6814 J. Org. Chem. 1996, 61, 6814−6817

Structure−Reactivity Correlations in the Dissociative Hydrolysis of 2′,4′-Dinitrophenyl 4-Hydroxy-X-benzenesulfonates[†]

Giorgio Cevasco*,[‡] and Sergio Thea*,[§]

C.N.R., Centro di Studio per la Chimica dei Composti Cicloalifatici ed Aromatici, Via Dodecaneso 31,
16146 Genova, Italy, and Dipartimento di Chimica, Via Vienna 2, Università di Sassari,
07100 Sassari, Italy

Received May 31, 1996[⊗]

The hydrolysis reactions of several title esters in water at 60 °C follow the rate law $k_{obs} = (k_a + k_b[OH^-])/(1 + a_H/K_a)$, where K_a is the ionization constant of the hydroxy group of the ester and k_b is the second-order rate constant for the $S_N2(S)$ attack of hydroxide ion on the ionized ester. Hammett and Brønsted correlations are consistent with a previous proposal that the mechanism related to k_a is dissociative. An unusual relationship between k_a values and redox equilibrium constants for substituted quinones is found to hold: this finding further supports the dissociative nature of the pathway related to k_a.

Our previous studies[1] on sulfonyl transfer reactions involving aryl esters of 3,5-dimethyl-4-hydroxybenzenesulfonic acid have provided evidence that their alkaline hydrolysis does not occur *via* the usual $S_N2(S)$ route (path A in Scheme 1) but follows a dissociative E1cB mechanism through the sulfoquinone intermediate **1** (path C). In strongly alkaline solution, however, a bimolecular anion−anion reaction takes over the reaction flux (path B). Similar behavior was demonstrated also for some aryl hydroxynaphthalenesulfonates.[1b]

A large amount of data on acyl transfer processes shows that the factors driving the mechanistic pathway (associative *vs* dissociative) are (i) leaving group ability, (ii) internal nucleophilicity of the substrate (it is related to the pK_a of the ionisable proton and represents a driving force for the expulsion of the leaving group from the conjugate base of the substrate), and (iii) stability of the putative unsaturated intermediate. In this connection it is generally thought that the dissociative route requires a reasonably (although not exceedingly) high substrate pK_a, a good nucleofuge, and a “stable” intermediate.[2]

Aimed at extending our knowledge on the role played by internal nucleophilicity on the E1cB mechanism in sulfonyl group transfer reactions, we have undertaken a study on the alkaline hydrolysis of 2,4-dinitrophenyl esters of 4-hydroxybenzenesulfonic acids having additional substituents in positions 3 and/or 5 of the sulfonyl moiety.

Results and Discussion

Reactions were carried out in aqueous buffered solutions at 60 °C and gave rise to quantitative liberation of 2,4-dinitrophenol and substituted 4-hydroxybenzenesulfonic acid.

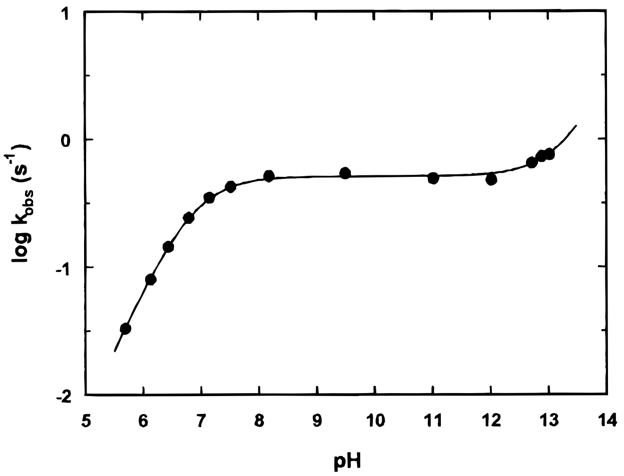
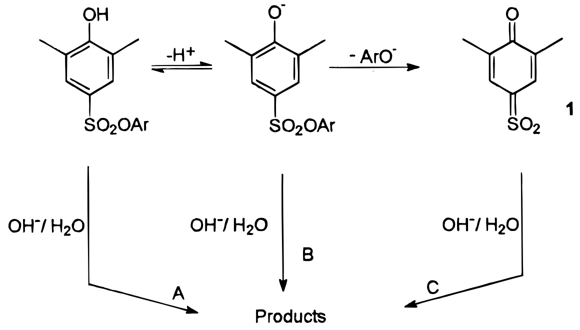


Figure 1. pH−rate profile for the hydrolysis of 2′,4′-dinitrophenyl 3,5-dimethyl-4-hydroxybenzenesulfonate in aqueous buffers at 60 °C, ionic strength made up to 1.0 M with KCl.

Scheme 1



Rates of hydrolysis, measured spectrophotometrically monitoring the increase in absorbance at 400 nm due to release of 2,4-dinitrophenol, were accurately first order in ester over at least 80% of the total reaction and depended on pH according to the rate law shown in eq 1:

$$k_{obs} = (k_a + k_b[OH^-])/(1 + a_H/K_a) \qquad (1)$$

The pH−rate profile for the hydrolysis of 2′,4′-dinitrophenyl 3,5-dimethyl-4-hydroxybenzenesulfonate is displayed in Figure 1; similar plots (not shown) were obtained for the other esters studied. In eq 1, according

---

[†] Dedicated to Professor Fernando Montanari on the occasion of his 70th birthday.

[‡] C.N.R.

[§] Università di Sassari.

[⊗] Abstract published in *Advance ACS Abstracts,* September 1, 1996.

(1) (a) Thea, S.; Guanti, G.; Hopkins, A. R.; Williams, A. *J. Am. Chem. Soc.* **1982**, *104*, 1128. (b) Thea, S.; Cevasco, G.; Guanti, G.; Hopkins, A. R.; Kashefi-Naini, N.; Williams, A. *J. Org. Chem.* **1985**, *50*, 2158. (c) Thea, S.; Cevasco, G.; Guanti, G. *Gazz. Chim. Ital.* **1987**, *117*, 705.

(2) See, for example: Williams, A.; Douglas, K. T. *Chem. Rev.* **1975**, *75*, 627. Douglas, K. T. In *Progress in Bioorganic Chemistry*; Kaiser, E. T., Kèzdy, F. J., Eds.; Wiley: New York, 1976; Vol. 4, p 194 and references cited therein.

S0022-3263(96)01024-9 CCC: $12.00

Table 1. Kinetic Data for the Hydrolysis of 2′,4′-Dinitrophenyl 4-Hydroxy-X-benzenesulfonates in Water at 60 °C and $\mu = 1.0$ ($pK_w = 13.017^a$)

X	k_a, s^{-1}	k_b, M^{-1} s^{-1}	log k_{app} ^{b}	$\Sigma\sigma^c$	N^d	pH^e
3,5-dichloro	(4.47 ± 0.14) ± 10^{-4}	0.98 ± 0.04	6.447	0.74	12	3.0−12.7
3,5-difluoro	(2.19 ± 0.19) ± 10^{-4}	1.07 ± 0.10	5.547	0.68	8	6.3−13.0
3-methyl-5-nitro	(1.94 ± 0.15) ± 10^{-4}	1.43 ± 0.12	5.335	0.64	8	5.8−12.0
3-chloro	(1.71 ± 0.05) ± 10^{-3}	0.54 ± 0.02	5.210	0.37	8	6.3−13.0
3-fluoro	(1.28 ± 0.04) ± 10^{-3}	0.55 ± 0.02	4.834	0.34	8	6.3−13.0
3-methyl-5-chloro	(1.37 ± 0.08) ± 10^{-2}	0.43 ± 0.03	5.834	0.30	12	4.6−13.0
3-methoxy	(5.34 ± 0.19) ± 10^{-2}	0.33 ± 0.02	5.165	0.08	10	5.8−13.0
unsubstituted	(6.06 ± 0.18) ± 10^{-3}	0.31 ± 0.01	4.139	0.00	10	5.7−13.0
3-methyl	(5.08 ± 0.31) ± 10^{-2}	0.25 ± 0.04	4.853	−0.07	11	5.2−13.0
3,5-dimethyl	0.51 ± 0.01	0.26 ± 0.03	5.874	−0.14	13	5.7−13.0

[a] Albert, A.; Serjeant, E. P. *Ionization Constants of Acids and bases*; Methuen & Co. Ltd.: London, 1962. [b] See text, K_a values are taken from Table 2. [c] For the 3,5-positions. Values taken from Barlin, G. B.; Perrin, D. D. *Qt. Rev.* **1966**, *20*, 75. [d] Number of data points, not including duplicates. [e] pH range employed.

to our previous mechanistic proposal,[1] K_a is the ionization constant of the hydroxy group of the ester and k_a is the pseudo-first-order rate constant, related to the E1 step (first step of path C, Scheme 1) which is responsible for the plateau region of the pH−rate profile, whereas k_b refers to the nucleophilic attack of hydroxide ion onto the conjugate bases of the substrate (path B). Table 1 collects experimental conditions and the values of the kinetic parameters, obtained from primary kinetic data by iterative nonlinear curve-fitting performed with the Fig.P program,[3] for the hydrolysis of the substrates. If a sufficently detailed pH−rate profile (in particular in and below the plateau region of pH) is available, this program provides, together with the rate constants, reliable kinetic K_a values. Table 2 indicates that the so-obtained pK_a values are in good agreement with the spectroscopic ones. The high reactivity of the ester of 3,5-dimethyl-4-hydroxybenzenesulfonic acid does not allow the spectrophotometric determination of its pK_a.

Table 2. Ionization Constants of 2′,4′-Dinitrophenyl 4-Hydroxy-X-benzenesulfonates in Water at 60 °C and $\mu = 1.0$

X	λ, nm^a	pH^b	$pK_a{}^c$	$pK_a{}^d$
3,5-dichloro	290	3.19−4.30	3.22 ± 0.01	3.21 ± 0.07
3,5-difluoro	305	3.52−4.27	3.81 ± 0.02	
3-methyl-5-nitro	290	3.04−4.17	3.97 ± 0.05	
3-chloro	305	4.26−5.65	5.04 ± 0.01	
3-fluoro	305	4.90−5.96	5.29 ± 0.01	
3-methyl-5-chloro	305	4.63−5.91	5.32 ± 0.02	5.11 ± 0.04
3-methoxy	290	6.04−7.01	6.58 ± 0.02	6.45 ± 0.02
unsubstituted	290	6.01−6.90	6.66 ± 0.01	6.62 ± 0.04
3-methyl	290	6.00−6.90	6.87 ± 0.01	6.72 ± 0.05
3,5-dimethyl				6.85 ± 0.02

[a] Wavelength employed for the spectroscopic determination. [b] At least five determinations at different pH were carried out in this range to obtain the spectroscopic values. [c] Spectroscopic values. [d] Measured from the kinetics.

The values of k_b obey a good Hammett correlation (eq 2, σ refers to the 3- and 5-substituted positions) consistent with an associative mechanism: indeed, the alkaline hydrolysis of phenyl esters of substituted benzenesulfonic acids, a *bona fide* $S_N2(S)$ process, has a Hammett dependence for *meta* and *para* substituents in the sulfonyl moiety.[4] In contrast, the apparent second-order rate constants for attack of hydroxide ion on neutral substrates ($k_{app} = k_aK_a/K_w$) give rise to a very poor Hammett relationship (eq 3).

$$\log k_b = (0.81 \pm 0.08)\sum\sigma - (0.53 \pm 0.03) \qquad (2)$$

$$\log k_{app} = (0.94 \pm 0.63)\sum\sigma - (5.04 \pm 0.27) \qquad (3)$$

These facts suggest that the mechanisms carrying the reaction flux in the k_b and k_{app} cases are different, *i.e.*, the mechanism related to k_{app} is not of the associative type. This conclusion further substantiates the proposed[1c] dissociative nature of this process.

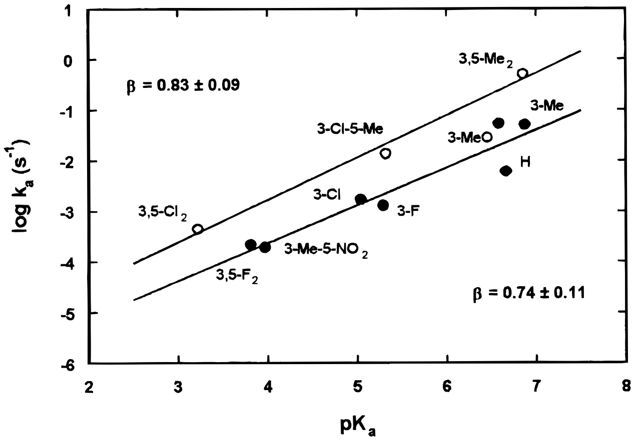


Figure 2. Brønsted-type plot of log k_a *vs* the pK_a values for the ionizable substrates.

The Brønsted-type plot of log k_a *vs* the pK_a of the esters is rather scattered (eq 4) however, a closer inspection of

$$\log k_a = (0.74 \pm 0.14)pK_a - (6.30 \pm 0.78) \qquad (4)$$

the data seems to indicate the existence of two different relationships: as shown in Figure 2 three 3,5-disubstituted esters (open circles) appear to react faster than predicted on the basis of the correlation based on the remaining esters (solid circles). This behavior can be rationalized by taking into account that the 3,5-substituents in the hydroxybenzenesulfonates are *ortho* to the hydroxy group as well, *i.e.*, these esters are phenol derivatives carrying substituents in both the *ortho* positions. Indeed, it is well-known[5] that steric inhibition to solvation (SIS) of the negative charge of the anionic form of 2,6-disubstituted phenols is responsible for an acid-weakening effect, due to an increase in the free energy content of the phenolate ions with respect to that of the corresponding undissociated phenols. Consequently, if such an effect operates also on the ionization of the three aforementioned esters, then the free energy of their conjugate bases (which are the ground states of the E1

---

(3) Program Fig.P from Biosoft, Cambridge, U.K., 1991.

(4) Palm, V. A.; Vizgert, V. *Dokl. Akad. Nauk. SSSR* **1962**, *142*, 1091.

(5) Rochester, C. H.; Rossall, B. *Trans. Faraday Soc.* **1968**, *65*, 1004 and references therein.

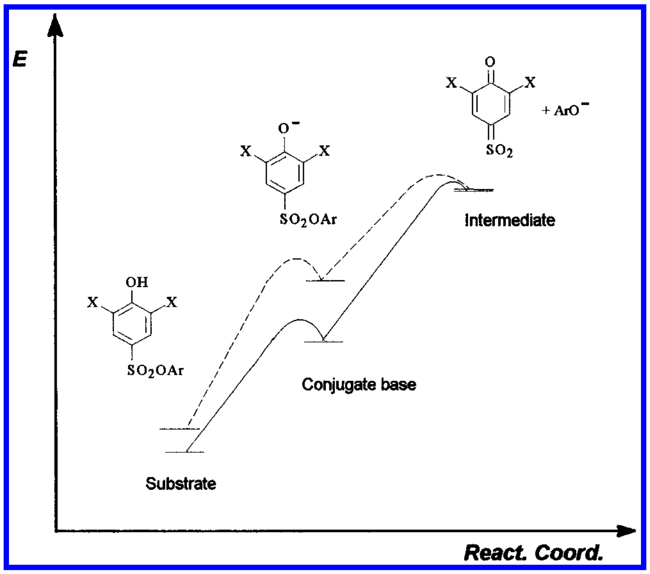


Figure 3. Hypothetical effect of SIS on the energy profiles (lines shown are merely notional).

reaction) will be significantly higher, other things being equal, than that in the absence of SIS. In contrast, it is reasonable to suppose that the differences in the energies of the E1 transition states, as due to SIS, will be negligible, since the negative charge is almost completely transferred onto the leaving group, as suggested by the very large value of the β_{LG} (-1.51) found for the alkaline hydrolysis of *meta*- and *para*-substituted aryl 3,5-dimethyl-4-hydroxybenzenesulfonates.[1c] Therefore, SIS will give rise to a decrease in the free energy of activation for the E1 reaction, matched by an increase in reactivity. However, since SIS is also responsible for an increase in the pK_a values of the 2,6-disubstituted phenols, positive deviation of the three esters from the regression line is probably due to the fact that phenol ionization is affected by SIS less than the E1 step. As a matter of fact, SIS will act also on hindered neutral phenols, raising their free energy although to a minor extent with respect to the corresponding phenoxide ions since solvation of the negative charge of the anion is more important energetically than solvation of the neutral species. In other words it is likely that the effect of SIS on the free energy content is only moderate for the undissociated substrates, rather strong for their conjugate bases, and negligible for the E1 transition states. This is tentatively illustrated in Figure 3, where hypothetical energy profiles in the presence (dashed line) or in the absence (solid line) of SIS are roughly represented.

As Figure 2 shows, two other 3,5-disubstituted esters (namely, the 3,5-difluoro- and the 3-methyl-5-nitro-substituted ones) nicely fit the relationship for the monosubstituted derivatives. In the former case, SIS is expected not to be very effective owing to the small size of the fluorine atoms; as for the latter compound, which is a 2-methyl-6-nitrophenol further substituted in position 4, it is well-known[6] that the acid strength of *o*-nitrophenols is diminished by the presence of a strong intramolecular hydrogen bond between the two groups. Furthermore, it has been suggested[7] that the presence of an additional alkyl substituent adjacent to the OH group further decreases the acidity of the phenol group by reinforcing such a hydrogen bond. It is therefore possible for this ester that, different from the 3,5-disubstituted ones considered before, the expected increase in reactivity is matched by a nearly equal corresponding increase in the pK_a, due partly to SIS and partly to the intramolecular hydrogen bond, so that no overall deviation from the regression line is observed.

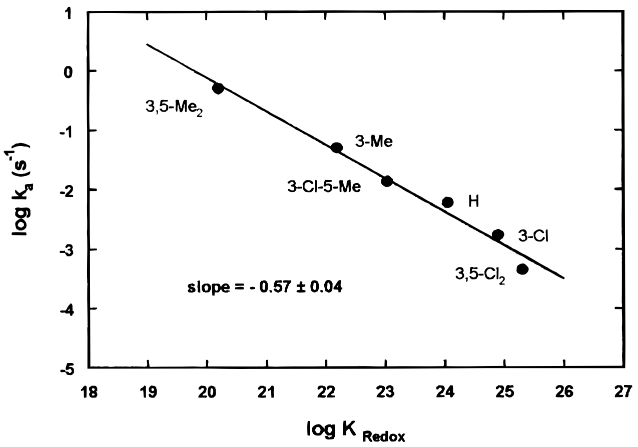
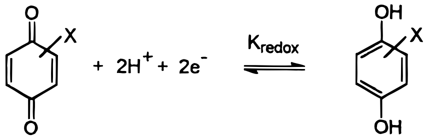


Figure 4. Plot of log k_a *vs* log K_{redox}. K_{redox} values were calculated (see text) from the following E_0 values (in mV) reported in increasing order of reactivity: 748, 736, 711, 681, 656, 597.

As an alternative to these speculations, one might postulate that reactivity–acidity correlations could not be quite satisfactory in this case simply because the chosen standard chemical equilibrium (substrate dissociation) is not well suited to the purpose. However, in a somewhat similar system, *i.e.*, the dissociative hydrolysis of 2′,4′-dinitrophenyl esters of substituted 4-hydroxybenzoic acids, such a Brønsted-type relationship was suggested to hold.[8] In light of the present findings we now believe that resort to additional suitably substituted 4-hydroxybenzoates might reconcile these seemingly conflicting behaviors.

Therefore, we suggest that a better standard for the reaction could be the redox equilibrium shown in eq 5.



(5)

The relevant equilibrium constants K_{redox} were obtained from the relationship $\Delta G° = -RT \ln K_{\mathrm{redox}} = -nFE_0$ making use of the E_0 values (in ethanol) reported in the literature for substituted quinones.[9]

As shown in Figure 4, the log k_a *vs* log K_{redox} plot is remarkably linear, thus suggesting that the transition state of the rate-determining step has an electronic structure resembling that of *p*-quinones[10] and, by inference, that it is similar to the intermediary sulfoquinone.

These results not only confirm that the reaction pathway related to k_a is dissociative in nature but also successfully introduces, to our knowledge for the first time, such a relationship between reactivity and K_{redox}.

---

[6] Arnold, R. T.; Sprung, J. *J. Am. Chem. Soc.* **1939**, *61*, 2475.

[7] Dearden, J. C.; Forbes, W. F. *Can. J. Chem.* **1960**, *38*, 1852.

[8] Thea, S.; Cevasco, G.; Guanti, G.; Kashefi-Naini, N.; Williams, A. *J. Org. Chem.* **1985**, *50*, 1867

[9] Conant, J. B.; Fieser, L. F. *J. Am. Chem. Soc.* **1923**, *45*, 2194. Scrocco, E.; Marmani, G. *Ann. Chim.* **1951**, *41*, 716.

[10] Thea, S.; Williams, A. *Chem. Soc. Rev.* **1986**, *16*, 125.

Experimental Section

General. Starting reagents and solvents were purified and/or distilled before use. Buffer materials were of analytical reagent grade. Water was double distilled and preboiled to free it from dissolved carbon dioxide. The ^{1}H-NMR spectra were recorded with a Varian Gemini 200 spectrometer (200 MHz) with TMS as internal standard and acetone-d_6 or $CDCl_3$ as solvent.

Synthesis. General Procedure for the Synthesis of the Esters. The appropriate phenol was sulfonated with concentrated sulfuric acid at 100 °C for 6 h. After being cooled to 0 °C, the reaction mixture was poured in brine and the sodium salt of the substituted 4-hydroxybenzenesulfonic acid was collected by filtration, dried, and treated with acetic anhydride and pyridine at room temperature overnight. The resulting pyridinium salt of the acetyl derivate was triturated, after removal of the excess of acetic anhydride and pyridine, with an excess of solid PCl_5 and finally poured in water−ice. The acetylated sulfonyl chloride was filtered, dried, and treated with equimolar amounts of 2,4-dinitrophenol and triethylamine in anhydrous methylene chloride for several hours at room temperature. After usual workup of the reaction, the ester was deacetylated by refluxing it for 30 min under nitrogen in a solution of dry hydrochloric acid in absolute ethanol. Finally the solvent was removed, affording the desired product in satisfactory yield. The structures of the final products were confirmed by ^{1}H-NMR spectroscopy. The esters recrystallized to constant melting point from toluene were as follows; mp is given together with analytical data for new esters. **2′,4′-Dinitrophenyl 4-hydroxy-X-benzenesulfonate. X = 3,5-dichloro**: mp 136−7 °C. Anal. Calcd for $C_{12}H_6N_2O_8Cl_2S$: C, 35.2; H, 1.5; N, 6.8. Found: C, 35.0; H, 1.4; N, 6.7. **X = 3,5-difluoro**: mp 137−9 °C. Anal. Calcd for $C_{12}H_6N_2O_8F_2S$: C, 38.3; H, 1.6; N, 7.4. Found: C, 38.4; H, 1.7; N, 7.3. **X = 3-methyl-5-nitro**: mp 127−8 °C. Anal. Calcd for $C_{13}H_9N_3O_{10}S$: C, 39.1; H, 2.3; N, 10.5. Found: C, 39.3; H, 2.2; N, 10.4. **X = 3-chloro**: mp 111−2 °C. Anal. Calcd for $C_{12}H_7N_2O_8ClS$: C, 38.5; H, 1.9; N, 7.5. Found: C, 38.7; H, 1.9; N, 7.3. **X = 3-fluoro**: mp 112−3 °C. Anal. Calcd for $C_{12}H_7N_2O_8FS$: C, 40.2; H, 2.0; N, 7.8. Found: C, 40.4; H, 1.9; N, 7.8. **X = 3-methyl-5-chloro**: mp 131−2 °C. Anal. Calcd for $C_{13}H_9N_2O_8ClS$: C, 40.2; H, 2.3; N, 7.2. Found: C, 40.2; H, 2.4; N, 7.2. **X = 3-methoxy**: mp 138−9 °C. Anal. Calcd for $C_{13}H_{10}N_2O_9S$: C, 42.2; H, 2.7; N, 7.6. Found: C, 42.2; H, 2.8; N, 7.6. **X = H**: mp 149−150 °C. Anal. Calcd for $C_{12}H_8N_2O_8S$: C, 42.4; H, 2.4; N, 8.2. Found: C, 42.5; H, 2.4; N, 8.2. **X = 3-methyl**: mp 144−5 °C. Anal. Calcd for $C_{13}H_{10}N_2O_8S$: C, 44.1; H, 2.8; N, 7.9. Found: C, 43.9; H, 2.8; N, 7.9.

The synthesis of 3,5-dimethyl derivative has been previously reported.[1b]

Methods. Kinetic and other methods including the determination of pK_a of the substrates were described in a previous paper.[11]

JO961024K

---

(11) Cevasco, G.; Thea, S. *J. Org. Chem.* **1994**, *59*, 6274.