Determination and Structural Correlation of pK_a Values of *p*-Substituted *trans*-2,3-Epoxy-4-oxo-4-phenylbutanoic Acids

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Summary

For a series of eight *p*-substituted *trans*-2,3-epoxy-4-oxo-4-phenyl butanoic acids (*p*-substituted *trans*-β-aroylepoxyacrylic acids), pK_a values were determined potentiometrically in aqueous media at 25 °C and at ionic strength 0.1 mol/dm^3 (NaCl). Transmission of polar effects from substituents on the phenyl nuclei to the carboxylic group through the side chain involving carbonyl group and epoxyde ring, was investigated. The pK_a values were correlated with structure using Hammett, Taft and Yukawa-Tsuno approach. 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.

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Introduction

The application of pK_a values is extremely diverse, ranging from the most fundamental one, *eg.* calculating the distribution functions in the given pH-interval, to exploring the transportation of substances through cell membrane. Therefore, the knowledge of pK_a is essential for various investigations in pharmacology, physiology, in structural, environmental, preparative and analytical studies, for industrial purposes, *etc.*[1] In the field of physical organic chemistry, polar effects of substituents on the ionisation of acids[2] have been frequently studied because they provide the possibility for establishing the suggestive 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 the system made of benzene ring, followed by carbonyl group, attached to epoxy ring, inserted between substituent and 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 acidity for series of *p*-substituted *trans*-β-aroylepoxyacrylic acids in aqueous medium, to establish the correlation between measured pK_a values using Hammet[6], Taft[7] and Yukawa-Tsuno[8] equation and to explain transmission of polar substituent effects along benzene ring and given side chain.

Experimental

Apparatus and Reagents

UV spectrophotometric measurements were carried out on GBC 911A spectrophotometer (GBC Scientific Equipment Pty. Ltd, Dandenog, Australia) equipped with 1 cm quartz cell. A PHM-240 pH-meter (Radiometer) with a GK 2401C combined electrode (Radiometer) was used for pH measurements. All potentiometric titrations were performed using TTT 60 titrator with automatic burette ABU 12, Radiometer. Burette size was 2.5 cm^3; least significant volume 0.001 cm^3; accuracy: ± 7×10^{-4} cm^3 ± 0.3 %. Solutions were stirred with mechanical stirrer M22 (Radiometer). Thermostat 'Ultra-Thermostat nach Höppler' type NBE (VEB Prüfgeräte-Werk Mendigen) was used. For the conversion of pH values to pc_H values ($pc_H = -\log [H_3O^+]$) the relationship: $pc_H = pH - A$ was used. The correction factor

A=0.1 was obtained by pH-metric titration of HCl standard solution with NaOH standard solution at 25 °C and constant ionic strength 0.1 mol/dm^3 (NaCl).[9]

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

Typical experimental procedure. In a 100 cm^3 flask equipped with magnetic stirrer, pH-meter and water-ice-bath, 15 mmol of finely powdered *trans*-β-aroylacrylic acid was suspended in 50 cm^3 of water. Acid was dissolved by adding 5 mol/dm^3 solution of sodium hydroxide at such a rate to keep temperature at 15-20 ^{o}C and pH below 9.0. The pH value was adjusted at 8.5 with 5% sulfuric acid, and 3.1 cm^3 30% of hydrogen peroxide (30 mmol) was added. The course of reaction was monitored by TLC, and 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 refrigerator over night. *trans*-β-Aroylepoxyacrylic acid was filtered, washed exhaustively with distilled water and dried in vacuum desiccator. Average yields 80-90%.

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

Other reagents (C_2H_5OH, HCl, NaOH and CH_3COONa) were analytical reagent grade (Merck). Redistilled water was used. Standardisation of 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/dm^3, were prepared in ethanol. In order to obtain the spectra of molecular (HA) and anionic (A^-) forms of acids, for each acid the two solutions of the same concentration (either 1×10^{-4} or 6×10^{-5} mol/dm^3) were prepared in 0.5 mol/dm^3 HCl and in acetate buffer (pH 5.5). Spectra were recorded in the range 220-500 nm, at scan rate 500 nm/min, against corresponding blank. The ethanole content in the solutions was up to 1% (vol) and practically without any effect on pH and spectra.

Determination of acidity constants. Acidity constants of *p*-substituted *trans*-β-aroylepoxyacrylic acids were determined in aqueous media potentiometricaly at 25 °C and at ionic strength of 0.1 mol/dm^3 (NaCl). The 20.3 cm^3 of the solution having concentration of the acid studied in the 1.1×10^{-3} - 1.6×10^{-3} mol/dm^3 range, and of HCl 1.458×10^{-3} mol/dm^3, was titrated with standard NaOH solution (0.08909 - 0.1162 mol/dm^3) in 0.050 cm^3 aliquots. Acidity constant of *trans*-epoxycrotonic acid was determined in the same way: The solution of the acid (5x10^{-3} mol/dm^3) was titrated with standard NaOH solution (0.1166 mol/dm^3). Titration for each acid was done in duplicate. The concentration of the acids studied in titrated solutions was selected according to their solubility.

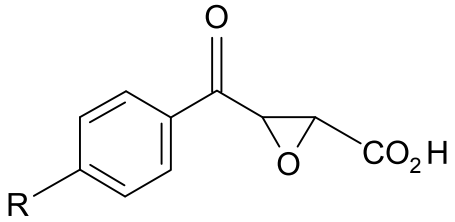
The formation function ($\bar{n}_H$), namely the mean number of bounded protons was calculated by following equation:

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

where c_{HA}^{tot} is the total concentration of investigated acid; [Cl$^-$] and [Na$^+$] are the concentrations of added HCl and NaOH, respectively; [H$_3$O$^+$] is the concentration of the free hydronium ions determined by pH-measurement; [OH$^-$] is the concentration of hydroxyl ions originated from the dissociation of water, that can be neglected in this case.

Results and Discussion

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



R = H, Me, Et, iPr, tBu, F, Cl and Br

Preliminary investigation included determination of spectral characteristics for all the studied acids. The dissociation caused the negligible difference in spectra of conjugated acid-base pair, making the spectrophotometric method not applicable. However, the general trend in all the acids studied in this work, was observed, *eg.* at wavelength 250-270 nm, the hypsochromic shift was caused by the deprotonation of carboxylic group (Table 1). In addition, this process was accompanied with unusual hyperchromic effect. (Opposite to the behaviour of benzoic and *trans*-cinnamic acids, but same as the effect observed in *trans*-β-aroylacrylic acids[11]) The conclusion that can be drawn from the noticed behaviour is that degree of protonation exhibits only small influence on the distribution of the electron density in chromophore.

Table 1. Spectral characteristics of molecular (HA) and anionic (A^-) forms of *p*-substituted *trans*-β-aroylepoxyacrylic acids.

Substituent	$\lambda_{max(HA)}$ (nm)	$\varepsilon_{max(HA)}/10^4$	$\lambda_{max(A^-)}$ (nm)	$\varepsilon_{max(A^-)}/10^4$
H	256	1.25	253	1.30
Me	268	1.36	266	1.39
Et	269	1.52	266	1.54
iPr	269	1.32	266	1.34
tBu	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

For the determination of pK_a^c (stoichiometric acidity constant) of these acids, a classical potentiometric method[12] based on the calculation of formation function was applied; for monoprotic acid (HA) the formation function is given by equation:

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

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

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

It is obvious, from the equation (3), that data should fit the linear function passing through the coordinate origin. K_a^c values were calculated by regression analysis, and results are shown in Table 2. Low standard deviations (sd) and high correlation coefficients (r) confirme the reliability of experimentally obtained data for all the acids studied. In Figure 1 the representative example of linear dependence for *p*-fluoro *trans*-β-aroylepoxyacrylic acid is shown.

Table 2. Results of linear regression analysis using equation (3) for determination of K_a^c of *p*-supstituted *trans*-β-aroylepoxyacrylic acids.

Substituent	K_a^c	sd	r	n
H	$2.95x10^{-3}$	$1.29x10^{-4}$	0.968	20
Me	$2.57x10^{-3}$	$2.96x10^{-5}$	0.989	18
Et	$3.02x10^{-3}$	$2.50x10^{-4}$	0.953	25
iPr	$2.88x10^{-3}$	$3.98x10^{-5}$	0.968	14
tBu	$2.63x10^{-3}$	$4.24x10^{-5}$	0.987	21
F	$3.24x10^{-3}$	$1.19x10^{-4}$	0.971	23
Cl	$3.63x10^{-3}$	$1.26x10^{-4}$	0.968	14
Br	$3.98x10^{-3}$	$1.51x10^{-4}$	0.975	20

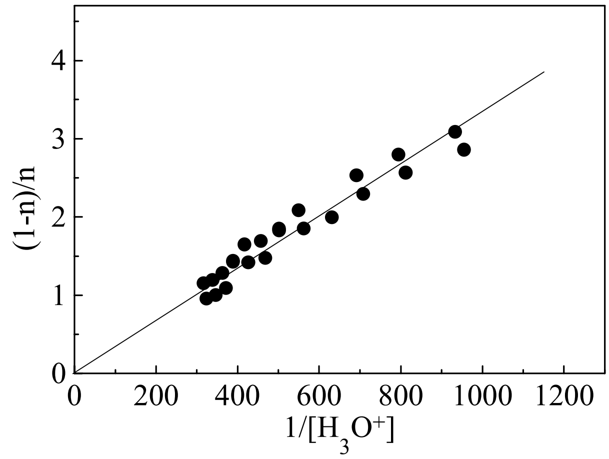


Figure 1. Plots for the determination of pK_a^c value according to the equation (3) for *p*-fluor- *trans*-β-aroylepoxyacrylic acid.

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

Table 3. pK_a values of *p*-substituted *trans*-β-aroylepoxyacrylic acids and substituent constants σ_p, σ_p^+, σ_I and σ_R

Substituent	H	Me	Et	iPr	tBu	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

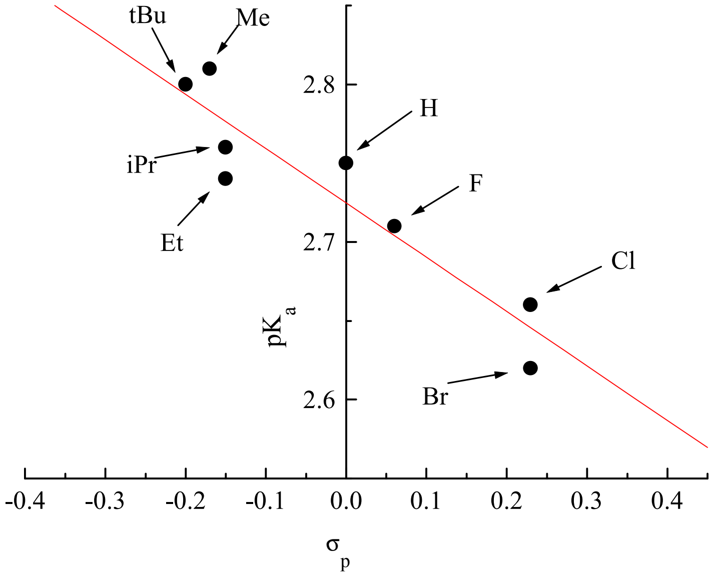


Figure 2. Plot of pK_a values of *p*-substituted *trans*-β-aroylepoxyacrylic acids against the corresponding Hammett σ_p constants.

In order to estimate the effect of substitution on pK_a values of acids studied, the correlation with Hammett σ_p constants[14] was performed. Plot of pK_a values against the corresponding substituent σ_p constants (Table 3) is shown in Fig. 2. The corresponding Hammett equation ($pK_a = pK_a^o - \rho\sigma_p$)[6] obtained in this case is:

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

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

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

In order to check which one of the effects, *e.g.* inductive or resonant, of substituents predominates (values for σ_I and σ_R are given in Table 3), the Taft equation ($pK_a=pK_a^o-\rho_I\sigma_I - \rho_R\sigma_R$)[7] was calculated:

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

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

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

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

Values for substituent constants σ_p^+ are given in Table 3. In this way, correlation is improved. Regression parameters are r=0.942 and s=0.02. The value of additional reaction parameter r^+ (-0.51) in Yukawa-Tsuno equation indicates that substituents in aromatic ring induce variation in molecular structure in the extent proportional to the value of σ_p^+.

It is interesting to compare the effectiveness by which this side chain transmits the polar influences of substituents. This could be done by comparison of the transmission coefficient, τ[17], for this reaction series, with the adequate literature values. Comparison of τ = 0.60 for protolytic reaction of *p*-substituted *trans*-β-aroylacrylic acids[11] with τ value determined in this work (0.34), shows that 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 with the greater mobility of electron density trough the system with double bond. At this point, it would be also interesting to note that transmission coefficient for the dissociation reaction of *p*-substituted *trans*-2-phenylcyclopropyl-1-carboxylic acid, τ = 0.182,[18] is smaller than the value calculated for *trans*-β-aroylepoxyacrylic acids, $\tau = 0.34$. It can be attributed to the fact that the length of C-C distance in epoxy ring is smaller than the length of C-C bond, causing the increase in π-character of all the bonds of the epoxy ring and therefore, increasing 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-ароилепоксиакрилних киселина). Вредности су одређене потенциометријски у воденој средини на 25 ^{O}C и јонској сили 0,1 mol/dm^3 (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.