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Computer programs for calculating pK_a: a comparative study for 3-(3-(2-nitrophenyl)prop-2-enoyl)-2*H*-1-benzopyran-2-one

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Abstract: Coumarin-based compounds containing a chalcone moiety exhibit antimicrobial activity. These substances are potential drugs and it is important to determine their pK_a values. However, they are almost insoluble in water. The dissociation constant was experimentally determined by potentiometric titration for 3-[3-(2-nitrophenyl)prop-2-enoyl]-2*H*-1-benzopyran-2-one because this compound shows good activity and solubility. A number of different computer programs for the calculation of the dissociation constant of chemical compounds have been developed. The pK_a value of the target compound was calculated using three different computer programs, *i.e.*, the ACD/pK_a, CSpKaPredictor and ADME/ToxWEB programs, which are based on different theoretical approaches. The analysis demonstrated good agreement between the experimentally observed pK_a value of 3-[3-(2-nitrophenyl)prop-2-enoyl]-2*H*-1-benzopyran-2-one and the value calculated using the computer program CSpKa.

Keywords: coumarin-based compounds; dissociation constant; computer programs; potentiometric titration.

INTRODUCTION

The presence of a reactive *α,β*-unsaturated keto function in chalcones was found to be responsible for their antimicrobial activity. The properties of this keto function may be altered depending on the type and position of substituents on the aromatic rings.[1]

From 3-acetyl-4-hydroxy-2*H*-1-benzopyran-2-one using an appropriate aromatic aldehyde with pyridine and piperidine as catalysts, two of chalcones were synthesized. The course of the reaction is presented in a previous work.[2]

Bearing in mind the potential of these compounds to be employed as drugs, it is important to investigate their dissociation constant (pK_a). Knowledge of the acid dissociation constant of a molecule is a critical step toward understanding its structure and reactivity.[3]

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The acid–base ionization/dissociation constant, pK_a, is a measure of the tendency of a molecule or ion to keep a proton (H^+) at its ionization center(s) and is related to the ionization ability of chemical species. The pK_a value is the core property of an electrolyte that defines chemical and biological behavior. In biological terms, the pK_a is important in determining whether a molecule will be taken up by aqueous tissue components or lipid membranes and is related to log *P* (the partition coefficient).

The widespread application of pK_a in chemistry and drug design explains the need for quick procedures to quantify the acid dissociation constant. As experimental measurements are time consuming and difficult, computational methods are very valuable tools for calculation of pK_a for large sets of compounds, particularly at the screening stage. A number of different computer programs for prediction have recently been developed.[4]

In this study, three computer programs, based on different theoretical approaches for predicting pK_a values, were compared with experimental data.

The aim of this work was to correlate the experimentally determined and calculated pK_a values for 3-[3-(2-nitrophenyl)prop-2-enoyl]-2*H*-1-benzopyran-2-one using three different computer programs.

EXPERIMENTAL

*Potentiometric determination of p*K$_a$

The pK_a value for 3-[3-(2-nitrophenyl)prop-2-enoyl]-2*H*-1-benzopyran-2-one was evaluated by potentiometric titration with a 0.005 M solution NaOH. From the stock solution (0.090 g 3-[3-(2-nitrophenyl)prop-2-enoyl]-2*H*-1-benzopyran-2-one in 8.25 g DMSO), solutions with different H_2O contents were made:

– 6.45 % H_2O (1.0 mL stock solution of 3-[3-(2-nitrophenyl)prop-2-enoyl]-2*H*-1-benzopyran-2-one, 12.6 g DMSO and 0.94 g H_2O);

– 7.83 % H_2O (1.0 mL stock solution of 3-[3-(2-nitrophenyl)prop-2-enoyl]-2*H*-1-benzopyran-2-one, 12.4 g DMSO and 1.14 g H_2O);

– 31.2 % H_2O (1.0 mL stock solution of 3-[3-(2-nitrophenyl)prop-2-enoyl]-2*H*-1-benzopyran-2-one, 9.0 g DMSO and 4.53 g H_2O);

– 40.0 % H_2O (1.0 mL primary solution of 3-[3-(2-nitrophenyl)prop-2-enoyl]-2*H*-1-benzopyran-2-one, 7.72 g DMSO and 5. 81 g H_2O).

The substance was dissolved in the organic solvent (DMSO) and diluted with water to avoid precipitation. This is followed by four titrations of the system water/DMSO, with different DMSO contents.

The solution was then titrated with 0.25 mL aliquots of a 0.005 M NaOH solution, under constant stirring using a magnetic mixer; the pH was measured after each added aliquot. The procedure was repeated until the pH value of the titrated solution reached and kept a constant value with further addition of aliquots. The dissociation constant of the tested coumarin derivative, with a given content of the solvent DMSO/H_2O was read from the potentiometric curve, using the semi-neutralization point where pH = pK_a.Through extrapolation of the results for pK_a at different DMSO contents, the pK_a value of the tested substance in pure aqueous medium was obtained.[5,6]

The program CurveExpert 1.3. was used for statistical analysis of the data and regression analysis.

Calculation methods

A number of different computer programs for the calculation dissociation constants of chemical compounds have been developed. The quality of these programs was evaluated by how well the computed pK_a values agreed with the experimentally determined pK_a value for the investigated compound. In this work, the SMILES (Simplified Molecular Input Line Entry System) notation created by the structure drawing program CambridgeSoft's ChemDrawPro was used as the chemical structure input.

ACD/pKa is a program which quickly and accurately predicts the acid–base ionization constant of a wide range of organic compounds. It uses Hammett equations derived from a library of highly curated compounds to predict an aqueous pK_a value. In addition, two reference databases are available that offer quick look-ups of published data: one contains > 31000 experimental pK_a values for approximately 16000 compounds in aqueous solutions; the other provides experimental data for more than 2000 molecules in non-aqueous solvents. This software is used by the majority of pharmaceutical and API companies worldwide and has been tested on a wide variety of chemical classes.[7-9]

The CSpKaPredictor program selects descriptors and searches for the optimal relation between pK_a values obtained through experiment and pK_a values obtained using the SpKa predictor. The program uses 519 topological and "E-state" descriptors that determine the electron availability for non-covalent, inert-molecular interactions in each atom.[10] 158 of the 519 descriptors are new molecular descriptors developed at ChemSilico. In order to validate the prediction results, cross-validations between the experimentally obtained pK_a values and the values predicted using the CSpKa predictor were performed.

ADME/ToxWEB consults powerful ADME and Tox prediction on-line systems from the Pharma Algorithms Company. ADME/ToxWEB is a scalable version of ADME Boxes and Tox Boxes designed to fit into departmental and corporate collaborative networks. ADME/ /ToxWEB has the flexible modular architecture of ADME and Tox Boxes while also offering powerful interface customization possibilities and direct programmatic access to its modules. With this prediction system, users can predict all the following: toxicity, acute toxicity (mouse and rat); genotoxicity, health effects (blood, liver, lungs); ADME, overall oral bioavailability, pK_a values, log *D* values, substrate and inhibitor specificity, solubility in pure water and in buffer, active transport properties, absorption, physicochemical properties, *etc*.

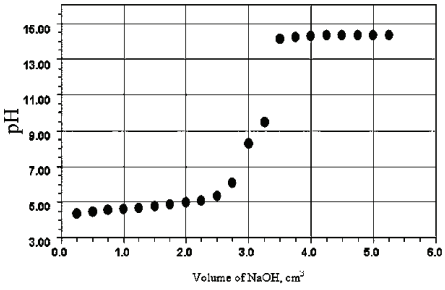
RESULTS AND DISCUSSION

Given that the derivates are almost insoluble in water, the dissociation constant was determined by the conventional method adjusted to the tested compound. The values of pK_a for 3-[3-(2-nitrophenyl)prop-2-enoyl]-2*H*-1-benzopyran-2-one in the system DMSO:H_2O were established through potentiometric titration by determining the pH values at the point of semi-neutralization, where pH = pK_a. The potentiometric titrations of 3-[3-(2-nitrophenyl)prop-2-enoyl]-2*H*--1-benzopyran-2-one with NaOH in the system DMSO:H_2O were performed in triplicate. The changes of the pH during the titration of 3-[3-(2-nitrophenyl)prop--2-enoyl]-2*H*-1-benzopyran-2-one in the DMSO:H_2O system having different contents of water are shown in Table I.

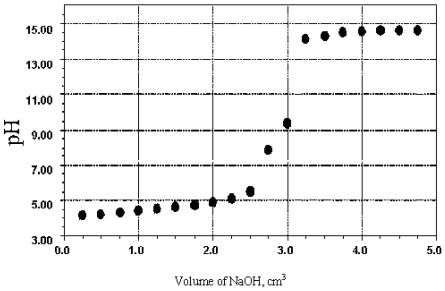
The titration curves for 3-[3-(2-nitrophenyl)prop-2-enoyl]-2*H*-1-benzopyran--2-one with NaOH in systems having different ratios of DMSO:H_2O are shown in Figs. 1a–1d.

TABLE I. Changes of pH during the titration of 3-[3-(2-nitrophenyl)prop-2-enoyl]-2*H*-1-benzopyran-2-one in DMSO:H_2O systems having different contents of water

V(NaOH) / mL	6.45 % H_2O	7.83 % H_2O	31.1 % H_2O	40.0 % H_2O
0	4.22	4.18	4.36	4.47
0.25	4.39	4.19	4.39	4.54
0.50	4.49	4.23	4.51	4.62
0.75	4.57	4.35	4.56	4.79
1.00	4.65	4.44	4.66	4.84
1.25	4.70	4.56	4.85	5.01
1.50	4.80	4.66	5.04	5.23
1.75	4.89	4.76	5.26	5.41
2.00	4.99	4.92	5.93	6.32
2.25	5.14	5.10	6.93	7.48
2.50	5.40	5.55	7.59	7.94
2.75	6.10	7.88	8.17	8.64
3.00	8.28	9.41	9.59	9.99
3.25	9.50	14.13	11.35	12.02
3.50	14.14	14.31	12.20	12.14
3.75	14.23	14.49	12.51	12.48
4.00	14.28	14.58	12.63	12.53
4.25	14.35	14.61	12.70	12.54
4.50	14.36	14.63	12.72	12.55
4.75	14.38	14.63	12.74	15.55
5.00	14.38	14.63	12.75	12.55
5.25	14.38	14.63	12.75	12.55

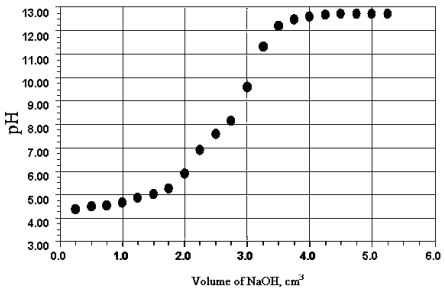


(a)

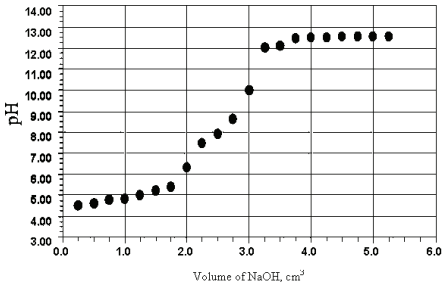


(b)

Fig. 1. Titration curves of 3-[3-(2-nitrophenyl)-prop-2-enoyl]-2*H*-1-benzopyran-2-one with NaOH in systems having a different ratio of solvents. a) H_2O:DMSO = 6.4:93.6 and b) H_2O:DMSO = = 7.8:92.2.



(c)



(d)

Fig. 1 continued. Titration curves of 3-[3-(2-nitrophenyl)prop-2-enoyl]-2*H*-1-benzopyran-2-one with NaOH in systems having a different ratio of solvents. c) H_2O:DMSO = 31.1:68.9 and d) H_2O:DMSO = 40.0:60.0.

Through extrapolation of the results for pK_a at different DMSO contents (60.0–93.6 %), Fig. 2, the theoretic pK_a value of the tested substance in pure aqueous water medium (DMSO, 0 %), p$K_a \approx 6.0$, was obtained.

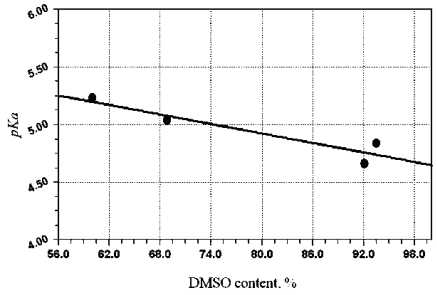


Fig. 2. Plot of the pK_a value obtained at different DMSO contents (60.0–93.6 %) *vs.* the content of DMSO. By extrapolation to zero content of DMSO, the pK_a value of the tested substance in pure aqueous medium, p$K_a \approx 6.0$, is obtained.

All the computer programs showed themselves to be relatively simple. The best correlation between the experimentally determined and the calculated pK_a values was found for the CSpKa program, ΔpK_a (log pK_a(exp) – log pK_a(cal)) = 0.56.

CONCLUSIONS

Three calculation methods, based on different theoretical approaches, were studied and the calculated pK_a values for 3-[3-(2-nitrophenyl)prop-2-enoyl]-2*H*--1-benzopyran-2-one were correlated with the experimentally determined pK_a values. The analysis showed that the agreement between the experimentally ob-

served pK_a value and the value calculated by the CSpKa program was the best. To obtain a reliable picture on the applicability of the calculation methods in pK_a studies of this kind of coumarin compounds, a larger number of substances with varying pK_a values should be studied.

И З В О Д

КОМПЈУТЕРСКИ ПРОГРАМИ ЗА РАЧУНАЊЕ pK_a: КОМПАРАТИВНА СТУДИЈА 3-[3-(2-НИТРОФЕНИЛ)ПРОП-2-ЕНОИЛ]-2*H*-1-БЕНЗОПИРАН-2-ОНА

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Једињења кумаринског типа, са халконском групом у својој структури, показала су антимикробну активност. Ове супстанце су потенцијални лекови, па им је важно одредити pK_a вредности. Вредност pK_a за 3-[3-(2-нитрофенил)проп-2-еноил]-2*H*-1-бензопиран-2-он експериментално је одређена потенциометријском титрацијом и израчуната уз употребу три различита компјутерска програма. Ова супстанца је скоро нерастворна у води, па је њена константа дисоцијације одређена уз употребу конвенционалне методе. Развијен је већи број различитих компјутерских програма за рачунање константе дисоцијације хемијских једињења. У нашем раду коришћена су три компјутерска програма базирана на различитим теоријским приступима: ACD/pK_a програм, CSpKaPredictor и ADME/ToxWEB програм. У нашем испитивању утврђено је најбоље слагање између експериментално добијене pK_a вредности за 3-[3-(2-нитрофенил)проп-2-еноил]-2*H*-1-бензопиран-2-он и вредности добијене компјутерским програмом CSpKaPredictor.

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