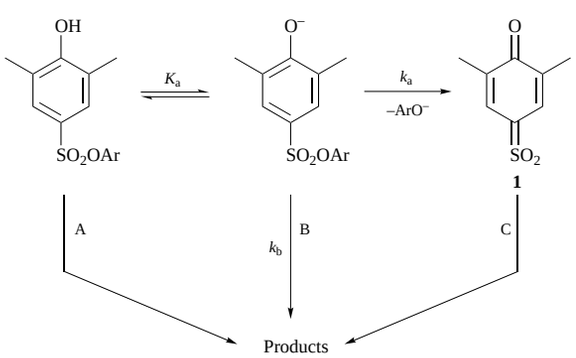
The effect of leaving group variation on reactivity in the dissociative hydrolysis of aryl 3,5-dimethyl-4-hydroxybenzenesulfonates

Giorgio Cevasco [a] **and Sergio Thea** [b]

[a] *CNR, Centro di Studio per la Chimica dei Composti Cicloalifatici ed Aromatici,*† *Via Dodecaneso 31, 16146 Genova, Italy*
[b] *Dipartimento di Chimica, Via Vienna 2, Università di Sassari, 07100 Sassari, Italy*

The hydrolysis of aryl esters of 3,5-dimethyl-4-hydroxybenzenesulfonic acid in moderately to strongly alkaline aqueous solution follows a dissociative pathway with the participation of a sulfoquinone (thioquinone dioxide) intermediate. Brønsted-type correlation between log k_{app} and pK_{LG} and inspection of the effective charge changes involved in the reaction further support the ElcB mechanism. From this and previous studies it appears that aryl esters of hydroxyarenesulfonic acids seem to be more inclined to hydrolyse through dissociative pathways than the corresponding hydroxyarenecarboxylic acids esters.

We have previously shown[1] that the alkaline hydrolysis of 2′,4′-dinitrophenyl 3,5-dimethyl-4-hydroxybenzenesulfonate does not occur through the usual $S_N2(S)$ route (path A in Scheme 1)



Scheme 1

but proceeds *via* an Elcb mechanism with the participation of the sulfoquinone (IUPAC name thioquinone dioxide) intermediate **1** (path C). The bimolecular, associative attack of hydroxide ion onto the conjugate base of the substrate is observed only at high pH (path B). The hydrolysis of some *o*- and *p*-hydroxyarenesulfonate esters of acidic phenols follows similar pathways.[1b]

It is now generally believed that dissociative acyl transfer processes are strongly favoured, over the associative ones, when the ionizable substrates—having suitable pK_a—also possess a good nucleofuge and give rise to a relatively 'stable' intermediate.

In this connection we have investigated in detail the role played by internal nucleophilicity, the driving force for the expulsion of the leaving group from the ionized form of the substrate, which is roughly related to the pK_a of the substrate itself, on the ElcB mechanism in the alkaline hydrolysis of 2′,4′-dinitrophenyl 4-hydroxy-X-benzenesulfonates.[2] The study of the effect of the nucleofugal ability of the leaving phenol (which is related to phenol pK_a) on the hydrolysis of some aryl 3,5-dimethyl-4-hydroxybenzenesulfonates was reported only as a preliminary communication.[3]

Owing to the significance of sulfonyl transfer processes in chemistry as well as in biochemistry, the elucidation of their mechanisms is of primary importance and is the target of a large body of research.[4] Since structure–reactivity correlations (linear free energy relationships) play an important role in the evaluation of the structure of transition states, we now report here new data on the hydrolysis of several aryl 3,5-dimethyl-4-hydroxybenzenesulfonates, as we think they may represent a helpful contribution to the understanding of the mechanism of this reaction.

† Associated to the Istituto Nazionale di Coordinamento per la Chimica dei Sistemi Biologici.

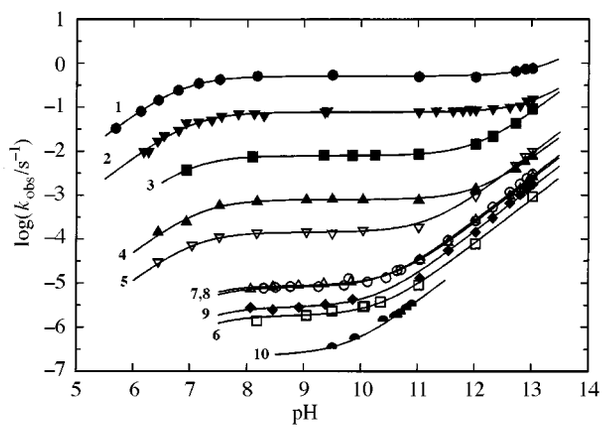


Fig. 1 pH-rate profiles for the hydrolysis of aryl 3,5-dimethyl-4-hydroxybenzenesulfonates in aqueous buffers at 60 °C and ionic strength 1.0 mol dm^{-3} (KCl). The numbering system for identification of substrates is given in the Tables.

Results and discussion

The hydrolyses of aryl 3,5-dimethyl-4-hydroxybenzenesulfonates were carried out in aqueous buffered solutions at 60 °C and were followed spectrophotometrically by monitoring, at the appropriate wavelength, the release of the substituted phenol, the sole products of the reactions being the sulfonic acid and the corresponding phenol. Reaction rates were accurately first order in substrate over at least 90% of the total reaction and were found to follow eqn. (1). Pseudo-first-order rate

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

constants for 3- and 4-nitrophenyl esters were obtained by the method of initial rates (see Experimental section).

The pH dependence of the pseudo-first-order rate constants for the hydrolysis of the esters reported in Table 1 are illustrated in Fig. 1. Table 1 collects experimental conditions and the values of the kinetic parameters obtained from primary kinetic

Table 1 Kinetic data for the hydrolysis of aryl 3,5-dimethyl-4-hydroxybenzenesulfonates in water at 60 °C and ionic strength, μ, 1.0 mol dm^{-3}

Phenoxide leaving group substituents	λ/nm[a]	k_a/s^{-1}	k_b/dm^3 mol^{-1} s^{-1}	N[b]	pH[c]	pK_a[d]
1 2,4-Dinitro[e]	400	0.51 ± 0.02	0.26 ± 0.03	13	5.7–13.0	6.85 ± 0.02[f]
2 2-Nitro-4,6-dichloro	434	(7.79 ± 0.20) × 10^{-2}	(6.66 ± 0.81) × 10^{-2}	25	6.2–13.0	7.01 ± 0.02[f]
3 2,5-Dinitro	445	(7.91 ± 0.13) × 10^{-3}	(7.36 ± 0.26) × 10^{-2}	10	6.9–13.0	7.00 ± 0.01
4 2-Chloro-4-nitro	407	(7.91 ± 0.24) × 10^{-4}	(6.62 ± 0.37) × 10^{-3}	12	6.4–13.0	7.18 ± 0.01
5 2-Nitro-4-chloro	430	(1.44 ± 0.05) × 10^{-4}	(8.94 ± 0.46) × 10^{-3}	12	6.4–13.0	7.07 ± 0.01
6 4-Nitro[g]	400	(1.84 ± 0.11) × 10^{-6}	(8.26 ± 0.57) × 10^{-4}	9	8.2–13.0	7.20 ± 0.01
7 2-Nitro	420	(8.14 ± 0.32) × 10^{-6}	(2.71 ± 0.09) × 10^{-3}	18	8.3–13.0	7.11 ± 0.02
8 2-Nitro-5-methyl	416	(8.80 ± 0.21) × 10^{-6}	(2.41 ± 0.05) × 10^{-3}	12	8.1–13.0	7.11 ± 0.02
9 2-Nitro-4-methyl	436	(2.87 ± 0.19) × 10^{-6}	(1.53 ± 0.08) × 10^{-3}	13	8.1–13.0	7.23 ± 0.01
10 3-Nitro[g]	400	(2.38 ± 0.27) × 10^{-7}	(3.88 ± 0.16) × 10^{-4}	9	9.5–11.0	7.21 ± 0.01

[a] Wavelength for kinetic runs. [b] Number of data points, not including duplicates. [c] pH range employed (see also Fig. 1). [d] Spectroscopic values of ionization constants of the substrates in water at 60 °C (measured at 290 nm), unless otherwise stated. [e] Data taken from ref. 2. [f] Calculated from kinetic data. [g] Initial rates.

Table 2 Apparent second-order rate constants for the hydrolysis of aryl 3,5-dimethyl-4-hydroxybenzenesulfonates in water at 60 °C and ionic strenth, μ, 1.0 mol dm^{-3} (pK_w = 13.017[a])

Phenoxide leaving group substituents	k_{app}/dm^3 mol^{-1} s^{-1}	log k_{app}	pK_{LG}[b]
1 2,4-Dinitro	7.4916 × 10^5	5.875	4.11
2 2-Nitro-4,6-dichloro	7.9167 × 10^4	4.898	4.40[c]
3 2,5-Dinitro	8.2259 × 10^3	3.915	5.22
4 2-Chloro-4-nitro	5.4348 × 10^2	2.735	5.45
5 2-Nitro-4-chloro	1.2746 × 10^2	2.105	6.46
6 4-Nitro	1.2073	0.082	7.15
7 2-Nitro	6.5710	0.818	7.23
8 2-Nitro-5-methyl	4.3801	0.641	7.32[c]
9 2-Nitro-4-methyl	1.7575	0.245	7.40[d]
10 3-Nitro	0.1526	−0.816	8.35

[a] A. Albert and E. P. Serjeant, *Ionization Constants of Acids and Bases*, Methuen & Co Ltd, London, 1962. [b] W. P. Jencks and J. Regestein, *Handbook of Biochemistry and Molecular Biology*, ed. G. Fasman, Chemical Rubber Co., Cleveland, 3rd edn., 1976. [c] This work. [d] M. Rapoport, C. K. Hancock and E. A. Meyers, *J. Am. Chem. Soc.*, 1961, **83**, 3489.

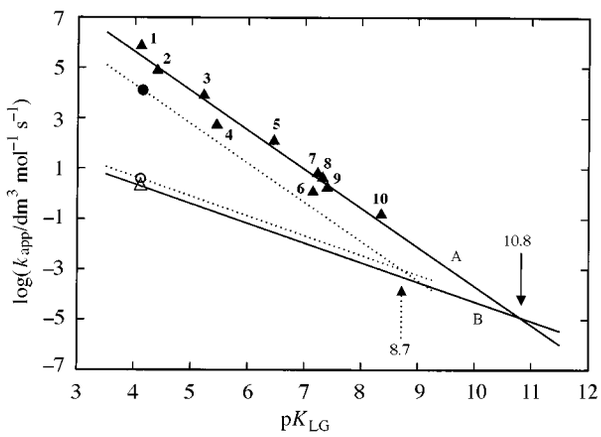


Fig. 2 Brønsted plot for the hydrolysis of aryl 3,5-dimethyl-4-hydroxybenzenesulfonates. The numbering system for identification of substrates is given in the Tables. Line A is calculated from eqn. (4); see the text for line B and dotted lines. The arrows show the calculated changeover points from ElcB to S_N2(S) mechanism (see text).

data (shown in Fig. 1) by iterative nonlinear curve-fitting performed with the Fig. P program.[5]

As previously stated,[1–3] k_a in eqn. (1) is the pseudo-first-order rate constant in the plateau region of the pH–rate profile, a_{H^+} is the activity of the hydrogen ion, and K_a is the ionization constant of the hydroxy group of the substrate, whereas the second order term k_b is related to the bimolecular attack of hydroxide ion on the ionized ester (path B in Scheme 1) and causes an upward curvature, at sufficiently high pH values, of the profile. The k_b term gains more and more weight as the reactivity of the ester decreases and the plateau region of pH is correspondingly reduced, becoming experimentally inaccessible for less reactive esters. Table 1 shows that, as expected, the ionization constants of the esters are scarcely influenced by the leaving group and this means that there should be only a small change in internal nucleophilicity through the series. In Table 2 are reported the values of the apparent second-order rate constants[1–3] for attack of hydroxide ion on neutral substrates ($k_{app} = k_aK_a/K_w$) together with the pK_a of the leaving substituted phenoxides (pK_{LG}).

All the kinetic parameters obey linear Brønsted-type relationships [eqns. (2)–(4)] correlating the pK_{LG} values.

$$\log k_a = (-1.47 \pm 0.08)\ pK_{LG} + (5.45 \pm 0.54) \quad (2)$$

$$\log k_b = (-0.62 \pm 0.07)\ pK_{LG} + (1.72 \pm 0.47) \quad (3)$$

$$\log k_{app} = (-1.55 \pm 0.09)\ pK_{LG} + (11.84 \pm 0.61) \quad (4)$$

These selectivities, now slightly refined, confirm our previous mechanistic proposals.[1a,3] The sensitivity of log k_b toward pK_{LG} is consistent[6] with an associative route (path B in Scheme 1); on the other hand, the large negative values of β_{LG} for both k_a and k_{app} are diagnostic for a ElcB process (the expected range being roughly from −1.5 to −2.4).[7] Furthermore, these very good linear free energy correlations suggest that within the range of substituents employed a single mechanism (*i.e.* the ElcB) holds.

However, we should take into account the possibility that the kinetically indistinguishable, associative mechanism could prevail with poorer leaving groups as previously observed in the hydrolysis of the carbonyl derivatives aryl 4-hydroxybenzoates,[8] 2-hydroxycinnamates[9] and 4-hydroxycinnamates,[10] when the pK_a of the leaving group rose above 6.0–6.5.

In order to check this possibility, an estimation of the (hypothetical) changeover point from the ElcB to the S_N2(S) mechanism can be made as follows. From the known value of the Hammett reaction constant for the alkaline S_N2(S) hydrolysis of phenyl esters of substituted benzenesulfonic acids (ρ = 2.24)[11] and the rate constant for the attack of hydroxide ion onto 2,4-dinitrophenylbenzenesulfonate (k = 27.6 dm^3 mol^{-1} s^{-1} in water at 60 °C),[3] it is possible to calculate, employing the appropriate σ values (−0.81 for *p*-O$^-$, −0.37 for *p*-OH and −0.07 for *m*-Me),[12] the second-order rate constant for the S_N2(S)-type attack of hydroxide ion on 2′,4′-dinitrophenyl 3,5-dimethyl-4-hydroxybenzenesulfonate both neutral (k_{calc} = 2 dm^3 mol^{-1} s^{-1}) and ionised (k'_{calc} = 0.2 dm^3 mol^{-1} s^{-1}, in very good agreement with the experimental value of 0.26 dm^3 mol^{-1} s^{-1}, Table 1).

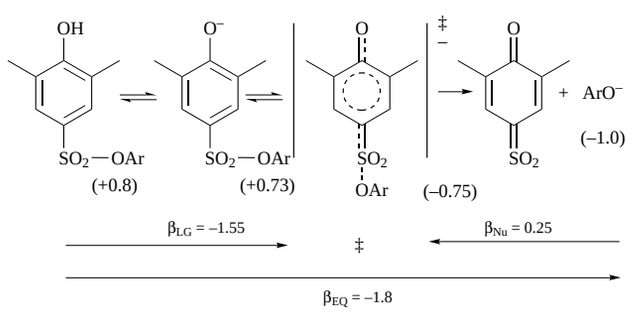
In Fig. 2 the point indicated as Δ represents log k_{calc} and if the line B having slope of −0.78 (this is the reported[6] Brønsted β_{LG} value for the bimolecular attack of hydroxide ion on aryl toluene-*p*-sulfonates, but it is reasonable to employ such a value for aryl benzenesulfonates as well) is drawn through this point,

it will go across the line A, calculated from eqn. 4, at pK_{LG} = 10.8 which is, therefore, the break-point (indicated by the solid arrow in Fig. 2). This implies that the change in mechanism, within this series, would be experimentally inaccessible since substituted phenols having a pK_a greater than 10.8 are not common. Resorting to poorer leaving groups, such as alkoxides, will not be useful since sulfonate esters of aliphatic alcohols usually react with C–O fission.[13]

It could seem surprising that in the present case the break-point lies at a pK_{LG} value considerably higher than those for carbonyl derivatives. However, it must be taken into account that in the system under scrutiny the acyl moiety bears two additional methyl groups and that the effect on rate of substituent is quite large, as we have recently shown.[2] Allowance for this can be made as follows: if the dotted line having slope −1.55 (this is again the β_{LG} value for the hydrolysis of aryl 4-hydroxy-3,5-dimethylbenzenesulfonates but it can be applied to aryl 4-hydroxybenzenesulfonates) is drawn through the point corresponding to log k_{app} for 2,4-dinitrophenyl 4′-hydroxybenzenesulfonate (4.139,[2] solid circle in Fig. 2) and another dotted line of slope −0.78 (see above) is drawn through the point referring to log k_{calc} for 2,4-dinitrophenyl 4′-hydroxybenzenesulfonate (0.613, open circle in Fig. 2; obtained through the procedure described before for the dimethyl derivative) then the intersection between these lines, which lies at pK_{LG} *ca.* 8.7, will represent the changeover point from ElcB to $S_N2(S)$ mechanism for the hydrolysis of aryl 4-hydrobenzenesulfonates.

However, such a break-point still occurs at a pK_{LG} value higher than those related to carbonyl derivatives, indicating that, as far as the influence on mechanism of the leaving group ability is concerned, aryl sulfonates seem to be more prone to react *via* the dissociative pathway (in juxtaposition with the associative one) than the corresponding carboxylates. This inference, which agrees with the well known fact that the carbonyl carbon atom undergoes nucleophilic attack considerably more readily than the sulfonyl sulfur,[11] will be thoroughly discussed in a forthcoming paper.

The dissociative nature of the process under investigation is also supported by the evaluation of the effective charge[14] on the leaving aryl oxygen in the transition state of the rate-limiting step. The effective charge changes involved in this reaction are depicted in Scheme 2. Since the overall change for an aryl



Scheme 2

sulfonate is −1.8,[14a] we can calculate, from the β_{LG} value determined in this work, the effective charge residing on the oxygen in the transition state (−1.55 + 0.8 = −0.75) which is indicative of extensive bond fission. In terms of Leffler's index,[14a] the value of α (0.86) supports this conclusion as well.

Experimental

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 [$^2H_6$]acetone or $CDCl_3$ as solvent.

Synthesis

General procedure for the synthesis of the esters. 2,6-Dimethylphenol was sulfonated with concentrated sulfuric acid at 100 °C for 6 h. After cooling to 0 °C the reaction mixture was poured into brine and the sodium salt of the 3,5-dimethyl-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 derivative was triturated, after removal of the excess of acetic anhydride and pyridine, with an excess of solid PCl_5 and finally poured into ice–water. The acetylated sulfonyl chloride was filtered, dried and treated with equimolar amounts of the appropriate substituted phenol and triethylamine in anhydrous methylene chloride for several hours at room temperature. After usual work-up 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 mp were as follows; mp is given together with analytical data.

Aryl 3,5-dimethyl-4-hydroxybenzenesulfonate. Aryl = 4-chloro-2-nitrophenyl. Mp 173–174 °C (from ethanol) (Found: C, 47.1; H, 3.4; N, 3.9. Calc. for $C_{14}H_{12}NO_6ClS$: C, 47.0; H, 3.4; N, 3.9%).

Aryl = 2-chloro-4-nitrophenyl. Mp 145–146 °C (from ethanol) (Found: C, 471; H, 3.4; N, 3.9. Calc. for $C_{14}H_{12}NO_6ClS$: C, 47.0; H, 3.4; N, 3.9%).

Aryl = 4-nitrophenyl. Mp 148–149 °C (from benzene) (Found: C, 52.3; H, 4.0; N, 4.5. Calc. for $C_{14}H_{13}NO_6S$: C, 52.0; H, 4.1; N, 4.3%).

Aryl = 3-nitrophenyl. Mp 145–146 °C (from benzene) (Found: C, 52.0; H, 4.0; N, 4.4. Calc. for $C_{14}H_{13}NO_6S$: C, 52.0; H, 4.1; N, 4.3%).

Aryl = 2,5-dinitrophenyl. Mp 162–163 °C (from toluene) (Found: C, 45.6; H, 3.2; N, 7.4. Calc. for $C_{14}H_{12}N_2O_8S$: C, 45.7; H, 3.3; N, 7.6%).

Aryl = 4-methyl-2-nitrophenyl. Mp 220–221 °C (from toluene) (Found: C, 54.0; H, 4.5; N, 3.9. Calc. for $C_{15}H_{15}NO_6S$: C, 53.4; H, 4.5; N, 4.1%).

Aryl = 5-methyl-2-nitrophenyl. Mp 134–135 °C (from toluene) (Found: C, 53.4; H, 4.4; N, 4.3. Calc. for $C_{15}H_{15}NO_6S$: C, 53.4; H, 4.5; N, 4.1%).

Aryl = 4,6-dichloro-2-nitrophenyl. Mp 174–175 °C (from toluene) (Found: C, 43.1; H, 2.8; N, 3.3. Calc. for $C_{14}H_{11}NO_6Cl_2S$: C, 42.9; H, 2.8; N, 3.6%). The synthesis of 2,4-dinitrophenyl ester 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.[10] The rate constants for the hydrolysis of 3- and 4-nitrophenyl esters were obtained by initial rates: they were measured for each run up to *ca.* 10% of the total reaction and were converted to pseudo-first-order rate constants using infinity values calculated from the known extinction coefficients of the products.

Ionization constant of substituted phenol. The spectrophotometric determinations of pK_a of 5-methyl-2-nitrophenol (7.32 ± 0.01) and 4,6-dichloro-2-nitrophenol (4.40 ± 0.02) were carried out in water 25 °C respectively in phosphate buffers at 416 nm and in acetate buffers at 434 nm.

References

1 (*a*) S. Thea, G. Guanti, A. R. Hopkins and A. Williams, *J. Am. Chem. Soc.*, 1982, **104**, 1128; (*b*) S. Thea, G. Cevasco, G. Guanti,

A. R. Hopkins, N. Kashefi-Naini and A. Williams, *J. Org. Chem.*, 1985, **50**, 2158.
2 G. Cevasco and S. Thea, *J. Org. Chem.*, 1996, **60**, 6814.
3 S. Thea, G. Cevasco and G. Guanti, *Gazz. Chim. Ital.*, 1987, **117**, 705.
4 I. M. Gordon, H. Maskill and M. F. Ruasse, *Chem. Soc. Rev.*, 1989, **18**, 123.
5 Fig. P® from Biosoft, Cambridge, UK, 1991.
6 V. M. Maremae and V. Palm, *Reakts. Sposobnost. Org. Soedin.*, 1964, **1**, 85. See also O. Exner, in *Advances in Linear Free Energy Relationships*, eds. N. B. Chapman and J. Shorter, Plenum Press, London, 1972, p.23.
7 M. B. Davy, K. T. Douglas, J. S. Loran, A. Steltner and A. Williams, *J. Am. Chem. Soc.*, 1977, **99**, 1196; S. Thea, G. Guanti, A. R. Hopkins and A. Williams, *J. Org. Chem.*, 1985, **50**, 5592.
8 G. Cevasco, G. Guanti, A. R. Hopkins, S. Thea and A. Williams, *J. Org. Chem.*, 1985, **50**, 479.
9 G. Cevasco and S. Thea, *J. Org. Chem.*, 1995, **60**, 70.
10 G. Cevasco and S. Thea, *J. Org. Chem.*, 1994, **59**, 6274.
11 R. V. Vizgert, *Russ. Chem. Rev.*, 1963, **32**, 1.
12 C. Hansch, A. Leo and R. W. Taft, *Chem. Rev.*, 1991, **91**, 165.
13 E. T. Kaiser, in *Organic Chemistry of Sulfur*, ed. S. Oae, Plenum Press, New York, 1977, p. 650.
14 (*a*) A. Williams, *Acc. Chem. Res.*, 1984, **17**, 425; (*b*) S. Thea and A. Williams, *Chem. Soc. Rev.*, 1986, **15**, 125.

Paper 7/03645K
Received 27*th May* 1997
Accepted 2*nd July* 1997