

Determination and structural correlation of the pK_a values of *p*-substituted *trans*-2,3-epoxy-4-oxo-4-phenylbutanoic acids

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The pK_a values for a series of eight *p*-substituted *trans*-2,3-epoxy-4-phenylbutanoic acids (*p*-substituted *trans*- β -aroylepoxyacrylic acids) have been determined potentiometrically in aqueous media at 25 °C at an ionic strength of 0.1 mol/dm³ (NaCl). The transmission of polar effects from the substituents on the phenyl nucleus to the carboxylic group through the side chain involving a carbonyl group and an epoxide ring was investigated. The pK_a values were correlated with structure using the Hammett, Taft and Yukawa-Tsuno approaches. The Hammett ρ constant (0.34) was compared with analogue values for structurally similar acids.

Keywords: α,β -epoxy acids, pK_a -values, LFER, transmission coefficients, synthesis of *trans*- β -aroylepoxyacrylic acids.

INTRODUCTION

The applications of pK_a values are extremely diverse, ranging from the most fundamental ones, *e.g.*, calculating the distribution functions in a given pH-interval, to exploring the transportation of substances through cell membrane. Therefore, the knowledge of the pK_a value of a substance is essential for various investigations in pharmacology, physiology, in structural, environmental, preparative and analytical studies and for industrial purposes, *etc.*¹ In the field of physical organic chemistry, the polar effects of substituents on the ionisation of acids² have been frequently studied because they provide the possibility of establishing a tentative relationship between structure and reactivity, by using the widespread linear free energy relationships (LFER's)³ and quantitative structure activity relationships (QSAR's).⁴

trans-Aroylepoxyacrylic acid derivatives are interesting substrates for the evaluation of structure reactivity relationships due to the presence of a system consisting of a

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benzene ring, followed by a carbonyl group, attached to an epoxy ring, inserted between the substituent and the reaction site. Further interest in investigating these acids arises from the fact that they are newly synthesized substances,⁵ with no data concerning their acidic behaviour, in any kind of solvent, reported so far. The aim of this work was to determine the acidity of a series of *p*-substituted *trans*- β -aroylepoxyacrylic acids in aqueous medium, to establish the correlation between the measured pK_a values using the Hammett,⁶ Taft⁷ and Yukawa-Tsuno⁸ equations and to explain the transmission of the effects of the polar substituent along the benzene ring and given side chain.

EXPERIMENTAL

Apparatus and reagents

UV spectrophotometric measurements were carried out on a GBC 911A spectrophotometer (GBC Scientific Equipment Pty. Ltd, Dandenog, Australia) equipped with a 1 cm quartz cell. A PHM-240 pH-meter (Radiometer) with a GK 2401C combined electrode (Radiometer) was used for the pH measurements. All potentiometric titrations were performed using a TTT 60 titrator with automatic burette ABU 12, Radiometer. The burette size was 2.5 cm³; least significant volume 0.001 cm³; and accuracy: $\pm 7 \times 10^{-4}$ cm³ ± 0.3 %. The solutions were stirred with a mechanical stirrer M22 (Radiometer). A thermostat 'Ultra-Thermostat nach Höppler' type NBE (VEB Prüfgeräte-Werk Mendigen) was used. For the conversion of pH values to p_{cH} values ($p_{cH} = -\log [H_3O^+]$) the relationship: $p_{cH} = pH - A$ was used. The correction factor $A = 0.1$ was obtained by pH-metric titration of a standard HCl solution with a standard NaOH solution at 25 °C and constant ionic strength 0.1 mol/dm³ (NaCl).⁹

The *p*-substituted *trans*- β -aroylepoxyacrylic acids were prepared from the corresponding *trans*- β -aroyleacrylic acids which were synthesized according to a previously published procedure.¹⁰ The synthesis of the *p*-substituted *trans*- β -aroylepoxyacrylic acids in this work was mostly based on the epoxydation procedure given in a previous paper.⁵ Our modifications resulted in a considerable improvement of the reaction yield.

Typical experimental procedure. In a 100 cm³ flask equipped with magnetic stirrer, pH-meter and water-ice-bath, 15 mmol of finely powdered *trans*- β -aroyleacrylic acid was suspended in 50 cm³ of water. The acid was dissolved by the addition of a 5 mol/dm³ solution of sodium hydroxide at such a rate to keep temperature between 15–20 °C and the pH below 9.0. The pH value was adjusted to 8.5 with 5 % sulfuric acid, and 3.1 cm³ of 30 % of hydrogen peroxide (30 mmol) was added. The course of the reaction was monitored by TLC, and the pH was maintained at 8.5 ± 0.5 by titration with 5 % sodium hydroxide. After 2–3 hours the reaction mixture was acidified with 5 % sulfuric acid to pH 1.3 and crystallized in a refrigerator over night. The solid *trans*- β -aroylepoxyacrylic acid was filtered off, washed exhaustively with distilled water and dried in a vacuum desiccator. Average yields 80–90 %.

The same procedure was used for the synthesis of *trans*-epoxycrotonic acid.

Other reagents (C₂H₅OH, HCl, NaOH and CH₃COONa) were analytical reagent grade (Merck). Redistilled water was used. Standardisation of the HCl and NaOH solutions was done potentiometrically.

Method

Spectrophotometric characterisation. Stock solutions for spectrophotometric characterisation of the *p*-substituted *trans*- β -aroylepoxyacrylic acids, concentration 1×10^{-2} mol/dm³, were prepared in ethanol. In order to obtain the spectra of the molecular (HA) and anionic (A⁻) forms of the acids, for each acid two solutions of the same concentration (either 1×10^{-4} or 6×10^{-5} mol/dm³) were prepared one in 0.5 mol/dm³ HCl and the other in acetate buffer (pH 5.5). The spectra were recorded in the range 220–500 nm, at a scan rate 500 nm/min, against the corresponding blank. The ethanol content in the solutions was up to 1 % (vol). The ethanol practically had no effect on either the pH nor the spectra.

Determination of acidity constants. The acidity constants of the *p*-substituted *trans*- β -arylepoxyacrylic acids were determined potentiometrically in aqueous media at 25 °C and at an ionic strength of 0.1 mol/dm³ (NaCl). For each acid 20.3 cm³ of a solution having an acid concentration in the 1.1×10⁻³–1.6×10⁻³ mol/dm³ range, and 1.458×10⁻³ mol/dm³ of HCl, was titrated with standard NaOH solution (0.08909–0.1162 mol/dm³) in 0.050 cm³ aliquots. The acidity constant of *trans*-epoxycrotonic acid was determined in the same way: The solution of the acid (5×10⁻³ mol/dm³) was titrated with standard NaOH solution (0.1166 mol/dm³).

The titration was done in duplicate for each acid. The concentration of the studied acids in the titration solutions was selected according to the solubility of the acid.

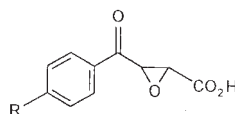
The formation function (\bar{n}_H), namely the mean number of bound protons, was calculated using the following equation:

$$\bar{n}_H = \frac{c_{HA}^{tot} + [H_3O^+] - [Na^+] - [H_3O^+] + [OH^-]}{c_{HA}^{tot}} \quad (1)$$

where c_{HA}^{tot} is the total concentration of the investigated acid; [Cl⁻] and [Na⁺] are the concentrations of the added HCl and NaOH, respectively; [H₃O⁺] is the concentration of free hydronium ions as determined by pH-measurement; [OH⁻] is the concentration of hydroxyl ions, originating from the dissociation of water, which can be neglected in this case.

RESULTS AND DISCUSSION

The general formula of the *p*-substituted *trans*- β -arylepoxyacrylic acids (*trans*-2,3-epoxy-4-oxo-4-phenylbutanoic acids) the p*K*_a values of which were determined is:



R = H, Me, Et, *i*Pr, *t*Bu, F, Cl and Br

Preliminary investigation included the determination of the spectral characteristics for all the studied acids. The dissociation caused negligible differences in the spectra of the conjugated acid-base pairs, making the spectrophotometric method not applicable for determination of acidity constant. However, a general trend for all the acids studied in this work was observed, *e.g.* at wavelength between 250–270 nm, deprotonation of the carboxylic group caused a hypsochromic shift in the absorption (Table I). In addition, this process was accompanied with an unusual hyperchromic effect (opposite to the behaviour of benzoic and *trans*-cinnamic acids, but same as the effect observed in *trans*- β -aroylacrylic acids¹¹). The conclusion that can be drawn from the noticed behaviour is that degree of protonation exhibits only a small influence on the distribution of the electron density in the chromophore.

For the determination of the p*K*_a^c (stoichiometric acidity constant) of these acids, a classical potentiometric method¹² based on the calculation of formation function was applied. For monoprotic acid (HA) the formation function is given by the equation:

$$\bar{n}_H = \frac{[HA]}{[HA] + [A^-]} \quad (2)$$

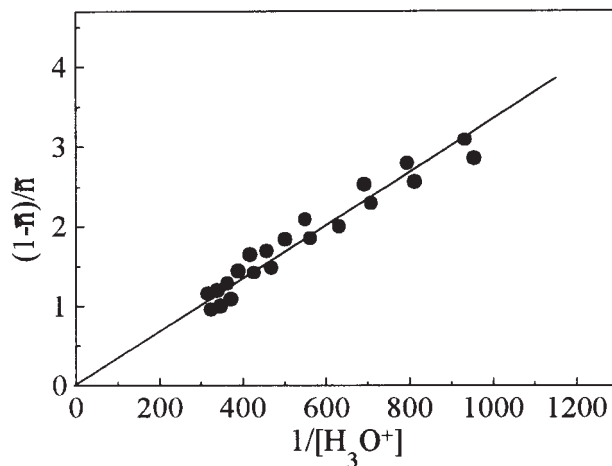


Fig. 1. Plots for the determination of the K_a^c value according to Eq. (3) for *p*-fluoro-*trans*- β -aroylepoxyacrylic acid.

The following relationship between acidity constant and formation function is given:

$$\bar{n}_H = \frac{1 - \bar{n}_H}{\bar{n}_H} = K_a^c \frac{1}{[H_3O^+]} \quad (3)$$

TABLE I. Spectral characteristics of the molecular (HA) and anionic (A^-) forms of the studied *p*-substituted *trans*- β -aroylepoxyacrylic acids

Substituent	$\lambda_{\max}(\text{HA})$ (nm)	$\epsilon_{\max}(\text{HA})/10^4$	$\lambda_{\max}(A^-)$ (nm)	$\epsilon_{\max}(A^-)/10^4$
H	256	1.25	253	1.30
Me	268	1.36	266	1.39
Et	269	1.52	266	1.54
<i>i</i> Pr	269	1.32	266	1.34
<i>t</i> Bu	268.5	1.47	267	1.52
F	258.5	1.18	258	1.21
Cl	268	1.60	266	1.62
Br	270	1.48	268	1.50

From Eq. (3) it is obvious, that the data should fit a linear function passing through the coordinate origin. The K_a^c values were calculated by regression analysis, and the results are shown in Table II. The low standard deviations (s) and high correlation coefficients (r) confirm the reliability of the experimentally obtained data for all the acids studied. A representative example of the linear dependence for *p*-fluoro *trans*- β -aroylepoxyacrylic acids is shown in Fig. 1.

The determined pK_a^c values were converted to thermodynamic values (pK_a) using the activity coefficient calculated from the Davies equation,¹³ and are shown in Table III. The pK_a values of all the studied acids obey the expected trend. All the studied acids are much stronger acids than the *p*-substituted *trans*- β -aroylacrylic acids (pK_a between 3.19 and 3.44 under the same conditions),¹¹ due to the strong, electron-withdrawing effect demonstrated by the epoxy ring. It was also possible to compare the obtained pK_a values with the pK_a of 3.15 for *trans*-epoxycrotonic acid (*trans*-2,3-epoxybutanoic acid). In this case, the observed difference is caused by the presence of the strongly electron-withdrawing benzoyl group.

TABLE II. Results of linear regression analysis using Eq. (3) for the determination of K_a^c of *p*-substituted *trans*- β -aroylpoxyacrylic acids.

Substituent	K_a^c	s	r	n
H	2.95×10^{-3}	1.29×10^{-4}	0.968	20
Me	2.57×10^{-3}	2.96×10^{-5}	0.989	18
Et	3.02×10^{-3}	2.50×10^{-4}	0.953	25
<i>i</i> Pr	2.88×10^{-3}	3.98×10^{-5}	0.968	14
<i>t</i> Bu	2.63×10^{-3}	4.24×10^{-5}	0.987	21
F	3.24×10^{-3}	1.19×10^{-4}	0.971	23
Cl	3.63×10^{-3}	1.26×10^{-4}	0.968	14
Br	3.98×10^{-3}	1.51×10^{-4}	0.975	20

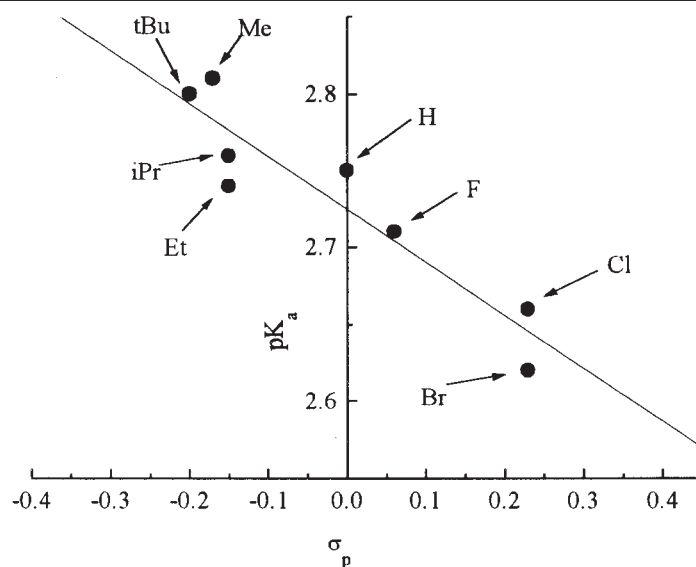


Fig. 2. Plot of the pK_a values of *p*-substituted *trans*- β -aroylpoxyacrylic acids against the corresponding Hammett σ_p constants.

In order to estimate the effect of substitution on the pK_a values of the acids studied, a correlation with Hammett σ_p constants¹⁴ was performed. A plot of pK_a values against the corresponding substituent σ_p constants (Table III) is shown in Fig. 2. The corresponding Hammett equation ($pK_a = pK_a^0 - \rho\sigma_p$)⁶ obtained in this case is:

$$pK_a = 2.72 - 0.34\sigma_p \quad (4)$$

with regression parameters $r = 0.933$, $s = 0.03$ and $n = 8$

As expected, when the correlation of the equilibrium constants of protolytic reactions is considered, the value of ρ is positive, meaning that the extent of acid dissociation is increased by electron-withdrawing substituents. For the *trans*- β -aroylepoxyacrylic acid series, ρ is 0.34, showing that this reaction series is much less sensitive to the influence of polar substituents than the dissociation of benzoic acid ($\rho = 1.00$)¹⁶ and *trans*- β -aroylepoxyacrylic acids ($\rho = 0.60$)¹¹ under the same conditions. This result is not surprising since the reaction site is effectively protected from the effect of substituents on the aromatic nucleus by insertion of a side chain, including a carbonyl group and an epoxy ring.

In order to check which one of the effects, *i.e.*, inductive or resonance, of the substituents dominates (values for σ_I and σ_R are given in Table III), the Taft equation ($pK_a = pK_a^0 - \rho_I\sigma_I - \rho_R\sigma_R$)⁷ was calculated:

$$pK_a = 2.72 - 0.34\sigma_I - 0.31\sigma_R \quad (5)$$

with the regression parameters $r = 0.922$ and $s = 0.03$. From the obtained results it is obvious that the application of Hammett and Taft equation gives practically the same correlation coefficients and standard deviations, meaning that both can be successfully applied for the analysis of the experimentally obtained data. Also, it can be seen that, if treated separately, the influence of resonance is somewhat smaller than the influence of induction.

TABLE III. pK_a values of *trans*- β -aroylepoxyacrylic acids and the substituent constants σ_p , σ_p^+ , σ_I and σ_R

Substituent	H	Me	Et	<i>i</i> Pr	<i>t</i> Bu	F	Cl	Br
pK_a	2.75±0.02	2.81±0.01	2.74±0.04	2.76±0.01	2.80±0.01	2.71±0.02	2.66±0.02	2.62±0.02
σ_p [Ref. 14]	0.00	-0.17	-0.15	-0.15	-0.20	0.06	0.23	0.23
σ_p^+ [Ref. 14]	0.00	-0.31	-0.30	-0.28	-0.26	-0.07	0.11	0.15
σ_I [Ref. 15]	0.00	-0.01	-0.01	0.01	-0.01	0.54	0.47	0.47
σ_R [Ref. 15]	0.00	-0.16	-0.16	-0.16	-0.18	-0.48	-0.25	-0.25

Although the structure of *trans*- β -aroylepoxyacrylic acids does not permit straightforward resonance between the substituent and the carboxyl group, the possibility of its existence was checked using the Yukawa-Tsuno equation $\{pK_a = pK_a^0 - \rho[\sigma_p + r^+(\sigma_p^+ - \sigma_p)]\}$ ⁸:

$$pK_a = 2.74 - 0.35(\sigma_p - 0.51(\sigma_p^+ - \sigma_p)) \quad (6)$$

The values for the substituent constant σ_p^+ are given in Table III. In this way, the correlation is improved. The regression parameters are $r = 0.942$ and $s = 0.02$. The value of the additional reaction parameter r^+ (-0.51) in the Yukawa-Tsuno equation indicates that substituents in the aromatic ring induce variations in the molecular structure to an extent proportional to the value of σ_p^+ .

It is of interest to compare the effectiveness by which this side chain transmits the polar influences of substituents. This can be done by comparison of the transmission coefficient, τ ,¹⁷ for this reaction series, with appropriate literature values. Comparison of $\tau = 0.60$ for the protolytic reactions of *p*-substituted *trans*- β -aroylepoxycarboxylic acids¹¹ with the τ value determined in this work (0.34), shows that the epoxy ring retains only half of the efficiency by which the C=C double bond transmits the polar effects of substituents. This could be explained by the greater mobility of the electron density through the double bond system. At this point, it would also be of interest to note that the transmission coefficient for the dissociation reaction of *p*-substituted *trans*-2-phenylcyclopropyl-1-carboxylic acid, $\tau = 0.182$,¹⁸ is smaller than the value calculated for *trans*- β -aroylepoxycarboxylic acids, $\tau = 0.34$. This can be attributed to the fact that the length of the C-C bond in the epoxy ring is smaller than the normal length of a C-C bond, causing an increase in the π -character of all the bonds of the epoxy ring which, therefore, increases the transmission efficiency.

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ИЗВОД

ОДРЕЂИВАЊЕ pK_a ВРЕДНОСТИ И КОРЕЛАЦИЈА СА СТРУКТУРОМ *p*-СУПСТИТУИСАНИХ *trans*-2,3-ЕПОКСИ-4-ОКСО-4-ФЕНИЛБУТАНСКИХ КИСЕЛИНА

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Одређене су pK_a вредности за серију од осам *p*-супституисаних *trans*-2,3-епокси-4-оксо-4-фенилбутанских киселина (*p*-супституисаних *trans*- β -ароилепоксиакричних киселина). Вредности су одређене потенциометријски у воденој средини на 25 °C и јонској сили 0.1 mol/dm³ (NaCl). Проучаван је пренос поларних ефеката са супституената на фенил језгру ка карбоксилној групи кроз бочни низ који садржи карбонилну групу и епоксидни прстен. pK_a вредности су корелисане са структуром применом Hammett-овог, Taft-овог и Yukawa-Tsuno-овог приступа. Hammett-ова ρ константа (0,34) је упоређена са аналогним вредностима за структурно сличне киселине.

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