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Chromatographic Study of Steric Hindrance in *ortho*-Substituted Alkyl Phenols

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The alkyl substituted phenols have been studied chromatographically to determine the effect of steric hindrance on the adsorption of the *ortho* isomer. *R* values of the *ortho* and *para* isomers of methylphenol, ethylphenol, isopropylphenol and -butylphenol, chromatographed on silicic acid employing benzene as developer, indicate that the 2-*t*-butyl group is most effective in blocking the approach of the phenol–OH to the adsorbent. *R* values observed for the *para* isomers of these phenols show that other effects are negligible relative to that of steric hindrance.

The factors which affect adsorption are numerous. The accurate description of any simple chromatographic process would demand critical study of the role of the solvent, the adsorptive, the adsorbent and of the complex interactions among the three. Attempts to correlate adsorption with the properties of any one of the three have been successful in a few cases. This is generally true when the molecular property involved is so large as to make other factors of slight consequence relative to it. A change in the system is usually sufficient to invalidate the relations which were previously established.

The purpose of the present study was to establish steric hindrance as a definite influence in the behavior of *ortho*-substituted benzenes on chromatographic columns. Earlier investigators[2-4] have mentioned steric hindrance, along with internal hydrogen bonding, inductive effects and resonance effects, as attributing to the chromatographic behavior of substituted aromatics. However, the compounds usually dealt with contained groups capable of self interactions which would demand interpretation in terms of the combined influence of all the factors mentioned above.

For the present work the alkyl substituted benzenes were chosen to eliminate, insofar as possible, all of these factors except steric hindrance. Comparison was made between the *ortho* and *para* isomers of methylphenol, ethylphenol, isopropylphenol and *t*-butylphenol. Adsorption was found to decrease markedly with increase in the size of the alkyl group in the *ortho*-position, but hardly at all when substituted in the *para*-position.

Experimental

Reagents.—2-Methylphenol and 4-methylphenol, Eastman Kodak Co., yellow label, were redistilled.

4-Ethylphenol, 2-isopropylphenol and 4-*t*-butylphenol, obtained from the Bios Laboratories, New York, were redistilled.

3,5-Dimethylphenol, 2,6-dimethylphenol and 2,6-diisopropylphenol were obtained from the Shell Development Co., Emeryville, Calif.

2,6-Di-*t*-butylphenol was provided by the Ethyl Corporation, New York.

2-*t*-Butylphenol was prepared by the method of Hart.[4] A mixture of 2-bromophenol and 98% sulfuric acid was alkylated for 5 hours with slightly over a mole of isobutylene. After neutralizing the mixture and draining off the aqueous phase, the benzene layer was dried and the solvent was removed *in vacuo*. The residue was fractionated in a Vigreux column to yield 4-bromo-2-*t*-butylphenol almost quantitatively. A mixture of this phenol, ethanol and Raney nickel was refluxed first with 10% aqueous sodium hydroxide and then with benzene. The cooled aqueous layer was poured over concentrated hydrochloric acid. Benzene extraction removed the 2-*t*-butylphenol which was then purified by distillation. A derivative, 2-*t*-butylphenoxyacetic acid, was prepared, recrystallized from ligroin, and gave a melting point of 145°; the literature value is 145.5–146.5°.

The 2-ethylphenol was prepared in the following manner.[5-7] One mole of sodium was mixed with one mole of phenol and one mole of ethylene chlorohydrin. The mixture was refluxed until neutral, the alcohol distilled off, 200 ml. of distilled water added, and the solution extracted with ether. The ether layer was washed with water, dilute sodium hydroxide and again with water; the ether layer was then evaporated and the remaining material distilled between 163 and 166° at 80 mm. pressure. This was a thick, oily liquid.

Fifty grams of this liquid was heated for 5 hours with 5 grams of anhydrous zinc chloride; the temperature first went to 225°, then dropped to 190°. The product was then distilled and the fraction collected which came over between 88 and 90° at 18 mm. pressure.

Ten grams of this material was dissolved in 10 ml. of ethanol, the solution made acid with 2 ml. of concentrated hydrochloric acid, and 10 ml. of a solution containing 3 g. of potassium iodide was added. This was refluxed for 3 hours, the alcohol distilled off and the remaining material made neutral with sodium bicarbonate. The solution was then extracted with ether, the ether was evaporated and the remaining liquid was distilled at atmospheric pressure. The fraction was collected which distilled between 206 and 209°. This fraction was dried over sodium sulfate and redistilled; the fraction was taken which came over from 207 to 209°. The 2-ethylphenoxyacetic acid derivative was prepared and recrystallized from ligroin. This derivative gave a melting point of 140°; the literature value is 141–143°.

The adsorbent columns were prepared by packing dry silicic acid in the standard number one chromatographic tube, 9 mm. outside diameter and 150 mm. long, manufactured by the Scientific Glass Apparatus Co., Bloomfield, N. J. The silicic acid employed in these experiments was less than 150 mesh and was used without pretreatment either by oven drying or prewashing. The adsorbent was packed to a height of 80 ± 2 mm. while tapping the sides of the tube and applying a vacuum of approximately 5 mm. with a Cenco Hyvac vacuum pump. Finally, the top of the adsorbent column was smoothed with a small dowel rod.

Five drops of a 0.01 *M* solution of the phenol in benzene were introduced into the column and followed immediately with small quantities of pure benzene, Merck reagent, until the sample was washed into the column. Then the tube above the adsorbent was filled with benzene and development was allowed to proceed until the solvent reached the bottom of the column. The column of adsorbent was extruded and streaked with alkaline permanganate[8] to detect the position of the phenol. The results of the study are listed in Table I. The zones were sharp and of very nearly the same width. The reported *R* values are the average of three runs, the deviation of a single run being no more than 0.02.

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(1) (a) Georgia Institute of Technology, Atlanta, Ga.; (b) Celanese Corporation of America, Clarkwood, Texas.

(2) (a) A. L. LeRosen, J. K. Carlton and P. B. Moseley, *Anal. Chem.*, **25**, 666 (1953); (b) W. A. Schroeder, THIS JOURNAL, **73**, 1122 (1951).

(3) T. S. Gore and K. Venkataraman, *Proc. Ind. Acad. Sci.*, **34**, 368 (1951).

(4) H. Hart, THIS JOURNAL, **71**, 1966 (1949).

(5) A. Bayer and C. Seuffert, *Ber.*, **34**, 52 (1901).

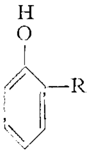
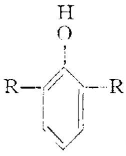
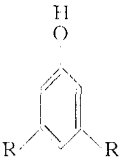
(6) R. E. Rindfusz, THIS JOURNAL, **41**, 665 (1919).

(7) W. H. Bentley, E. Haworth and W. H. Perkin, *J. Chem. Soc.*, **69**, 164 (1896).

(8) A. L. LeRosen, *et al.*, *Anal. Chem.*, **22**, 809 (1950).

TABLE I

R VALUES OF ALKYL SUBSTITUTED PHENOLS

Type formula R				
Hydrogen	0.26	0.26	0.26	0.26
Methyl	.37	.28	.55	.28
Ethyl	.43	.30		
Isopropyl	.52	.30	.95	
t-Butyl	.74	.31	1.00	
Cyclohexyl	.49			

Discussion

Disubstituted benzenes have been studied chromatographically to determine the effect of substituent position on adsorption behavior.[2c] From this study it became evident that the complexity of interactions, particularly when substitution was *ortho*, made interpretation extremely difficult. As a consequence, the present work was undertaken in hopes that by minimizing functional group interactions at least one of the factors contributing to the differences in adsorption of *ortho* and *para* isomers might be isolated. To do this a substituent was chosen which by space limitations would hinder the approach of the functional group to the surface of the adsorbent, and at the same time offer a minimum possibility for interactions such as strong inductive effects and chelation. Hence the *ortho*- and *para*-substituted alkyl phenols were chromatographed on silicic acid with benzene serving as developer.

It is readily seen from Table I that the adsorption affinity of the *ortho* isomers decreases with increasing size of the alkyl group, the effect of the *t*-butyl group being very pronounced. It has been shown by several workers that the methyl and *t*-butyl groups can influence ionization of aromatic compounds, the effect depending on the position of the alkyl substituent relative to that of the ionizable group. Among the first quantitative estimates of this effect were the sigma values of Hammett.[9] An examination of these values indicates the order of influence of the 4-alkyl substituent to be *t*-butyl > methyl > ethyl = isopropyl (actually, the differences as ascertained from these values are relatively small and the absolute sigma value of an alkyl group, in general, is small in comparison to those of other substituents). On the basis of inductive effects alone one would predict the order of influence to be *t*-butyl > isopropyl > ethyl > methyl. Since this is not the observed order an alternative or supplementary explanation is sought. Hyperconjugation has been proposed as the phenomenon accounting for the methyl group having a greater influence on the above-mentioned ionization than either the ethyl or the isopropyl group. Also, it would account for the fact that the 4-methyl group has a greater effect than the 3-methyl group. Lichtin and Bartlett,[10] observing the effect of 4-alkyl substitution on the ionization of triphenylmethyl chloride in liquid sulfur dioxide, have estimated the hyperconjugative effects and inductive effects of the *t*-butyl group to be approximately the same, while the hyperconjugative effect of the methyl group is considerably higher than its inductive effect. A combination of the two effects, however, results in very nearly the same influence for the two groups on the ionization of the chloride. Obviously, the combined hyperconjugative and inductive effects of all the alkyl groups included in this study have about the same influence on the chromatographic adsorption of phenol, since the *R* values of the *para* compounds are, within the limits of experimental error, the same.

The alkyl group substituted in the *ortho*-position gives rise to *R* values which are markedly greater than those observed for the *para* isomer. Since the methyl group has a low inductive effect, and since the hyperconjugative effect of the *ortho* and *para* isomers is the same, these authors feel the significant influence of the alkyl group in *ortho*-substituted phenols in steric hindrance. The approach of the strongly adsorbed –OH group to the surface of the adsorbent is effectively blocked, the more so the larger the size of the alkyl group.

If the adsorption process is considered to take place through hydrogen bonding between the adsorbent and adsorptive then the increased electron density around the oxygen of the phenol group, resulting from the influence of the alkyl group as described above, may affect the *R* value in one of two ways. First, if the hydrogen bond is formed between an electron pair on the oxygen of the phenol and a hydrogen from silicic acid adsorption affinity of the phenol should increase and its *R* value decrease with alkyl substitution in the *ortho*- and *para*-positions. The alternative possibility is for hydrogen bonding to take place between the hydrogen of the –OH group and an electron pair provided by an oxygen of the adsorbent. In this case one would expect adsorption to decrease because the hydrogen would be more tightly bound to the phenol oxygen by virtue of its increased electron density. Results of *R* value measurements for the 4-alkyl substituted phenols indicate a trend favoring this latter possibility but the increase in *R* value from methyl to *t*-butyl is too small to consider this trend significant.

The R_f value of 2-cyclohexylphenol is seen to be about the same as that of the isopropylphenol, even though the cyclohexyl group is somewhat heavier. The steric configuration of the two groups in the vicinity of the –OH group are very similar, and both demonstrate the same effect in preventing the approach of the phenolic group to the adsorbent.

Another interesting point is contained in the above data. The 3,5-dimethylphenol is shown to have the same *R* value as 4-methylphenol. From this one might speculate that the combination of the inductive and hyperconjugative effects of the *p*-methyl group equals the sum of the inductive

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(9) L. P. Hammett, "Physical Organic Chemistry," 1st ed., chap. 7, McGraw-Hill Book Co., New York, N. Y., 1940.

(10) N. N. Lichtin and P. D. Bartlett, THIS JOURNAL, **73**, 5530 (1951).

effects from two *m*-methyl groups, at least insofar as its effect on adsorption affinity of phenols is concerned.

The 2,6-disubstituted phenols show a very marked decrease in adsorption affinity over their monosubstituted analogs. This is clearly evident even with the relatively small methyl group.

The data obtained in this study substantiate the hypothesis that the steric hindrance of the alkyl substituent is the most important influence of that group on the chromatographic adsorption of *ortho*-alkyl substituted phenols. Equally important from the point of view of a practical application, this information affords the chromatographer a simple method for the separation of *ortho* and *para* isomers of these alkyl phenols. It can also serve as a simple purification procedure for small quantities of the *ortho*-substituent.

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COMMUNICATIONS TO THE EDITOR

SPECIFIC MEDIUM EFFECTS IN NUCLEAR MAGNETIC RESONANCE SPECTRA OF LIQUIDS

Sir:

It has been accepted generally that two molecular properties affect $\mathcal{H}$ (the strength of the applied field necessary to induce resonance) in the high-resolution nuclear magnetic resonance spectra of liquids: (1) intramolecular diamagnetic shielding by the valence electrons, and (2) alteration of the effective field at the molecule by the bulk of the liquid. The latter effect is usually assumed to be strictly derivable from the shape of the sample and the volume susceptibility (κ) of the liquid.[1] For a molecule residing in a spherical cavity in a cylindrical liquid sample oriented transversely to the magnetic field, the prediction of classical magnetostatics is a decreasing $\mathcal{H}$ with decreasing volume susceptibility of the liquid. In agreement with this model, methylene chloride ($\kappa = -0.73 \times 10^{-6}$)[2] shows[3] a lower $\mathcal{H}$ by 6.1 ± 0.2 milligauss when diluted with nine volumes of methylene bromide ($\kappa = -0.95 \times 10^{-6}$).[2] However, when methylene chloride is dissolved in tetrachloroethylene ($\kappa = -0.83 \times 10^{-6}$)[2] no change in $\mathcal{H}$ is observed.

In our experience *such anomalies may arise whenever there is a possibility of a preferred orientation of magnetically anisotropic molecules adjacent to the molecule under study.* This orientational interaction will be a highly specific one. Therefore, the addition to several liquids of a single substance intended to serve as a reference may result in unpredictable shifts in the $\mathcal{H}$ for the added substance, which thereby loses its value as a standard. Moreover, $\mathcal{H}$ for the aromatic hydrogens of *t*-butylbenzene is unaltered on dilution with nine volumes of carbon tetrachloride while $\mathcal{H}$ for the methyl hydrogens is lowered by 5.1 ± 0.5 milligauss. Thus, extreme care must be exercised in the use of so-called internal standards.

This orientational effect may be largely eliminated by surrounding the molecule with solvent molecules which are more nearly magnetically isotropic. For example, Table I displays $\mathcal{H}$ for the *para*-hydrogen[4] in several mono-substituted benzenes as found by measurement on the pure liquid, and as extrapolated for the infinitely dilute solution in carbon tetrachloride from data obtained on five and ten volume-per cent. concentrations.

TABLE I

para-HYDROGEN RESONANCES IN MONOSUBSTITUTED BENZENES

Substituent	$\mathcal{H}$ (milligauss)[a] Pure liquid	$\mathcal{H}$ (milligauss)[a] Extrapolated[b]	σ_p[c]
$-NH_2$	+10.2	+3.8	−0.66
$-OCH_3$	+ 2.6	+0.8	−0.27
$-CH_3$	+ 4.5	+0.5	−0.17
—H	+ 5.7	0.0	0.0
$-C(CH_3)_3$	+ 0.2	−0.2	−0.20
—Cl	+ 3.1	−1.5	+0.23
—Br	+ 4.5	−1.3	+0.23
—I	+ 0.5	−1.5	+0.28
—CN	+ 0.9	−4.5	+1.00
—CHO	− 0.2	−5.8	+1.13
$-NO_2$	+ 1.9	−6.3	+1.27

[a] Relative to the extrapolated $\mathcal{H}$ for benzene in carbon tetrachloride. All measurements with a probable error of ±0.5 milligauss. [b] See text. [c] Reference 5.

While the $\mathcal{H}$'s for the pure liquids do not seem to fall in any recognizable order, those found by extrapolation follow the order expected from the electrical effects of the substituents, and, within experimental error, fit the equation

$$\mathcal{H} - \mathcal{H}_0 = -5.0\sigma_p$$

where $\mathcal{H}_0$ is the extrapolated $\mathcal{H}$ for benzene, and σ_p is Hammett's *para* substituent constant.[5] Other classes of substances show similar trends toward order consistent with known molecular properties when treated in a corresponding manner.

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(1) B. P. Dailey and J. N. Shoolery, THIS JOURNAL, **77**, 3977 (1955), who point out, however, that non-ideal behavior is observed in the case of mixtures of methyl iodide and benzene.

(2) P. Pascal, *Ann. Chim.*, (8) **19**, 5 (1910).

(3) Measurements were made on a Varian NMR Spectrometer at 40 megacycles using a 5-mm. spinning sample tube containing a 1-mm. sealed capillary of reference substance. Separate experiments have shown that $\mathcal{H}$ for the reference is independent of sample susceptibility in this geometry.

(4) E. B. Baker, *J. Chem. Phys.*, **23**, 984 (1955).

(5) L. P. Hammett, "Physical-Organic Chemistry," McGraw-Hill Book Co., Inc., New York, N. Y., 1940, p. 188.