constant Values for 2,4-dinitrophenol in the Mixture of 1-Propanol-Water at 360 nm and 400 nm [Der Pharma Chemica 4 (4): 1375-1384 (2012)].

W, % 1-propanol	pK_a^{T} (360 nm)	pK_a^{T} (400 nm)
0	4.09	4.09
5	3.81	3.82
10	3.74	3.73
20	3.66	3.64
30	3.85	3.87
40	3.89	3.91

These approaches show that the choice of the wavelength is not a major problem. Yet, the process of determining pK_a^{T} at several wavelengths simultaneously is more cumbersome and less environmental friendly, for the solutions of strong acids and alkali have to be used. Besides, the traditional method

of spectrophotometric titration has another shortcoming, the abovementioned cases of the compounds with poor spectral resolution.

Unlike the classical spectrophotometric approaches to determining the thermodynamic dissociation constants, the multiwave spectrophotometry method (WApH) uses more extensive spectral information [22]. As suggested in [23-25], since calculations are performed at the entire test range of wavelengths, the results tend to be more reliable than those rendered by the traditional spectrophotometric methods, where one or several wavelengths are used for the analysis. Moreover, WApH method can be used for calculating pK_a^T of the compounds with insignificant changes of absorption spectra with the changing of pH [26]. Besides, this method allows to determine microconstants through several titrations at different ratios of water solution and organic solution, and they don't require the assumptions that have to be introduces in the one-wavelength measurements [24].

The authors of [27] suggests that the multiwave spectrophotometric method of absorption spectroscopy with the submerged probe (D-PAS) and other related methods have certain limitations. Thus, the spectral shift that depends on pH can become invisible if the distance between the chromophore and the ionization center exceeds three sigma bonds. Moreover, the maximum absorption of the test compound can be located at the wavelength of <230 nm, and thus the optical data can be affected by the background noise.

Other case studies where the method of derivative spectrophotometry is used successfully for determining the thermodynamic dissociation constants for a number of compounds are also of interest [28, 29]. Same as in the potentiometric titration, where the first or the second-order derivative from the titration curve helps to precisely locate the endpoint, the derivative graphs in spectrophotometric titration are often more informative than the initial absorption spectra [29]. Thus, the graph of the first-order derivative ($dA/d\lambda$ of λ) differs from the initial curve and can be used for precise fixation of the maximum absorption wavelength [30, 25] (Fig. 3).
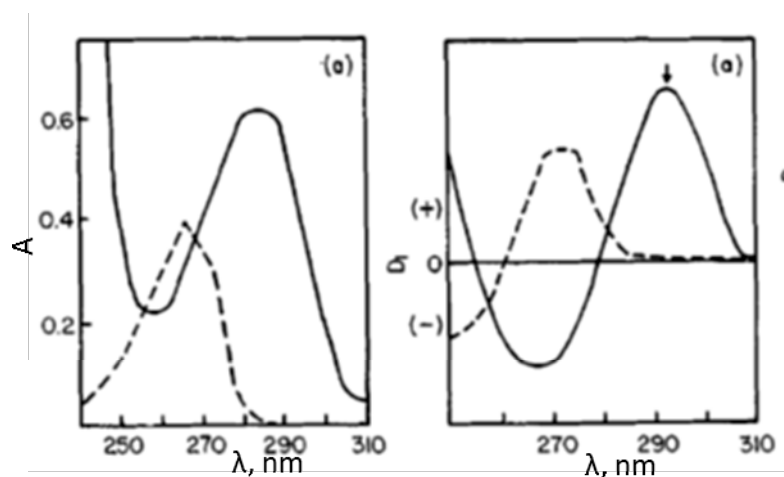
Fig. 3. Absorption Spectrum and First-Order Derivative Graph for 2.5 mg% Phenol in 0.1 H Solution of Sodium Hydroxide (-) and in 0.1 H Solution of Hydrochloric Acid (---) [Journal of Clinical Pharmacy and Therapeutics 17: 233-239 (1992)]

The peak of the curve on the graph is the sought for value of the wavelength. Even though the derivative spectrophotometry method is by no means new, it seems to have a potential because of the breakthroughs in computer science, since it is now possible to make the necessary calculations almost instantaneously [31–33]. As a rule, first-order derivative spectrophotometry is used for the compounds that have one or two pK_a^T values only, with the two being far apart; this is a major limitation of the method. Unlike the multiwave spectrophotometry, this method presents certain difficulties in determining the dissociation constant values for the compounds that have similar absorption spectra of the extreme prototropic forms [25].

Concentration spectrophotometry method: choosing the wavelenght

The method of concentration spectrophotometry that we introduced over 10 years ago seems to be a feasible alternative to the existing methods of choosing the wavelength. In the beginning of our series of works on determining the thermodynamic dissociation constants, we followed in the footsteps of most researchers and opted for the traditional choice of the analytical wavelength, i. e.

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our measurements and calculations were conducted at the wavelength that corresponds to the maximum of the absorption spectrum of the test compound. Still, our approach to measuring and determining the thermodynamic dissociation constants was different from the methods suggested elsewhere. While most of the existing spectrophotometric methods or determining pK_a^T are based on the dependence of absorbance on the acidity of the pH medium [34, 35], the proposed method uses the dependence of the absorbance on the concentration of the test compound for the primary experimental data [36]. The method of concentration UV/vis spectrophotometry can also be used for determining the reliable values of thermodynamic dissociation constants of the solutions with similar absorption spectra of the prototropic forms, thus meeting a major challenge in spectrophotometric pH-titration. This approach has been tested on the solutions of various structures and strengths, such as weak one-base acids: benzoic, phenoxyacetic, acetic, propionic, picric, phenol [37, 38]; monoacid bases: aniline, triethylamine [38]; weak mono- and polyelectrolytes [39]; heterocyclic thiols: (5-(4-nitrophenyl)-1H-tetrazole, 5-phenyl-1H-tetrazole, 5-(methylthio)-1H-tetrazole, 5-(4-chlorobenzyl)-1H-tetrazole, 5-(phenoxymethyl)-1H-tetrazole) [36]; 8-amino-4-hydroxyphtalazine-1(2H)-one and 2,4-diaminoisoindoline-1,3-dione [40]; as well as on the compounds that were measured in isopropyl alcohol: picric acid, benzoic acid, 3,5-dinitrobenzoic acid, 4-nitrobenzoic acid, phenol, 4-nitrophenol, 3-nitrophenol [41]. Besides, algorithms for calculating the thermodynamic dissociation constants of acids, bases and ampholytes in water solutions and organic solutions have also been developed [38, 41, 42].

To improve the method even further, we have developed a new approach to determining the wavelength. We believe that the analytical wavelength should be established at the maximum difference of the molar absorption coefficients of the test compound at two different concentrations: the initial (C_{max}) and the final (C_{min}), i. e. $\Delta\varepsilon = (\varepsilon_{max} - \varepsilon_{min})$ and $\lambda_{опт} \equiv \Delta\varepsilon_{max}$, as shown below, using 4-nitrophenol as the sample (Fig. 4).

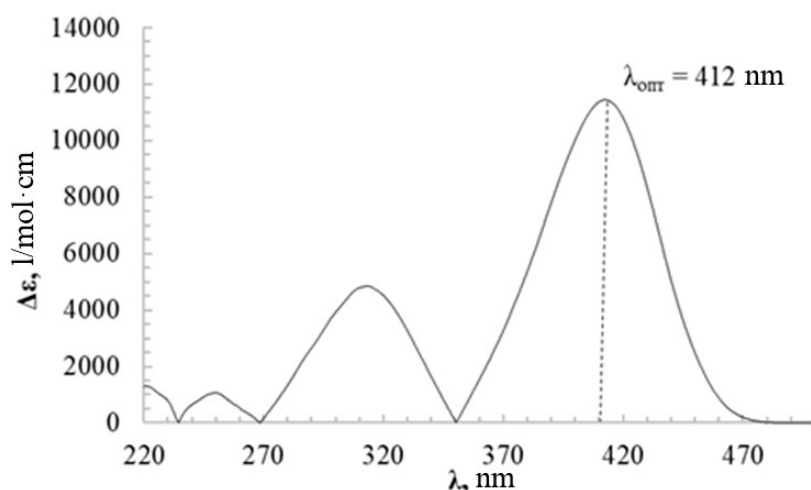**Fig. 4.** Choosing the optimal wavelength λ_{opt} through the difference between the molar absorption coefficients for 4-nitrophenol at the concentrations of C_{max} = $2.0 \cdot 10^{-3}$ mol/l and $C_{min} = 3.3 \cdot 10^{-4}$ mol/l, with added NaOH ($C_b = 2.0 \cdot 10^{-4}$ mol/l) in isopropyl alcohol [Russian Journal of Physical Chemistry A 95: 826–1830 (2021)].

The absorbance at these concentrations is ca. 2.0 and 0.2 units. If the graph of $\Delta\varepsilon$ on λ dependence features several tantamount wavelengths, the one that is located in the longwave range should preferably be used.

Apart from 4-nitrophenol, the method of choosing the optimal wavelength has been tested on the following compounds: picric acid, benzoic acid, 3,5-dinitrobenzoic acid; 4-nitrobenzoic acid; phenol, 3-nitrophenol [41]. All the measurements were conducted using the method of concentration UV/vis spectrophotometry in isopropyl alcohol. For all the compounds, the calculated thermodynamic dissociation constant values are well in agreement with the published data (Table 4).

Table 4. Thermodynamic acid dissociation constants pK_a^T in isopropyl alcohol obtained by the concentration UV/vis spectrophotometry method, versus published data [Russian Journal of Physical Chemistry A 95: 826–1830 (2021)].

Acid	pK_a (pub.)	pK_a^T	λ, nm	C_i, mol/l
Picric acid	3.74 [43] 4.02 [44] 4.08 [45]	3.30±0.01	362	$1.5 \cdot 10^{-3} \div 4.3 \cdot 10^{-4}$
Benzenoid acid	10.2 [46] 11.75 [47]	10.53±0.05	280	$3.2 \cdot 10^{-3} \div 2.3 \cdot 10^{-4}$
3,5-dinitrobenzenoid acid	8.31 [43]	9.03±0.05	250	$1.2 \cdot 10^{-3} \div 2.1 \cdot 10^{-4}$
4-nitrobenzenoid acid	9.6 [43]	10.62±0.04	285	$1.6 \cdot 10^{-3} \div 1.2 \cdot 10^{-4}$
Phenol	15.41 calc[48]	15.83±0.07	241	$5.5 \cdot 10^{-3} \div 1.6 \cdot 10^{-4}$
4-nitrophenol	11.19 [43] 12.45 [44]	12.13±0.01	412	$2.0 \cdot 10^{-3} \div 3.3 \cdot 10^{-4}$
3-nitrophenol	12.65 [10] 13.92 [14]	11.81±0.08	298	$1.4 \cdot 10^{-3} \div 2.3 \cdot 10^{-4}$

The suggested method is user-friendly, universal (since it works for the compounds with low spectral resolution), and the measurements can be conducted without using concentrated solutions of acids or bases to obtain dissociated and non-dissociated forms of the compounds; besides, no complicated calculations have to be involved.

Conclusion

The analysis of the published sources shows that for almost a century the principles of choosing the analytical wavelength have remained the same, while the equipment, as well as the methods of calculating dissociation constants, kept

improving, the reason being that the experimental basics of spectrophotometric titration have hardly changed at all. The faulty choice of wavelength and buffer solutions, inaccuracies in determining pH, challenges of sustaining the same ionic force and introducing the respective corrections add up and contribute to the inaccuracy of determining thermodynamic dissociation constants. That is why, apart from developing new approaches to processing experimental data, it's imperative to improve the method as such. Concentration spectrophotometry seems to show promise, for, apart from providing reliable wavelength data, this method has a number of other advantages that make it widely usable in various media, including the organic ones.

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