Journal of Chromatography, 483 (1989) 390–393
Elsevier Science Publishers B.V., Amsterdam — Printed in The Netherlands

CHROM. 21 909

Note

Correlation between chromatography and ^{1}H NMR parameters in sterically substituted phenols

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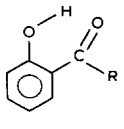
(Received July 4th, 1989)

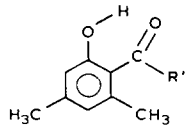
It is well established from previous work[1–3] that the formation of a hydrogen bond between the hydroxy proton in substituted phenols and a proton acceptor (oxygen, nitrogen, etc.) causes the chemical shift of the hydroxy proton (δ_{OH}) to move to a higher frequency (low field) relative to its position in the unassociated phenols[1–4]. Thus δ_{OH} in NMR spectroscopy can be used as a probe for measuring inter- and intramolecular hydrogen bonding strength[5–7].

The chromatography of substituted phenols has received some attention. Freedman and Charlier[8] studied the effect of substituting an *o*-alkyl group in phenol on the order of elution of the isomers. Hrivňák *et al.*[9] studied the gas chromatographic behaviour of nitrophenols and anisoles, and Habboush and Al-Bazi[10] used chromatographic data to study the strength of hydrogen bonds in *o*-halophenols. Clifford and Watking[11] studied the steric effect on hydrogen bonding in alkyl-substituted dinitrophenols and anisoles.

In this investigation, six substituted phenols were studied, three of which have methyl substituents in the 3- and 5-positions (**4–6**):



R



R'

1	methyl	**4**	methyl
2	phenyl	**5**	phenyl
3	mesityl	**6**	mesityl

The aim of this work was to investigate the presence of a qualitative correlation between chromatographic and ^{1}H NMR data for these systems.

0021-9673/89/$03.50

EXPERIMENTAL

Compounds **1** and **2** were obtained from Aldrich and **4** and **5** were prepared as described elsewhere[12]. Other compounds were prepared as follows.

2-Mesitoylphenol (**3**) was prepared from 2-methoxybenzoyl chloride (8.53 g, 0.15 mol), mesitylene (80 ml) and anhydrous aluminium chloride (19.99 g, 0.15 mol) in benzene as described for 2-hydroxyacetophenone[12]. The product was obtained as white crystals (7.8 g), m.p. 94–95°C. Found, C 79.72, H 6.65; $C_{16}H_{16}O_2$ requires C 79.96, H 6.71%. λ_{max} at 1646 cm^{-1} (C=O) and 3240 cm^{-1} (OH). ^1H NMR signals in C^2H-Cl_3 at 2.1 (2,6-dimethyl), 2.32 (4-CH_3), 6.8–7.44 (aromatic) and 11.1 ppm (OH).

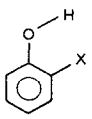
To prepare 2-mesitoyl-3,5-dimethylphenol (**6**), a solution of 3,5-dimethylphenol (6.1 g, 0.05 mol) in nitromethane (20 ml) was added slowly (10 min) at 25°C to a stirred mixture of mesitoyl chloride (9.13 g, 0.05 mol) and anhydrous aluminium chloride (6.66 g, 0.05 mol) in nitromethane (20 ml). The mixture was stirred continuously for 2 h, then refluxed for 1.5 h. After cooling, the mixture was poured onto a mixture of ice and dilute hydrochloric acid. The product was obtained as creamy crystals (5.20 g), m.p. 116–117°C. Found, C 87.82, H 4.36; $C_{18}H_{20}O_2$ requires C 88.18, H 4.57%. λ_{max} at 1640 cm^{-1} (C = O) and 3210 cm^{-1} (OH). ^1H NMR signals (C^2HCl_3) at 1.75 (s, 4-CH_3), 1.89 (s, 2,6-dimethyl), 2.22 (s, 3-CH_3), 1.66 (s, 5-CH_3), 6.27 (s, 6-H), 6.53 (s, 4-H), 7.61 (s, 3,5-H in mesitoyl) and 13.01 ppm (s, OH).

All melting points are uncorrected. IR spectra were obtained for KBr discs. ^1H NMR spectra of **1**–**6** were measured on a Varian FT/80A instrument as dilute solutions (0.1 mol%) in cyclohexane or dimethyl sulphoxide (DMSO) in a 5-mm tube with tetramethylsilane as an internal reference. The spectra were recorded after several accumulations.

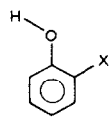
A Pye Model 104 gas chromatograph with dual flame ionization detectors (Pye Unicam, Cambridge, U.K.) was used. The columns employed were two 150 × 0.4 cm I.D. glass tubes with nitrogen as the carrier gas at a flow-rate of 80 ml/min. One column was packed with 25% (w/w) silicone OV-275 on Chromosorb W HP (80–100 mesh) and the other with 25% (w/w) silicone OV-101 on Chromosorb W HP (80–100 mesh). The column, injector and detector temperatures were 260, 320 and 320°C, respectively. The sample sizes were 0.4 ml of a 10% solution of each compound in acetone using a 1-ml Hamilton microsyringe. The chromatograph was connected with a Trivector (Sandy, U.K.) 3400 data system.

RESULTS AND DISCUSSION

Ortho-substituted phenols can exist as A or B or as a mixture of them[13,14]:



A



B

In the present series, the presence of a proton acceptor (carbonyl group) in position 2 forces the hydroxyl group to adapt conformation A[15–17]. The hydroxyl chemical shift (δ_{OH}) in such an intramolecular hydrogen bonding system (IAMHB) does not change with temperature or solvent polarity[18,19]. The presence of a steric effect will change the strength[20,21] of this IAMHB; hence it will be more influenced by the polarity of the solvent or the stationary phase used and under these conditions one expects the population of molecules adopting conformer B to increase owing to the influence of the intermolecular hydrogen bonding (IMHB) between the polar stationary phase/solvent and the molecule.

The ^{1}H NMR chemical shifts of the hydroxyl proton (δ_{OH}) are given in Table I. The compounds can be divided into two groups: (i) **1–3**, with a small steric effect; and (ii) **4–6**, with a large steric effect and molecular crowding.

On examining the δ_{OH} values of **1–6**, one could classify them according to decreasing IAMHB in DMSO as **2**<**3**<**1** and in cyclohexane as **3**<**2**<**1**, and for the more sterically affected compounds in both DMSO and cyclohexane as **5**<**4**<**6**.

In the chromatographic measurements, two stationary phases were used: strongly polar OV-275 (dicyanoallylsilicone polymer) and non-polar OV-101 (dimethylsilicone polymer). The McReynolds parameter *Y* for OV-101 and OV-275 is 57 and 872 respectively[22]. This parameter is an indicator of the interaction of the stationary phase with ethanol, which represents compounds with a hydroxy functional group.

Table II shows the relative retention times for **1–6**, from which the following conclusions could be drawn. For **1–3** the interaction with polar OV-275 results in a trend of decreasing IAMHB in the order **2**<**3**<**1**, whereas for OV-101 the trend is **3**<**2**<**1**. These results are in agreement with those obtained by ^{1}H NMR spectroscopy. For **4–6**, the interaction with polar OV-275 results in a decrease in IAMHB in the order **5**<**4**<**6**, whereas for non-polar OV-101 the order is **6**<**5**<**4**. There is agreement between the strength of the interactions of **4–6** with the polar solvent and with the polar stationary phase obtained using ^{1}H NMR and chromatographic techniques.

It is believed that with OV-101, substituted phenols will tend to undergo intramolecular hydrogen bonding (IAMHB), whereas on OV-275 intermolecular hydrogen bonding (IHMB) predominates and the elution order of the compounds

TABLE I

^{1}H NMR CHEMICAL SHIFTS OF THE HYDROXYL PROTON, δ_{OH}, OF COMPOUNDS **1–6**

Compound	δ_{OH} *(ppm)*	
	Cyclohexane	*DMSO*
1	12.06	11.97
2	11.87	10.48
3	11.68	11.94
4	12.41	9.79
5	9.41	9.54
6	12.88	10.84

TABLE II

RELATIVE RETENTION TIMES[a] OF COMPOUNDS **1–6** ON OV-101 AND OV-275

Compound	*Relative retention time*	
	OV-101	*OV-275*
1	1.00	1.00
2	2.09	5.02
3	2.95	2.20
4	0.93	4.00
5	3.03	>10
6	4.72	3.42

[a] Relative to compound **1**.

would follow the strength of that bond, which is influenced by the structure and steric crowding in the molecule. It is interesting that the interaction of **1–6** with the polar solvent or the polar stationary phase depends on the strength of IAMHB more than the strength of IMHB. In this respect, the values obtained for δ_{OH} in DMSO and those obtained with OV-275 stationary phase are comparable.

In conclusion, it could be suggested that in intramolecular hydrogen-bonded phenols **1–6**, the data obtained by ^{1}H NMR spectroscopy agree qualitatively with those obtained by chromatography, and that both techniques give good results concerning steric effects on the stability of IAMHB.

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