Kinetic Studies of the Effect of Substituents on the Strength of the Internal Hydrogen Bond in Salicylate Ions

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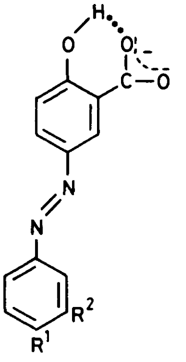
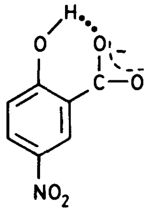
Kinetic and equilibrium results have been obtained for removal of the hydrogen-bonded proton from substituted salicylate ions by hydroxide ion and buffer bases in 50% (v/v) Me_2SO-H_2O. From the values of the rate coefficients for proton removal it is concluded that the hydrogen bond is strengthened by electron-releasing substituents and by the change from aqueous solution to 50% (v/v) Me_2SO-H_2O. Curvature in the plots of rate against hydroxide ion concentration is observed above 0.02 mol dm^{-3} and this may mean that opening of the hydrogen bond is partially rate-limiting under these conditions.

The mechanism of proton-transfer from 5-(3-nitrophenylazo)salicylate ion (**2**) to hydroxide ion and buffers in aqueous solution has previously been shown[1] to involve reversible opening of the intramolecular hydrogen bond followed by proton removal from a low concentration of the open form. It was considered that the proton-transfer step occurred with a diffusion-controlled rate coefficient but nevertheless was rate-limiting because unimolecular closing of the hydrogen bond occurred more rapidly. Catalytic coefficients for the reaction of 5-(3-nitrophenylazo)salicylate ion with a series of substituted amines were therefore found to be independent of the strength of the amine base. It has previously been argued[2] that studies of proton-transfer from a series of substituted hydrogen-bonded acids would provide information about the effect of substituents on the value of the equilibrium constant between open and closed forms of the hydrogen-bonded acid. The substituted 5-(phenylazo)salicylate ions (**1**)—(**5**) provide a suitable series because the substituents are sufficiently far removed from the reaction site that steric effects are unimportant. Rate coefficients for proton removal by hydroxide ion have been measured in 50% (v/v) Me_2SO-H_2O using the temperature-jump technique. In this solvent the reaction occurs more slowly than in aqueous solution and a wider range of reactivity can be covered. The reactions of 5-(3-nitrophenylazo)salicylate ion (**2**) with benzimidazole in 50% (v/v) Me_2SO-H_2O and with indazole in 70% (v/v) Me_2SO-H_2O have also been studied. In addition the reaction of 5-nitrosalicylate ion (**6**) with hydroxide ion has been studied in 30% (v/v) dioxane-H_2O.



(**1**) $R^1 = H, R^2 = H$
(**2**) $R^1 = H, R^2 = NO_2$
(**3**) $R^1 = NO_2, R^2 = H$
(**4**) $R^1 = OMe, R^2 = H$
(**5**) $R^1 = NH_2, R^2 = H$



(**6**)

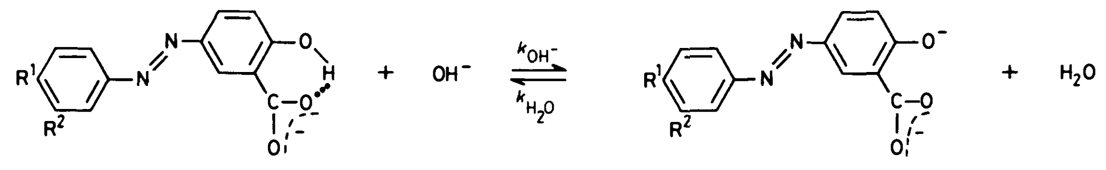
Experimental

Materials.—Commercial samples of (**2**), (**5**), and (**6**) were used. The preparations of (**1**), (**3**), and (**4**) were achieved by reaction of the appropriate diazonium salt with salicylic acid. The products were recrystallised from ethanol and characterised by their n.m.r. spectra taken in $(CD_3)_2SO$: (**1**) had m.p. 201—207 °C and δ(250 MHz) 11.8 (vbr s, *ca.* 2 H, COOH and OH), 8.37 (d, 1 H, 6-H), 8.10 (dd, 1 H, 4-H), 7.91—7.85 (m, 2 H, 2'- and 6'-H), 7.63—7.52 (m, 3 H, 3'-, 4'-, and 5'-H), and 7.17 (d, 1 H, 3-H); (**3**) m.p. 239—242 °C, δ(250 MHz) 12.5 (vbr s, *ca.* 1 H, COOH), 8.38 (d, 2 H, 3'- and 5'-H), 8.35 (s, 1 H, 6-H), 7.98 (d, 2 H, 2'- and 6'-H), 7.88 (d, 1 H, 4-H), and 6.76 (d, 1 H, 3-H); (**4**) m.p. 208—209 °C and δ(60 MHz) 10.5 (vbr s, *ca.* 2 H, COOH and OH), 8.37 (d, 1 H, 6-H), 8.28—7.88 (m, 3 H, 4-, 2'-, and 6'-H), 7.33—7.18 (m, 3 H, 3-, 3'-, and 5'-H), and 3.93 (s, 3 H, OMe).

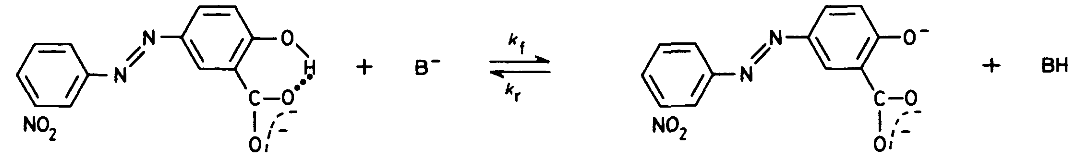
Solutions for kinetic and equilibrium measurements were prepared from double distilled water and A.R. Me_2SO. For studies in dioxane–water, dioxane (A.R.) was refluxed over sodium and distilled. Measurements were made in the presence of tetramethylammonium hydroxide and in buffers prepared by partial neutralisation of benzimidazole or indazole with tetramethylammonium hydroxide. The ionic strength of the solutions was maintained constant by addition of tetramethylammonium chloride which had been dried under vacuum.

Kinetic and Equilibrium Studies.—The reactions between the salicylate ions (**1**)—(**5**) and hydroxide ion, equation (1), and between 5-(3-nitrophenylazo)salicylate ion (**2**) and benzimidazole anion (B^-), equation (2), were studied in 50% (v/v) Me_2SO-H_2O. The reaction of (**6**) with hydroxide ion was studied in 30% (v/v) dioxane–water and the reaction of (**2**) with indazole anion (B^-) was studied in 70% (v/v) Me_2SO-H_2O. The equilibria and the kinetics of the equilibration were observed spectrophotometrically at 288 K and ionic strength 0.1 mol dm^{-3}. The most suitable wavelength for observation was usually *ca.* 500 nm, except for (**6**) which was studied at 420 nm. The salicylate ions were present at low concentrations (*ca.* 3×10^{-5} mol dm^{-3}) in comparison with hydroxide ion or buffer. Spectra of the fully dissociated species were obtained in the presence of 0.1 mol dm^{-3} hydroxide ion and the monoanions were generated in a 1:1 chlorophenol buffer in the appropriate solvent mixture. Values of the equilibrium constant for reaction (1), K_{OH^-} = [dianion]/[monoanion][OH^-], and reaction (2), K = [dianion][BH]/[monoanion][B^-], are given in the Table.

Relaxation times (τ) for equilibration of reactions (1) and (2) at 288 K were measured using the temperature-jump method. A temperature perturbation of 1.7 K was employed and depending on the hydroxide ion and buffer concentration the



(1)



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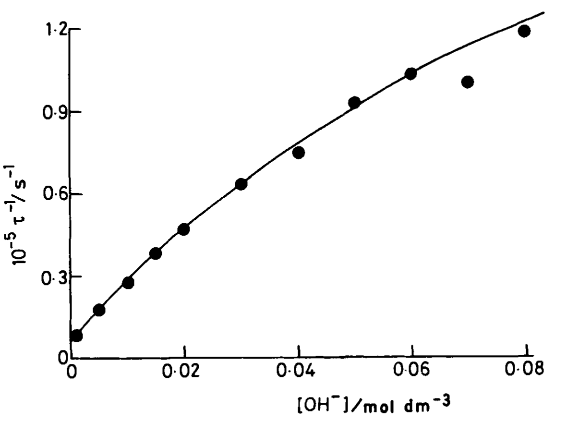


Figure 1. Dependence of reciprocal relaxation time on hydroxide ion concentration for proton-transfer from 5-phenylazosalicylate ion in 50% (v/v) Me_2SO-H_2O. The line is a plot of equation (8) using the values k_1 3.3 × 10^5 s^{-1} and k_{-1}/k_2 0.141 mol dm^{-3}

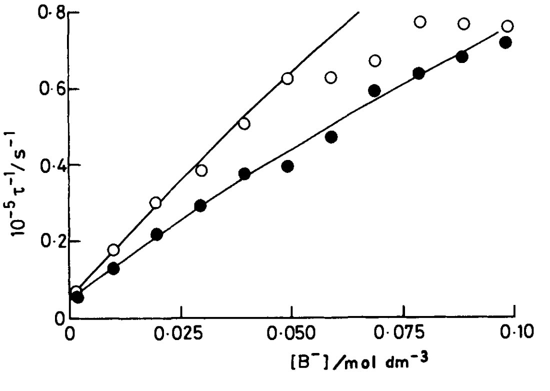


Figure 2. Dependence of reciprocal relaxation time on buffer concentration for 5-(3-nitrophenylazo)salicylate ion in 50% (v/v) Me_2SO-H_2O at two benzimidazole buffer ratios $r = [B^-]/[BH]$; r = 0.973 (solid circles) and r = 0.492 (open circles). The lines are plots of equation (7) using k_1 2.0 × 10^5 s^{-1} and k_{-1}/k_2 0.5 mol dm^{-3}

relaxations occurred with half-lives in the range 5—1 000 μs. Each relaxation time was taken as the average of at least five determinations. For the reaction of 5-nitrosalicylate ion in 30% (v/v) dioxane–H_2O the magnitude of the temperature-jump was 2.5 K but the initial temperature was adjusted so that the reaction temperature was 288 K.

Results and Discussion

The intramolecular hydrogen bond in the monoanion of salicyclic acid causes the first ionisation to occur at lower pK (2.97)[3] and the second dissociation to occur at higher pK (13.59)[3] than observed for carboxy groups and hydroxy groups which do not take part in an internal hydrogen bond. In choosing substituted salicylate ions for which the kinetics of proton removal from the hydrogen bond can be studied using the temperature-jump technique, it is necessary to find species which have lower pK than 13.59. In order to be able to observe a measureable relaxation amplitude the reaction must be studied at hydroxide ion concentrations at which the salicylate ion and the dissociated species are both present in significant amounts. For salicylate ion at such hydroxide ion concentrations, the relaxation occurs with reciprocal relaxation times *ca.* 10^5—10^7 s^{-1} which are too rapid for our technique. For this reason the species studied in this work carry phenylazo groups which have the effect of reducing the hydroxide ion concentration at which half-dissociation occurs so that the reciprocal relaxation times are reduced into the range 10^3—10^5 s^{-1}. In aqueous solution the second dissociation of 5-phenylazosalicylate ion occurs[4] with pK 11.64 and for 5-nitrosalicylate ion pK 10.33 is observed.[3]

The concentration dependence of the reciprocal relaxation time for equilibria (1) and (2) would be expected to follow equations (3) and (4), respectively. In equation (4) r is the buffer

$$\tau^{-1} = k_{OH^-}[OH^-] + k_{H_2O} \qquad (3)$$

$$\tau^{-1} = k_f[B^-] + k_r[BH] = k_f(1 + 1/Kr)[B^-] \qquad (4)$$

ratio $[B^-]/[BH]$ and it is assumed that in buffer solutions the reaction with hydroxide ion makes only a small contribution to the rate. Experimental results for the reaction of 5-phenylazosalicylate ion (**1**) with hydroxide ion are shown in Figure 1. At hydroxide ion concentrations below *ca.* 0.02 mol dm^{-3} the expected linear dependence is observed. For (**1**), (**4**), (**5**), and (**6**) the values of the intercepts k_{H_2O} when combined with the values of the gradients in the linear region are in good agreement with the separately measured values of the equilibrium constants for the reactions. In the case of (**2**) and (**3**) the intercepts were too small to be determined accurately, but this in itself is compatible with the high values of the equilibrium constants for these reactions. The values of k_{OH^-} and k_{H_2O} obtained for (**1**)—(**6**) are given in the Table. The departure of the plots from linearity at high hydroxide ion concentrations is discussed below.

Results for the reaction of 5-(3-nitrophenylazo)salicylate ion (**2**) in 70% (v/v) Me_2SO-H_2O with indazole buffer up to concentrations of 0.1 mol dm^{-3} were fitted by equation (4). At two buffer ratios, values of k_f calculated from the gradients of

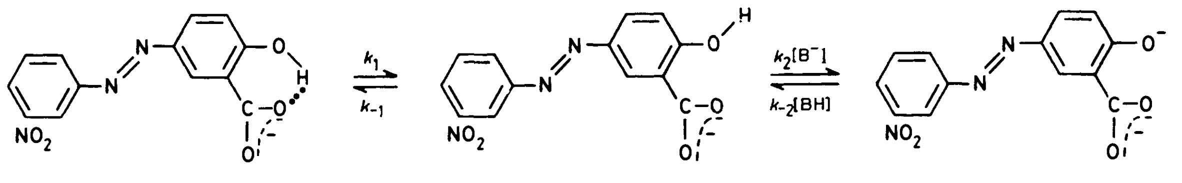
Table. Equilibrium and kinetic results for substituted salicylate ions

HA^-	Solvent	Base	K_{OH^-}/ $dm^3\ mol^{-1}$	$10^{-6}\ k_{OH^-}$/ $dm^3\ mol^{-1}\ s^{-1}$	$10^{-4}\ k_{H_2O}$/ s^{-1}	K	$10^{-5}\ k_f$/ $dm^3\ mol^{-1}\ s^{-1}$	$10^{-5}\ k_r$/ $dm^3\ mol^{-1}\ s^{-1}$
(1)	50% (v/v) Me_2SO–H_2O[a]	OH^-	293 ± 20	2.01 ± 0.1	0.69 ± 0.05			
(2)	H_2O[b]	OH^-	1 900 ± 200	24.0 ± 2	1.1 ± 0.2			
(2)	50% (v/v) Me_2SO–H_2O[a]	OH^-	814 ± 70	2.17 ± 0.1	0.27 ± 0.05			
(2)	50% (v/v) Me_2SO–H_2O[a]	Benzimidazole				0.91 ± 0.1	3.8 ± 0.2	4.2 ± 0.2
(2)	70% (v/v) Me_2SO–H_2O[a]	Indazole				1.49 ± 0.07	0.75 ± 0.05	0.50 ± 0.03
(3)	50% (v/v) Me_2SO–H_2O[a]	OH^-	1 636 ± 100	3.0 ± 0.1	0.18 ± 0.01			
(4)	50% (v/v) Me_2SO–H_2O[a]	OH^-	166.6 ± 5	1.75 ± 0.1	1.05 ± 0.05			
(5)	50% (v/v) Me_2SO–H_2O[a]	OH^-	77 ± 7	1.51 ± 0.2	2.3 ± 0.2			
(6)	30% (v/v) Dioxane–H_2O[a]	OH^-	1 950 ± 250	6.5 ± 0.5	0.33 ± 0.08			

[a] Temperature 288 K, ionic strength 0.1 mol dm^{-3}. [b] Temperature 279.5 K, ionic strength 0.5 mol dm^{-3}, previous work.[1]

the accurately linear plots of τ^{-1} against $[B^-]$ using the value of K determined in separate equilibrium measurements were the same within experimental error and the values of k_f and k_r are given in the Table. The results for **(2)** in 50% (v/v) Me_2SO–H_2O in the presence of benzimidazole buffers at two buffer ratios are shown in Figure 2. The data at concentrations of $[B^-]$ below 0.02 mol dm^{-3} were treated in the same way as the results for the reaction in the presence of indazole buffers and consistent values of k_f and k_r were obtained. The results are given in the Table. The curvature in the plots in Figure 2 observed at high buffer concentrations will be considered below.

The mechanism proposed for the reaction of 5-(3-nitrophenylazo)salicylate ion with buffers and hydroxide ion in aqueous solution is shown in equation (5) in which B^- represents buffer species or hydroxide ion.[1] The expressions in equation (6) are obtained for the overall rate coefficients (k_f and k_r for reaction with buffer and k_{OH^-} and k_{H_2O} for reaction with hydroxide ion) on the assumption that the open intermediate is present in low concentration and the rate of closing of the hydrogen bond is greater than the rate of the proton-transfer step, $k_{-1} > k_2[B^-]$. For the reaction of 5-(3-nitrophenylazo)salicylate ion in 50% (v/v) Me_2SO–H_2O the results k_{OH^-} 2.17×10^6 $dm^3\ mol^{-1}\ s^{-1}$ for reaction with hydroxide ion and k_f 0.38×10^6 $dm^3\ mol^{-1}\ s^{-1}$ for reaction with benzimidazole are obtained. The basicities of hydroxide ion and benzimidazole under these conditions differ by a factor of *ca.* 900 as shown by the difference in K_{OH^-} and K for the equilibria involving **(2)** (see Table). The much smaller difference in the rate coefficients for proton-transfer is to be expected on the basis that the proton-transfer step in equation (5) is encounter-controlled and that the diffusion limit for reaction with hydroxide ion will be higher than for reaction with benzimidazole.



(5)

$$k_f \text{ or } k_{OH^-} = (k_1/k_{-1})k_2 \quad \text{and} \quad k_r \text{ or } k_{H_2O} = k_{-2} \tag{6}$$

If it is assumed that the mechanism in equation (5) applies for the reaction of salicylate ions **(1)**—**(5)** in 50% (v/v) Me_2SO–H_2O, the values of k_{OH^-} can be used to assess the effect of substituents on the strength of the internal hydrogen bond. The values of the equilibrium constants (K_{OH^-}/$dm^3\ mol^{-1}$) for dissociation of the salicylate ions are increased by electron-withdrawing substituents which stabilise the dianions. The results are well correlated by the Hammett σ values[5] for the substituents; NH_2: σ_p −0.57, K_{OH^-} 77; MeO: σ_p −0.28, K_{OH^-} 166.6; H: σ 0.00, K_{OH^-} 293; 3-NO_2: σ_m 0.74, K_{OH^-} 814; 4-NO_2: σ_p 0.78, K_{OH^-} 1 636. The values of K_{OH^-} are fairly insensitive to the substituents (ρ = 0.92) because the substitution is remote from the reaction site. The values of k_{OH^-} increase along the series 4-NH_2 < 4-MeO < H < 3-NO_2 < 4-NO_2, with a two-fold overall change. The variation in k_{OH^-} reflects the increase in the value of k_1/k_{-1} because the value of k_2 is diffusion-limited and will be independent of the substituent. The effect on k_1/k_{-1} and on the strength of the hydrogen bond will be dominated by the interaction of the substituent with the negative charge on the carboxylate group. Thus electron-withdrawing substituents reduce the basicity of the carboxylate group, weaken the hydrogen bond, and increase the value of k_1/k_{-1}. The lower value of k_{OH^-} for 5-nitrosalicylate ion compared with 5-phenylazosalicylate ion is also accounted for in this way: $\sigma_m(NO_2)$ 0.74 and $\sigma_m(PhN_2)$ 0.29.

The change in solvent from aqueous solution to 50% (v/v) Me_2SO–H_2O reduces the value of k_{OH^-} for 5-(3-nitrophenylazo)salicylate ion **(2)** at least 10-fold.* A similar solvent effect has been observed for proton removal from the internally hydrogen-bonded monoanion of cyclopropane-1,1-dicarboxylic acid.[6] The reduction in k_{OH^-} could be due to a strengthening of the intramolecular hydrogen bond in 50% (v/v) Me_2SO–H_2O or to a reduction in the rate of the encounter-controlled deprotonation[7] of the open form of the salicylate ion and both effects can be accounted for from the known solvent properties of Me_2SO.[8,9] The former explanation is preferred.

The kinetic data for the substituted salicylate ions in 50% (v/v) Me_2SO–H_2O at hydroxide ion and buffer concentrations below *ca.* 0.02 mol dm^{-3} are well fitted by the mechanism in equation (5) and the expressions in equation (6). However, at higher concentrations the dependence of rate on hydroxide ion

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* The ratio of rate coefficients is 11.1, but this is likely to be an underestimate since the value in aqueous solution refers to a lower temperature (279.5 K) than the value in 50% (v/v) Me_2SO–H_2O.

and buffer concentration is curved. Typical results are shown in Figures 1 and 2. Similar though more pronounced curvature has been observed previously for proton-transfer from other intramolecularly hydrogen-bonded acids to buffer species[10] in 70% (v/v) Me_2SO–H_2O and has been interpreted in terms of a mechanism similar to that in equation (5). The curvature was considered to arise because at high buffer concentration the rate of the proton-transfer step ($k_2[B^-]$) becomes comparable with the rate at which the open species reverts to the closed form (k_{-1}). The expressions in equation (6) were derived in the assumption that the proton-transfer was rate-limiting ($k_2[B^-] < k_{-1}$). If this condition is not satisfied the expressions in equations (7) and (8) are obtained for reaction with buffer and hydroxide ion respectively. Equations (7) and (8) predict that the rate becomes independent of buffer and

$$\tau^{-1} = k_1(1 + 1/Kr)[B^-]/(k_{-1}/k_2 + [B^-]) \qquad (7)$$

$$\tau^{-1} = k_1(1/K_{OH^-} + [OH^-])/(k_{-1}/k_2 + [OH^-]) \qquad (8)$$

hydroxide ion concentration at high concentrations and opening of the intramolecular hydrogen bond becomes rate-limiting. In the present work the reaction cannot be studied at sufficiently high hydroxide ion concentrations to test this prediction fully. Although the reactions in the presence of buffer could have been studied at higher concentrations this was not attempted because it is known[11] that in 70% (v/v) Me_2SO–H_2O buffer association becomes important at concentrations above 0.1 mol dm^{-3}. Kinetic studies in Me_2SO–H_2O mixtures appear to be more susceptible to buffer association and other electrolyte effects[12] than studies in aqueous solution and it is possible that such effects could be responsible for the curvature in Figures 1 and 2. To find out whether equations (7) and (8) provide a satisfactory explanation for the observed curvature we attempted to fit the kinetic data for 5-(3-nitrophenylazo)salicylate ion in benzimidazole buffers to equation (7) at two buffer ratios ($r = 0.492$ and $r = 0.973$) using the separately measured value of the equilibrium constant for the reaction ($K = 0.91$) and best-fit values of k_1 and k_{-1}/k_2. A small intercept in the plots of τ^{-1} against buffer concentration was assumed to correspond to reaction with the low concentration of hydroxide ion present in these solutions. Plots of equation (7) using k_1 2.0 × 10^5 s^{-1} and k_{-1}/k_2 0.5 mol dm^{-3} are shown as the solid lines in Figure 2. The fit to the experimental data at $r = 0.973$ is excellent but at $r = 0.492$ the fit at high buffer concentrations is poor. The data for salicylate ions (**1**)—(**5**) in the presence of hydroxide ion were fitted by means of equation (8). Since the amount of curvature observed was quite small the fits were not very sensitive to the particular values of k_1 and k_{-1}/k_2. The solid line in Figure 2 was obtained with k_1 3.3 × 10^5 s^{-1} and k_{-1}/k_2 0.141 mol dm^{-3}. The values required to fit the experimental results for the other salicylate ions were in the range k_1 2—11 × 10^5 s^{-1} and k_1/k_2 0.13—0.35 mol dm^{-3} depending on the substituent. These results are close to those which have been obtained for other intramolecularly hydrogen-bonded acids.[10] However, in view of the small amount of curvature observed and the consequent uncertainty in the fitted values of k_1 and k_{-1}/k_2 the results will not be discussed in detail at this stage.

In future work we will attempt to find conditions where the curved dependence of reciprocal relaxation time on hydroxide ion concentration can be analysed more accurately. It is necessary to find conditions where the balance between k_{-1} and $k_2[OH^-]$ occurs at lower hydroxide ion concentrations. The value of k_{-1} will depend on the strength of the intramolecular hydrogen bond. The hydrogen-bond acceptor and anion-solvating properties of the medium will be important and the reaction of salicylate ions in different solvent mixtures will be investigated. Modifications to the strength of the internal hydrogen bond can be achieved by the introduction of suitable substituents into the salicylate ion.

Acknowledgements

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