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Reactivity of *N*-Arenesulfonyl-ε-aminocaproic Acids

V. P. Chernykh, O. A. Brizitskaya, E. N. Svechnikova, A. N. Brizitskaya, and L. I. Boryak

National Pharmaceutical University, Kharkov, Ukraine

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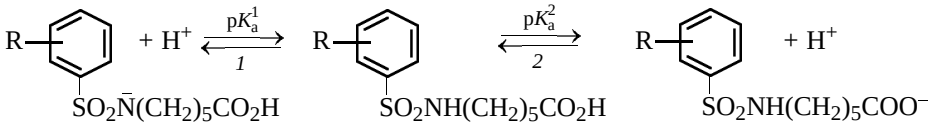
Abstract — *N*-Arenesulfonyl-ε-aminocaproic acids behave in aqueous dioxane as weak dibasic acids; their ionization constants were determined. The correlation of pK_a with Hammett σ constants was revealed, and the reaction parameters ρ were evaluated. The reaction centers (carboxy and amide groups) are weakly sensitive to the effect of substituents in the benzene rings. Formation of an intramolecular hydrogen bond in the molecules of these acids was proved.

ε-Aminocaproic acid and its derivatives are widely used in medicine as compounds exhibiting diverse pharmacological effects [1–3]. The study of the reactivity of *N*-arenesulfonyl-ε-aminocaproic acids allows optimization of the synthesis of these compounds and modeling of active pharmacophores in this series. The reactivity of compounds of this class was estimated by studying acid–base equilibria:

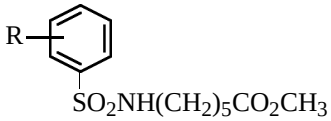


I–**VII**

R = H (**I**), 4-CH_3 (**II**), 4-Cl (**III**), 4-Br (**IV**), 4-NO_2 (**V**), 2-NO_2 (**VI**), 4-$NHCO_2CH_3$ (**VII**).

The constants of acid–base equilibria *1* and *2* of the synthesized *N*-arenesulfonyl-ε-aminocaproic acids were determined by potentiometric titration in aqueous dioxane (60 vol % dioxane) at 25°C (Table 1).

Preliminary experiments showed that compounds **I**–**VII** are dibasic acids with close ionization constants. Therefore, pK_a^1 and pK_a^2 were determined by the Neyes method [4]. To assign the pK_a values obtained to definite acid centers, we determined under the same conditions the ionization constants of model compounds, methyl *N*-arenesulfonyl-ε-aminocaproates **VIII**–**X** (Table 1).



VIII–**X**

R = 4-CH_3 (**VIII**), 4-Cl (**IX**), 4-NO_2 (**X**).

Table 1 shows that, within the experimental error, the ionization constants of the respective methyl esters coincide with the constants of equilibrium *1*. Data on the acid–base equilibria of *N*-arenesulfonyl-ε-aminocaproic acids show that these compounds show weak acidic properties depending on the nature and position of substituents in the benzene ring. The acidity of the amide group is somewhat higher than that of the carboxy group.

According to the experimental data, introduction of electron-withdrawing substituents into the benzene ring enhances the acidity of compounds. Apparently, the anions are stabilized by delocalization of their charge. Electron-donor substituents exert an opposite effecrt, but the extent of their effect on the amide and carboxylic reaction centers are different. For example, introduction of the 4-NO_2 group into the benzene ring increases the acid dissociation constant of the amide group by 0.44 pK_a unit and that of the carboxy group, by only 0.06 pK_a unit.

The effect of substituents on the acid–base properties of *N*-arenesulfonyl-ε-aminocaproic acids **I**–**VII** was quantitatively evaluated by correlation analysis

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Table 1. Properties of *N*-arenesulfonyl-ε-aminocaproic acids **I**–**VII** and their methyl esters **VIII**–**X**

Comp. no.	Yield, %	mp, °C	R_f[1]	pK_a^1	pK_a^2	Found N, %	Formula	Calculated N, %
I	84	119–121	0.81	8.26 ± 0.03	8.48 ± 0.02	5.33	$C_{12}H_{17}NO_4S$	5.16
II	77	106–108	0.68	8.30 ± 0.02	8.49 ± 0.03	5.17	$C_{13}H_{19}NO_4S$	4.91
III	78	117–119	0.85	8.13 ± 0.05	8.46 ± 0.05	4.72	$C_{12}H_{16}ClNO_4S$	4.58
IV	68	121–123	0.82	8.13 ± 0.04	8.46 ± 0.03	4.12	$C_{12}H_{16}BrNO_4S$	4.00
V	78	131–133	0.77	7.82 ± 0.02	8.42 ± 0.03	8.76	$C_{12}H_{16}N_2O_6S$	8.86
VI	37	124–126	0.72	7.72 ± 0.03	8.40 ± 0.02	8.97	$C_{12}H_{16}N_2O_6S$	8.86
VII	74	144–145	0.83	8.20 ± 0.04	8.47 ± 0.03	8.37	$C_{14}H_{20}N_2O_6S$	8.13
VIII	93	47–48	0.65	8.28 ± 0.01	–	4.59	$C_{14}H_{21}NO_4S$	4.68
IX	98	59–60	0.71	8.15 ± 0.04	–	4.51	$C_{13}H_{18}ClNO_4S$	4.38
X	89	90–92	0.69	7.87 ± 0.03	–	8.60	$C_{13}H_{18}N_2O_6S$	8.48

[a] R_f was determined in 2-propanol–chloroform, 1 : 1 by volume.

using the Hammett equation within the framework of the linear free energy relationship. The correlation between pK_a and σ constants for the whole set of the compounds is statistically unreliable ($r < 0.7$). Elimination of *N*-(2-nitrobenzenesulfonyl)-ε-aminocaproic acid **VI** from the correlations considerably improves all the statistical characteristics [Eqs. (1), (2)].

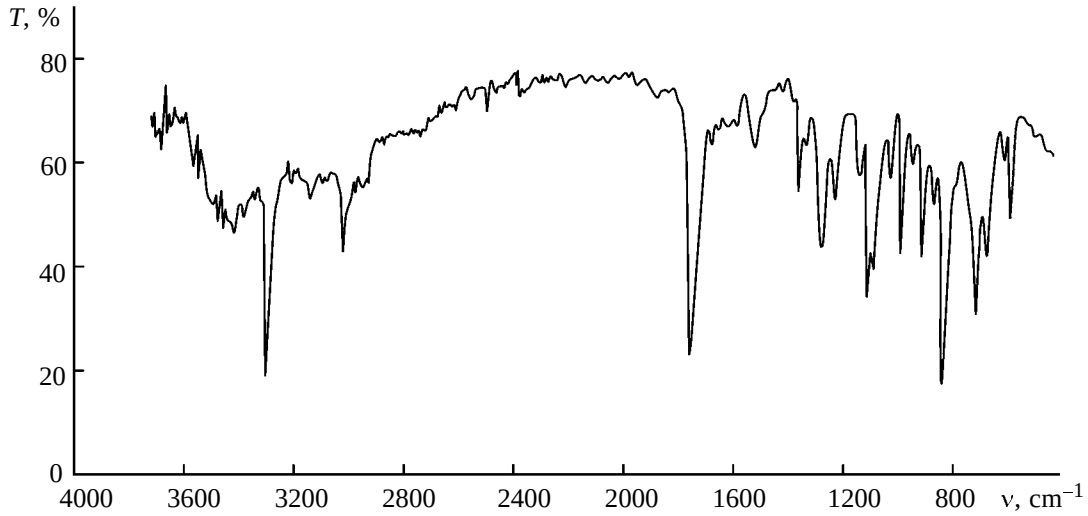
$$pK_a^1 = (8.26 \pm 0.08) - (0.56 \pm 0.04)\sigma; \quad (1)$$

$$n\ 6,\ r\ 0.994,\ s\ 0.021,$$

$$pK_a^2 = (8.48 \pm 0.02) - (0.07 \pm 0.01)\sigma; \quad (2)$$

$$n\ 5,\ r\ 0.998,\ s\ 0.002.$$

This may be due to the *ortho* effect [5] for **VI**. It is interesting that the reaction constants for both equilibria are low, indicating that the reaction centers are weakly sensitive to the substituent effects. The carboxy group (ρ 0.08) is by a factor of 7 less sensitive than the sulfonamide group (ρ 0.36), probably owing to considerably longer distance of the former from the substituents in the benzene ring. Comparison of the reaction constants of arenesulfonamides (ρ 1.06) [6], arenesulfonylhydrazides (ρ 0.88) [7], and *N*-arenesulfonyl-ε-aminocaproic acid derivatives (ρ 0.56) shows that introduction of the ε-aminocaproic acid residue considerably decreases the sensitivity of the reaction center (amide group) to the substituent effect in the benzene ring. Such an effect may be due to formation of a strong hydrogen bond between the amide NH atom and carbonyl oxygen atom. According to published data, the stretching vibration band of the free C=O bond in carboxy group is located at ~1760 cm^{-1}. Low C=O stretching frequencies in the IR spectra of *N*-arenesulfonyl-ε-aminocaproic acids (Table 2; see figure) are indicative of the hydrogen bonding [8].



IR spectrum of *N*-(4-chlorobenzenesulfonyl)-ε-aminocaproic acid **III**.

Table 2. Frequencies of NH and CO stretching vibrations in *N*-arenesulfonyl-ε-aminocaproic acids **I**–**VII**

Comp. no.	ν(C=O), cm^{-1}	ν(NH), cm^{-1}
I	1712	3280
II	1708	3272
III	1708	3272
IV	1712	3264
V	1716	3248
VI	1712	3280
VII	1696, 1656	3328, 3232

To determine the type of the hydrogen bond characteristic of *N*-arenesulfonyl-ε-aminocaproic acids, we measured the IR spectra of chloroform solutions of these acids of varied concentration.

In contrast to intermolecular hydrogen bonds, intramolecular bonds formed by a substance in solution are independent of the solution concentration, being intrinsic characteristics of individual molecules. Therefore, intramolecular hydrogen bonds are preserved even in very dilute solutions, as indicated by the corresponding bands in the IR spectra [8].

The experimental data obtained for acid **V** showed the validity of the Bouguer–Lambert–Beer law for the concentration range $(0.5–5) \times 10^{-3}$ M.

These facts, along with the lack of the shift of ν(C=O) on heating the sample, confirm the formation of an intramolecular hydrogen bond.

EXPERIMENTAL

The IR spectra of **I**–**VII** were taken on a Specord M-80 spectrophotometer (KBr pellets, 1 wt % substance) in the frequency range 4000–400 cm^{-1}.

To prove the type of the hydrogen bond, we measured the IR spectra of chloroform solutions of **I**–**VII** with the substance concentrations of 0.005, 0.0025, and 0.0005 M. The transmission coefficient was determined at the CO and NH stretching frequencies. The transmission coefficient was measured three times for each concentration, and the mean value was used to calculate the optical density.

The acid–base equilibria were studied by the procedure described in [9], with 0.05 M aqueous CO_2-free KOH as titrant. The concentration of the titrated solutions was 0.005 M in the half-neutralization point. Potentiometric titration was performed on an EV-74 ionometer with glass (ESP 43-074) and silver chloride (EVL-1) electrodes at 25°C. Three titration runs were performed with each sample. The accuracy of the results was evaluated by methods of mathematical statistics (confidence level 0.95) [10].

The mixed solvent was prepared from freshly double-distilled CO_2-free water and freshly distilled dioxane.

Acids **I**–**VII** and esters **VIII**–**X** were prepared by procedures from [11].

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