Direct solubility determination in optically dense solutions of highly soluble chromophores by the optoacoustic technique: Acidity dependence for Phenol Red

M.A. Shishkin [a], D.S. Volkov [a], I.M. Pelivanov [a, b], M.A. Proskurnin [a, *]
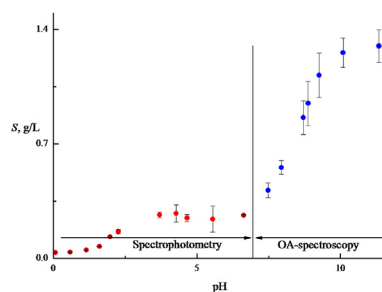
[a] M.V. Lomonosov Moscow State University, Chemistry Department, Leninskie Hills 1/3, 119991, GSP-1, Moscow, Russia
[b] University of Washington, Department of Bioengineering, Seattle, WA, 98195, USA

HIGHLIGHTS

- Optoacoustic spectroscopy is applied for direct solubility determination in highly light-absorbing saturated solutions.
- No dilution or sample preparation is required.
- The dependence of solubility of Phenol Red on solution acidity in the wide pH range is obtained.
- Optoacoustic and conventional spectrophotometric measurements provide complementary data.

GRAPHICAL ABSTRACT

ARTICLE INFO

ABSTRACT

The optoacoustic (OA) technique capable for light-absorption measurements in highly concentrated solutions is applied for direct solubility assessment in highly absorbing saturated solutions without any dilution or sample preparation. Maximum solubility of Phenol Red in aqueous solutions at pH > 11 is found to be 1.3 ± 0.1 g/L. The experimental dependence of solubility of Phenol Red on solution acidity was obtained with optoacoustic and conventional spectrophotometric measurements. The data from both methods show complementary results. The model of the solubility of Phenol Red on solution acidity describing the experimental dependence is proposed, which cannot be attained at pHs above 7 without the OA-technique.

1. Introduction

Solubility is a parameter that is relevant in a wide range of research and technology applications [1]. Nowadays, many papers dealing with the solubility of organic compounds are aimed towards advancing pharmaceutical chemistry and are demanded in novel drug development [2–6]. Rather often, in such studies the dependence of the target organic compound solubility on pH is to be investigated because it influences on the chemical composition of drugs and their pharmaceutical properties [7–13].

The determination of solubility usually requires the

* Corresponding author.
E-mail addresses: wild9chemist@gmail.com (M.A. Shishkin), dmsvolkov@gmail.com (D.S. Volkov), ivanp3@u.washington.edu (I.M. Pelivanov), proskurnin@gmail.com (M.A. Proskurnin).

measurement of a high concentration in a saturated solution of the test substance. Common analytical methods sometimes cannot give satisfactory results due to their limitations in highly concentrated solutions [14–16]. Thus, they can be used provided the solubility of the target substance is rather low or sample dilution is possible. In these cases, HPLC with UV/Vis detection is often used [2–4,6,17–20]. Cyclic voltammetry [21,22] and potentiometric titration [23] are also common choices. If the solubility is high or dissolution cannot be used, the saturation shake-flask method is most widespread [7,12,22,24,25]. Despite the advantages of this approach (relative simplicity, developed methodology, etc.), the shake-flask method usually results in a lower accuracy for high solubilities and is relatively time-consuming.

The above-mentioned methods for solubility assessment are based on laws of chemical thermodynamics and the signal is determined by the chemical potential of the analyte directly related to the concentration. However, when dealing with highly soluble compounds, most suitable methods for solubility—titrimetry, gravimetry, electrochemical methods, or chromatography—require the separation of the precipitate from solution and often a dilution before the analysis. Therefore, the conditions of the target equilibrium are not reached or they change at the measurement stage, which affects the accuracy.

The approaches based on probing or monitoring unchanged precipitation equilibria with spectroscopy are more advantageous as the precision in such a case is determined by physical principles and limited by the error of signal measurement mainly. However, these methods cannot be simply applied to highly concentrated solutions of strong chromophores (dyes, chelates etc.), because high absorbances would lead to very high errors. Moreover, in optically dense media, the intensity of the transmitted light is very low, which does not allow for absorbance measurements.

The optoacoustic (OA) technique is a method of molecular absorption spectroscopy that is alternative to light-transmission methods and especially developed for high absorbances (10–200 or higher) [26]. The main advantage of this technique is the direct measurement of light absorption with a pressure signal (the OA-pulse) generated in the sample with an intensity-modulated optical field. Thus, the information on the light absorption of the medium is delivered by acoustic signals. An optically dense and even light-scattering media are frequently acoustically transparent, i.e. have a weak acoustic attenuation that makes it possible to use the OA-technique in the diagnostics of materials [27–31] and in medical applications [32–44]. These features are very advantageous for solubility measurements.

In this paper, we demonstrate that the OA-technique is reliable for solubility determination using a model system of pH-dependent indicator dye, Phenol Red. This dye is a weak diprotic acid with two acidity constants:

$$K_{a1} = \frac{a_{H^+} a_{HP^-}}{a_{H_2P}}, \tag{1}$$

$$K_{a2} = \frac{a_{H^+} a_{P^{2-}}}{a_{HP^-}}, \tag{2}$$

$pK_{a1} = 1.2$ [45] and $pK_{a2} = 7.66$ [46]. It has been selected as its protonated forms have high molar absorptivities.

2. Materials and methods

2.1. Reagents

Doubly distilled deionized water (specific resistance no less than 18.0 MΩ cm, Milli-Q Integral, Millipore, France) was used

throughout. The following reagents were used throughout: Phenol Red, CAS 143-74-8, puriss. (MPBiomedicals, USA), glacial acetic acid, CAS 64-19-7, p.a. (density, 1.049 g ml^{-1}; 98.5% wt.; Reakhim, Russia), orthophosphoric acid, CAS 7664-38-2, conc. p.a. (density, 1.633 g ml^{-1}; 80% wt.; Reakhim, Russia), boric acid, CAS 10043-35-3, p.a. (Reakhim, Russia), Hydrochloric acid, CAS 7647-01-0, puriss. (density, 1.18 g ml^{-1}; 38% wt, ROSHIMREAKTIV, Russia), sodium hydroxide, CAS 1310-73-2 p.a. (Reakhim, Russia). Buffer solutions in the range of pH 3–12 were prepared by mixing solutions of acetic, orthophosphoric, and boric acids, concentrations 0.04 M each, and a 0.2 M sodium hydroxide solution in appropriate proportions.

2.2. Optoacoustic setup

The scheme of the OA-setup is given in Fig. 1. The details are presented in Ref. [26]. The optoacoustic setup implements a Nd:YAG laser (LOTIS TII, LS–2137-3, Belarus) with a wavelength of 532 nm (energy, 330 mJ; duration, 22 ns at the $1/e^2$ level; pulse repetition rate, 10 Hz). Laser radiation is transmitted through an adjustable attenuator with a polarization filter (transmission range, 1–99%), a blue filter, and the system of adjustable neutral-density filters (10CWA168, Standa, Lithuania). Next, the laser beam propagates through a blue filter and is turned onto the surface of the OA-cell by a prism. A home-made PVDF film (Precision Acoustics, UK) detector is connected to the channel one of a digital oscilloscope (Tektronix TDS 1012, USA). The laser pulse and the beginning of the acquisition are synchronized by a photodetector (PDA10A-EC, ThorLabs, USA).

The optoacoustic cell (Fig. 1, inset) is made of a quartz ring and a round quartz plate on its upper surface. The cell is placed directly onto the surface of the piezoelectric detector and filled with a test solution. The quartz ring is laid directly onto the surface of the detector and filled with a test solution. Next, a quartz plate is laid onto the edge of the ring and is slid to cover the ring, the excess of the solution is wiped away. After the measurement, the OA-cell is disassembled and cleaned.

Signal processing and absorbance calculations are described previously [26]. The leading edge of the OA-signal resembles the spatial distribution of laser energy in the medium under study and it makes it possible to measure the absorption-coefficient changes very precisely [26]. Thus, the acquisition equation is $\log U = a + bt$, where a is a constant. The slope $b = \mu_a c_0$, where c_0 is the speed of sound and μ_a is the light absorption coefficient, is then used to assess the coefficient μ_a. The experimental dependence $\log U = f(t)$ is approximated to figure out a and b parameters. Then, the coefficient μ_a (in cm s^{-1}) was calculated as

$$\mu_a = \frac{b}{c_0}. \tag{3}$$

2.3. Spectrophotometry

UV/Vis spectra were recorded on an Agilent Cary 60 spectrophotometer using quartz cells with an optical path length of 0.1 cm. All spectra were recorded from 300 to 700 nm with a step of 1 nm.

2.4. Auxiliary measurements

An Ohaus Discovery analytical balance (precision ±0.1 mg, the USA) was used. To intensify the dissolution of test compounds, a GRAD 38-35 ultrasonic bath (power 350 W, Grad Technology, Russia) was used. To separate the precipitate from the solution, an Armed CH90-2S centrifuge (Russia) was used (4000 rpm, 5 min).