JOURNAL OF PHYSICAL ORGANIC CHEMISTRY, VOL. 5, 239–243 (1992)

SUBSTITUENT EFFECT ON THE RELATIVE STRENGTH OF SOME ARYLTHIOMETHYL- AND ARYLSULPHONYLMETHYLBENZOIC ACIDS

ALI A. EL-BARDAN, NABILA M. EL-MALLAH AND EZZAT A. HAMED*

Chemistry Department, Faculty of Science, Alexandria University, P.O. 426 Ibrahimia Alexandria 21321, Egypt

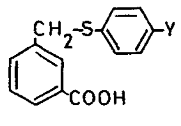
The p*K* values of some arylthiomethylbenzoic acids and the corresponding sulphones were determined spectrophotometerically. The role of substituent and the position of the carboxylic group are discussed.

INTRODUCTION

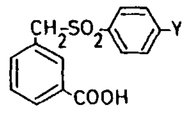
It has been found that compounds containing thioether and sulphonyl linkages have wide chemotherapeutic properties.[1] However, some phenylsulphonylmethylbenzoic acid derivatives such as 4-[(4′-bromophenylsulphonyl)methyl]-3-nitrobenzoic acid were found to be effective against bacteria in addition to being non-toxic to the tested crops, including weeds.[2]

The conjugative effect of the sulphonyl group, in conjunction with the rehybridization of the carbon atom from sp^3 to sp^2, and the conjugative overlap of the 3d orbitals on the sulphur atom with the sp^2 orbitals of the carbon atom have been used to explain the unusual acidity of hydrogens attached to an α-carbon atom.[3–7] On the other hand, it was reported that the substituents have an effect on the dissociation of carboxylic acids[8] and of the α-hydrogen of the sulphonyl group.[7,9] Agrawal and Shukla[10] reported that the thermodynamic ionization constants of *para*-substituted benzohydroxamic acids gave a straight line when plotted against Hammett σ constants. Others[8,11] found a good linear relationship between the ionization constants and Hammett σ values, indicating the role of the substituent.

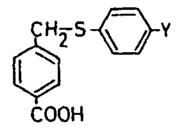
In this paper, we report the synthesis of 3-[(4′-substituted phenylthio)methyl]benzoic acids (**1a**–**f**) and 3-[(4′-substituted phenylsulphonyl)methyl]benzoic acids (**2a**–**f**). We also investigated the acid dissociation constants of **1a**–**f**, **2a**–**f**, 4-[(4′-substituted phenylthio)methyl]benzoic acids (**3a**–**f**) and 4-[(4′-substituted phenylsulphonyl)methyl]benzoic acids (**4a**–**f**) and the effect of the 4′-substituents (Y) on the ionization constants of thioether derivatives **1a**–**f** and **3a**–**f** and of the acidity of the α-hydrogen in sulphonyl derivatives **2a**–**f** and **4a**–**f**.



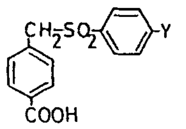
1_{a-f}



2_{a-f}



3_{a-f}



4_{a-f}

a, Y = H; b, Y = OCH_3; c, Y = CH_3; d, Y = Br; e, Y = Cl; f, Y = NO_2

RESULTS AND DISCUSSION

The series of compounds **1**–**4** were prepared following the literature procedure.[12–14]

The ionization constants of the compounds were determined spectrophotometrically in 50% (v/v) ethanol–water at 25°C. Two clear isosbestic points covering all the pH range utilized (2·8–10) at 248 and 272 nm were observed for **1a**, while **1d** showed five isosbestic points at 281 and 246 nm (pH 6·5–10), 278 and 252 nm (pH 2·8–5·7) and 248 nm (pH 5–10), indicating that the equilibrium under investigation was pH dependent. These values show that different absorbing species are present in equilibrium.

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* Author for correspondence.

0894–3230/92/050239–05$05.00

Received 27 August 1991
Revised 6 January 1992

Table 1. pK values of 3-[(4′-substituted phenylthio)methyl]benzoic acids **1a–f** and 4-[(4′-substituted phenylthio)methyly]benzoic acids **3a–f** in 50% v/v ethanol–water at 25 °C

	pK	
Y	**1a–f**	**2a–f**
H	4·22	3·91
OCH_3	5·41	5·22
CH_3	4·84	4·63
Br	4·51	4·45
Cl	4·53	4·32
NO_2	4·91	4·81

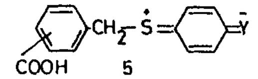
The variation in A_s with pH could be used to calculate the pK values of the acid sulphides **1a–f** and **3a–f** and the acid sulphones **2a–f** and **4a–f**. The A_s versus pH plot gave titration curves of acid–base features. Reproducible results were obtained from the relationship[15]

$$\log\left(\frac{A_{\max} - A}{A - A_{\min}}\right) = \mathrm{p}K - \mathrm{pH}$$

where $A_{\max}$ is the maximum absorption, $A_{\min}$ is the minimum absorption and A is the absorption at various pH values. Colleter's method[16] gave nearly the same results.

The absorbance versus pH curves of acid sulphide derivatives **1a–f** and **3a–f** show one sharp inflection, indicating that one proton is available for ionization. The pK values calculated by the least-squares method are given in Table 1. It is observed that both electron-donating and electron-withdrawing substituents decrease the acidity.

Generally, the thiophenyl group acts as an electron-withdrawing substituent[17] which leads to an increase in the acidity of the acid sulphides **1a–f** and **3a–f**. Attempts were made to rationalize the effect of 4′-substituents and pK_a values. Plots of pK versus Hammett σ values for **1a–f** and **3a–f** gave upward concave curves (Figure 1). This break in the Hammett plots can be explained on the basis that the sulphur atom resonates with the Y-substituent, leading to resonance structures[4] (**5** and **6**) which can inhibit the electron-withdrawing ability of the thioaryl group more than the thiophenyl group, i.e. the decrease in acidity presumably due to the intrinsic effect of the relayed electrostatic force from the full or partial charge imposed at the sulphur atom.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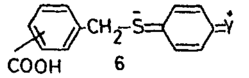
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The A_s versus pH curves of the acid sulphones **2a–f** and **4a–f** show two separate inflections, indicating that two protons are available for ionization. This is due to the presence of the active methylene group α to the sulphonyl group (pK_2) in addition to the carboxylic group (pK_1). the pK values calculated by the least-squares method are given in Table 2.

Plots of pK values for the ionization of the carboxylic groups in the acid sulphones **2a–f** and **4a–f** against Hammett σ values gave straight lines (Figure 2) with slopes of −0·55 and −0·32, respectively. Again, the charge imposed on the sulphonyl sulphur atom by resonance between itself and the 4′-substituent (Y) presumably affects the ionization of the carboxylic group.

Table 2. pK values of 3-[(4′-substituted phenylsulphonyl)-methyl]benzoic acids **2a–f** and 4-[(4′-substituted phenylsulphonyl)methyly]benzoic acids **4a–f** in 50% v/v ethanol–water at 25 °C

	2a–f		**4a–f**	
Y	pK_1	pK_2	pK_1	pK_2
H	5·81	8·88	5·31	8·62
OCH_3	6·82	8·52	5·84	8·81
CH_3	6·43	8·72	5·62	8·73
Br	5·33	9·53	4·84	8·24
Cl	5·42	9·42	5·01	8·32
No_2	3·51	10·81	3·93	7·53

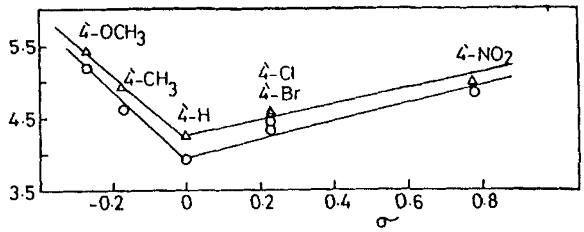


Figure 1. Plots of pK values of carboxylic groups in (△) **1a–f** and (○) **3a–f** against Hammett σ constants

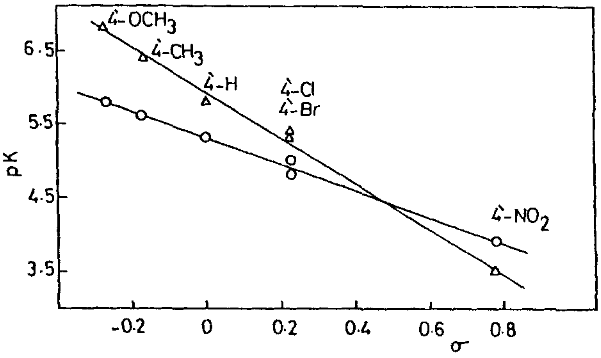
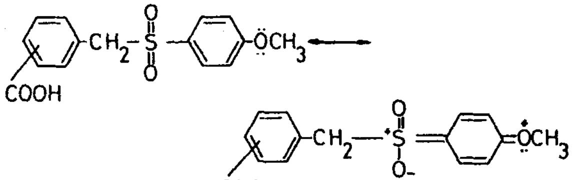


Figure 2. Plots of pK values of carboxylic groups in (△) **2a–f** and (○) **4a–f** against Hammett σ constants



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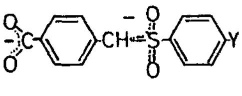
Electron-donating substituents, e.g. 4′-OCH$_3$, can resonate with the sulphonyl group[4] (**7**), leading to inhibition of its electron-withdrawing effect and reflecting a decrease in the ionization of the carboxylic group, whereas electron-withdrawing substituents enhance the electron-withdrawing effect of the aryl sulphonyl group, thus increasing the ionization constant.[4] This effect is greater in the case of the 4′-NO$_2$ substituent owing to the proximity of the 4′-NO$_2$-benzenesulphonyl moiety to the carboxylic group at position 3 in **2f**.

Similarly, the plots of p*K* values of the ionization of the α-hydrogen of the acid sulphones **2a–f** and **4a–f** against Hammett σ constants gave straight lines with slopes of 0·44 and −0·81, respectively (Figure 3), indicating the opposite effects of the substituents in the two types of sulphones. This is explained by the suggestion that in sulphones **4a–f** the developed carbanion can resonate with the 4-carboxylate anion, giving the possible resonance structures **8**, **9** and **10**. Consequently, the electron-withdrawing substituents stabilize these resonance structures, leading to an increase in the acidity of the α-hydrogen, whereas electron-donating substituents can resonate further between themselves and the sulphonyl group to give **11**, which involves the d-orbital on the sulphur atom.[7] Structure **11** seems to be less stable than **8–10**, leading to a lowering in the acidity of the α-hydrogens.



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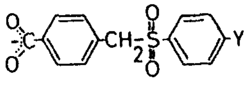

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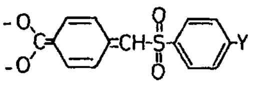

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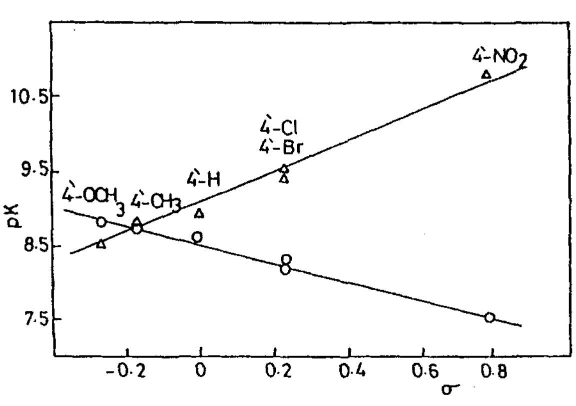
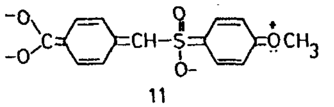


Figure 3. Plots of p*K* values of —CH$_2$SO$_2$— protons in (△) **2a–f** and (○) **4a–f** against Hammett σ constants



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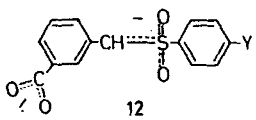
On the other hand, the effect of the 4′-substituent (Y) on the acidity of the α-hydrogens in the sulphones **2a–f** reveals the direct interaction occurring between the developed carbanion and the sulphonyl group (**12**).



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This interaction derives much stability from rehybridization from sp^3 to sp^2, thus allowing delocalization of charge to the more electronegative oxygen atoms of the sulphonyl group. According to resonance hybrid **12**, electron-withdrawing substituents stabilize whereas electron-donating substituents destabilize this sulphone dianion, leading to the behaviour shown in Figure 3. This is consistent with the observation of different isosbestic points at 296 nm (pH 2·8–10), 252 nm (pH 2·8–6·5), 226 nm (pH 2·8–5·7) and 216 nm (pH 5·5–10) for the 4′-bromo derivative **3d**, which suggests the presence of different absorbing species.

It appears that the position of the carboxylic group plays an important role in the acidity of the α-hydrogen, which consequently leads to different effects of the 4′-substituent (Table 2). Also, the data obtained led to the conclusion that the thioether linkage and sulphonyl group of the compounds under investigation can transmit the electrical effect of the 4′-substituents.

EXPERIMENTAL

Infrared and ultraviolet spectra were measured on Pye Unicam SP 1025 and SP 800 spectrometers, respectively. ^{1}H NMR spectra were measured on a Varian EM-390 90 MHz spectrometer (Alexandria University, Egypt). Microanalyses were performed at Cairo University, Egypt. Melting points are uncorrected.

Preparation of materials. 4-[(4′-Substitutedphenylthio)methyl]benzoic acids **3a–f** and 4-[(4′-substitutedphenylsulphonyl)methyl]benzoic acids **4a–f** were prepared as reported.[12–14]

3-[(4′-Substitutedphenylthio)methyl] benzoic acids (**1a–f**). A mixture of 3-chloromethylbenzoic acid[18,19] (0·1 mol) and the sodium salt of an arylthiol (0·1 mol) in ethanol was refluxed on a water-bath for 1–2 h. The reaction mixture was cooled, diluted with cold water and acidified with 10% hydrochloric acid, giving a solid that was crystallized from dilute ethanol.

3-[(Phenylthio)methyl] benzoic acid (**1a**). Colourless needles, yield 97%, m.p. 105–107 °C. Analysis: calculated for $C_{14}H_{12}O_2S$, C 68·85, H 5·35, S 14·28; found, C 68·40, H 5·4, S 14·60%. UV: $\lambda_{max} = 208$ nm ($\varepsilon = 21\,070$). ^1H NMR(acetone-d_6): δ 4·22 (s, 2H, benzylic), 7·18 (m, 4H, $H_{2',3',4',5',6'}$), 7·48 (t, 1H, H_5), 7·75 (d, 2H, $H_{4,6}$) and 7·88 ppm (s, 1H, H_2).

3-[(4′-Methoxyphenylthio)methyl] benzoic acid (**1b**). Colourless needles, yield 88%, m.p. 115–116 °C. Analysis: calculated for $C_{15}H_{14}O_3S$, C 65·69, H 5·11, S 11·68; found, C 65·30, H 5·00, S 11·90%. UV: $\lambda_{max} = 213$ nm ($\varepsilon = 24\,260$). ^1H NMR (acetone-d_6): δ 3·68 (s, 3H, 4′-OCH_3), 4·02 (s, 2H, benzylic), 6·72 (d, 2H, $H_{3',5'}$), 7·18 (d, 2H, $H_{2',6'}$), 7·32 (d, 2H, H_5), 7·72 (d, 2H, $H_{4,6}$) and 7·80 ppm (s, 1H, H_2).

3-[(4′-Methylphenylthio)methyl] benzoic acid (**1c**). Colourless needles, yield 94%, m.p. 136–138 °C. Analysis: calculated for $C_{15}H_{14}O_2S$, C 69·97, H 5·42, S 12·40; found, C 69·60, H 5·30, S 12·00%. UV: $\lambda_{max} = 210$ nm ($\varepsilon = 23\,150$). ^1H NMR (acetone-d_6): δ 2·20 (s, 3H, 4′-CH_3), 4·15 (s, 2H, benzylic), 7·00 (d, 2H, $H_{3',5'}$), 7·15 (d, 2H, $H_{2',6'}$), 7·44 (d, 1H, H_5), 7·78 (d, 2H, $H_{4,6}$) and 7·82 ppm (s, 1H, H_2).

3-[(4′-Bromophenylthio)methyl] benzoic acid (**1d**). Pale yellow needles, yield 93%, m.p. 128–129 °C. Analysis: calculated for $C_{14}H_{11}BrO_2S$, C 52·01, H 3·40, S 9·91; found, C 52·50, H 3·50, S 9·90%. UV: $\lambda_{max} = 208$ nm ($\varepsilon = 21\,169$). ^1H NMR (acetone-d_6):δ 4·25 (s, 2H, benzylic), 7·18 (d, 2H, $H_{2',6'}$), 7·35 (d, 2H, $H_{3',5'}$), 7·50 (t, 1H, H_5), 7·82 (d, 2H, $H_{4,6}$) and 7·92 ppm (s, 1H, H_2).

3-[(4′-Chlorophenylthio)methyl] benzoic acid (**1e**). Colourless needles, yield 93%, m.p. 107–108 °C. Analysis: calculated for $C_{14}H_{11}ClO_2S$, C 60·32, H 3·92, S 11·49; found, C 60·70, H 3·70, S 11·90%. UV: $\lambda_{max} = 208$ nm ($\varepsilon = 21\,040$). ^1H NMR (acetone-d_6): δ 4·20 (s, 2H, benzylic), 7·22 (m, 4H, $H_{2',3',5',6'}$), 7·45 (t, 1H, H_5), 7·80 (d, 2H, $H_{4,6}$), and 7·90 ppm (s, 1H, H_2).

3-[(4′-Nitrophenylthio)methyl] benzoic acid (**1f**). Yellow needles, yield 85%, m.p. 192–194 °C. Analysis: calculated for $C_{14}H_{11}NO_4S$, C 58·13, H 3·80, S 11·07; found C 58·30, H 3·90, S 11·00% UV: $\lambda_{max} = 206$ nm ($\varepsilon = 17\,810$). ^1H NMR (acetone-d_6): δ 4·45 (s, 2H, benzylic), 8·00 (d, 2H, $H_{2',6'}$), 8·10 (d, 2H, $H_{3',5'}$), 7·35 (t, 1H, H_5), 7·68 –7·85 (dd, 2H, $H_{4,6}$) and 7·50 ppm (s, 1H, H_2).

3-[(4′-Substituted phenylsulphonyl)methyl] benzoic acids (**2a–f**). Compounds **1a–f** (0·1 mol) in glacial acetic acid (10 ml) were treated with excess of 30% hydrogen peroxide. The mixture was refluxed for 24 h and the product was crystallized from dioxane–water.

3-[(4′-Phenylsulphonyl)methyl] benzoic acid (**2a**). Colourless needles, yield 90%, m.p. 210 °C. Analysis: calculated for $C_{14}H_{12}O_4S$, C 60·86, H 4·34, S 11·59; found, C 60·90, H 4·50, S 11·20%. UV: $\lambda_{max} = 207$ nm ($\varepsilon = 18\,070$). ^1H NMR (acetone-d_6): δ 4·55 (s, 2H, benzylic), 7·32 (s, 2H, $H_{2',6'}$), 7·33 (s, 3H, $H_{3',4',5'}$), 7·54 (d, 2H, $H_{4,6}$), 7·78 (s, 1H, H_2) and 7·88 ppm (t, 1H, H_5).

3-[(4′-Methoxyphenylsulphonyl)methyl] benzoic acid (**2b**). Colourless needles, yield 80%, m.p. 225 °C. Analysis: calculated for $C_{15}H_{14}O_5S$, C 58·82, H 4·57, S 10·45; found, C 59·30, H 4·40, S 10·90%. UV: $\lambda_{max} = 208$ nm ($\varepsilon = 20\,028$). ^1H NMR (acetone-d_6): δ 3·78 (s, 3H, 4′-OCH_3), 4·45 (s, 2H, benzylic), 7·26 (d, 2H, $H_{2',6'}$), 6·92 (d, 2H, $H_{3',5'}$), 7·42 (d, 2H, $H_{4,6}$), 7·72 (s, 1H, H_2) and 7·83 ppm (t, 1H, H_5).

3-[(4′-Methylphenylsulphonyl)methyl] benzoic acid (**2c**). Colourless needles, yield 85%, m.p. 227 °C. Analysis: calculated for $C_{15}H_{14}O_4S$, C 62·06, H 4·82, S 11·03; found, C 62·10, H 4·80, S 11·10%. UV: $\lambda_{max} = 206$ nm ($\varepsilon = 18\,250$). ^1H NMR (acetone-d_6): δ 2·38 (s, 3H, 4′-CH_3), 4·50 (s, 2H, benzylic), 7·28 (d, 2H, $H_{2',6'}$), 7·15 (d, 2H, $H_{3',5'}$), 7·45 (d, 2H, $H_{4,6}$), 7·74 (s, 1H, H_2) and 7·90 ppm (t, 1H, H_5).

3-[(4′-Bromophenylsulphonyl)methyl] benzoic acid (**2d**). Pale yellow needles, yield 85%, m.p. 321 °C. Analysis: calculated for $C_{14}H_{11}BrO_4S$, C 47·32, H 3·09, S 9·01; found, C 47·60, H 3·60, S 9·30%. UV: $\lambda_{max} = 207$ nm ($\varepsilon = 19\,000$). ^1H NMR (DMSO-d_6): δ 4·80 (s, 2H, benzylic), 7·60 (d, 2H, $H_{2',6'}$), 7·70 (d, 2H, $H_{3',5'}$), 7·35 (d, 2H, $H_{4,6}$), 7·75 (s, 1H, H_2) and 7·88 ppm (t, 1H, H_5).

3-[(4′-Chlorophenylsulphonyl)methyl] benzoic acid (**2e**). Pale yellow needles, yield 85%, m.p. 310 °C. Analysis: calculated for $C_{14}H_{11}ClO_4S$, C 54·10, H 3·54, S 10·30; found, C 54·40, H 3·50, S 10·60%. UV: $\lambda_{max} = 207$ nm ($\varepsilon = 18\,360$). ^1H NMR (DMSO-d_6): δ 4·75 (s, 2H, benzylic), 7·55 (m, 4H, $H_{2',3',5',6'}$), 7·32 (d, 2H, $H_{4,6}$), 7·70 (s, 1H, H_2) and 7·85 ppm (t, 1H, H_5).

3-[(4′-Nitrophenylsulphonyl)methyl] benzoic acid (**2e**). Yellow crystals, yield 80%, m.p. 230 °C. Analysis: calculated for $C_{14}H_{11}NO_4S$, C 52·33, H 3·42, S 9·96;

found, C 52·80, H 3·60, S 10·30%. UV: $\lambda_{max} = 209$ nm ($\varepsilon = 22210$). ^{1}H NMR (DMSO-d_6): δ 4·90 (s, 2H, benzylic), 7·58 (d, 2H, $H_{2',6'}$), 7·90 (d, 2H, $H_{3',5'}$), 7·35 (d, 2H, $H_{4,6}$), 7·72 (d, 1H, H_2) and 8·20 ppm (t, 1H, H_5).

The IR spectra (KBr) for all compounds showed a broad band at 3100 cm^{-1} (OH) and a sharp band at 1680–1710 cm^{-1} (C=O). In addition, a stretching band at 630–650 cm^{-1} (C—S) for the sulphides **1a–f** and a strong band at 1350, 1150 cm^{-1} (SO_2) for the sulphones **2a–f** were detected.

Spectrophotometeric measurements. The measurements were made on a Pye Unicam SP8-400 double-beam spectrophotometer. The cell compartment was maintained at 25 °C. The ionic strength was 0·03 M KCl and the concentration of the studied compounds was 5×10^{-5} M. The measurements were carried out in 50% (v/v) ethanol–water.

A Radiometer PHM 62 pH meter fitted with a combined glass electrode (type GK 2401 C) was used to record the pH of the solutions. The pH meter was calibrated by standard Radiometer buffers of pH 4·0 and 7·0. The instrument was accurate to ±0·01 pH unit.

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