PPO in acetone was condensed a large excess of cyclopropane. The tube was carefully sealed under nitrogen and irradiated for 10 hr at room temperature. There was a large amount of polymer so the yellow solution was filtered before concentration and analysis by gas chromatography. Two products in the ratio ~4:1 (retention times 4 and 9 min at 85°, colum B) were observed in addition to several higher boiling components. The major component was identified as allylbenzene by comparison with an authentic sample. It was obtained in 3-4% yield, as determined by using *tert*-butylbenzene as an internal standard. The minor product has not been isolated in sufficient quantity for identification, although it has been established that it is *not* indan.

Registry No.—Benzyne, 462-80-6; PPO, 4733-52-2.

Linear Free-Energy Relationships between Partitioning Solvent Systems[1]

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Received October 16, 1970

The relationships between the octanol–water partitioning system and 20 others are examined from the viewpoint of the relative contribution of both hydrophobic bonding and hydrogen bonding forces. A classification of solute functional groups according to relative hydrogen-bond donating and accepting ability is presented. Fifty-eight new values for log P octanol–water are reported.

Information on how organic solutes are distributed between water and an immiscible solvent has been of primary interest to chemists working in two different fields: the physical chemist can use the data to help define the intramolecular forces acting between the solute and each of the solvents, and the biochemist can employ it in an approach to structure–activity relationships.[2] In this paper, the relationships between 21 partitioning systems are examined and discussed in reference to their application to both the physical and biological disciplines.

Since, in essence, partition coefficients are equilibrium constants, it should not be surprising that one can find extrathermodynamic relationships[3] between partition coefficients measured in different solvent systems. Certainly such an assumption was implicit in the work of Meyer[4] and Overton[5] who used oil–water partition coefficients to correlate narcotic action of drugs. Later, Smith[6] discussed the possibility of such relationships between two solvent systems if the solute sets chosen were not too dissimilar. Collander[7] was the first to express the relationship clearly in formal terms. Collander showed that a good linear relationship

$$\log P_2 = a \log P_1 + b \quad (1)$$

existed between partition coefficients in one system (P_1) and those in a second system (P_2) if the polar phase was water and the nonpolar phases contained the same functional group. In particular, he showed that eq 1 held between the systems isobutyl alcohol–water, isopentyl alcohol–water, octanol–water, and oleyl alcohol–water.

Hansch,[8] using Smith's data, later extended the comparison of relatively nonpolar systems using $CHCl_3$–water as P_1 and the following systems for P_2: CCl_4, xylene, benzene, and isoamyl acetate.

While eq 1 allows any partitioning system to be compared with any other, the most useful relationships for the study of solute–solvent interactions are obtained if each system is compared to a standard reference system; that is to say, a reference system should be chosen and made the independent variable P_1 in a set of equations of the form of eq 1.

Of course, objections can be raised to the choice of *any* of the systems for use as a reference standard. We have chosen the octanol–water system for a number of practical reasons: first, it is the system with the largest number of measured values, and it also contains the widest selection of solute functional groups; second, most of these values have been determined in a single laboratory and therefore they are more self-consistent than the values from any other system; and third, the usefulness of the octanol–water system as a model for describing the binding forces between small molecules and macromolecules has already been established.[2]

One might argue that the organic phase in the reference system should be as free of polar binding forces as possible. While in principle a hydrocarbon solvent such as cyclohexane or heptane might make a better reference system than octanol, there are several practical reasons why such a system cannot be constructed at the present time. Of the almost 500 values available in the cyclohexane–water system, a large fraction are for unusual molecules not reported in other systems. Only about 200 values are available in the heptane–water system and these are heavily weighted toward the nonpolar solutes. Furthermore, a basic disadvantage in using a hydrocarbon–water system is that in these solvents dimerization of the solute is maximized. While in principle this factor can be taken into account by measuring the variation of the apparent coefficient with concentration, many of the values reported in the early literature have not been corrected in this manner. Besides it being much more laborious to obtain true partition coefficients in hydrocarbons in which association occurs, the very limited solubility of many polar molecules in these solvents often sets an impossible requirement on the sensitivity of the analytical techniques available.

Another interesting feature of octanol which enhances its value as a partition reference solvent is that, while water is very soluble in it (see Table I), it is very insoluble in water (4.5×10^{-3} M). Thus, in comparison with many of the solvents in Tables I and II, it has relatively little effect on the aqueous phase.

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[1] This work was supported by Grant CA-11110 from the National Institutes of Health.

[2] C. Hansch, *Accounts Chem. Res.*, **2**, 232 (1969).

[3] J. E. Leffler and E. Grunwald, "Rates and Equilibria of Organic Reactions," Wiley, New York, N. Y., 1963.

[4] H. Meyer, *Arch. Exp. Pathol. Pharmakol.*, **42**, 109 (1899).

[5] E. Overton, "Studien uber die Narkose," Fischer, Jena, Germany, 1901.

[6] H. Smith, *J. Phys. Chem.*, **25**, 204, 605 (1921).

[7] R. Collander, *Acta Chem. Scand.*, **5**, 774 (1951).

[8] C. Hansch, *Farmaco*, **23**, 294 (1968).

TABLE I

$\text{Log } P_{solv} = a \text{ Log } P_{octanol} + b$

Solvent (*vs.* H_2O)	Table of solutes[a]	(Mol of H_2O/l.) × 10^3	Equation "A"					Equation "B"				
			a[b]	*b*[b]	*n*	*r*	*s*	*a*	*b*	*n*	*r*	*s*
Cyclohexane	III	2.5	0.675 (±0.24)	−1.842 (±0.48)	26	0.761	0.503	1.063 (±0.12)	−0.734 (±0.25)	30	0.957	0.360
Heptane	IV	3.3	1.056 (±0.73)	−2.851 (±1.46)	10	0.764	0.916	1.848 (±0.44)	−2.223 (±0.93)	11	0.954	0.534
CCl_4[c]	V	10.0	1.168 (±0.12)	−2.163 (±0.15)	24	0.974	0.282	1.207 (±0.27)	−0.219 (±0.37)	11	0.959	0.347
Xylene	VI	18.8	0.942 (±0.13)	−1.694 (±0.21)	19	0.963	0.225	1.027 (±0.08)	−0.595 (±0.16)	21	0.986	0.230
Toluene	VII	25.6	1.135 (±0.11	−1.77 (±0.16)	22	0.980	0.194	1.398 (±0.22)	−0.922 (±0.37)	14	0.971	0.274
Benzene	VIII	26.0	1.015 (±0.11)	−1.402 (±0.14)	33	0.962	0.234	1.223 (±0.19)	−0.573 (±0.20)	19	0.958	0.291
$CHCl_3$[d]	IX	68.4	1.126 (±0.12)	−1.343 (±0.21)	28	0.967	0.308	1.276 (±0.14)	+0.171 (±0.17)	21	0.976	0.251
Oils	X	72.5	1.099 (±0.06)	−1.310 (±0.09)	65	0.981	0.271	1.119 (±0.11)	−0.325 (±0.19)	14	0.988	0.233
Nitrobenzene	XI	180	1.176 (±0.23)	−1.072 (±0.20)	9	0.977	0.217					
Isopentyl acetate	XII	456	1.027 (±0.08)	+0.072 (±0.13)	22	0.986	0.209					
Ether	XIII	690	1.130 (±0.04)	−0.170 (±0.05)	71	0.988	0.186	1.142 (±0.13)	−1.070 (±0.12)	32	0.957	0.326
			"Sole" equation									
			a	*b*	*n*	*r*	*s*					
Oleyl alcohol	XIV	712	0.999 (±0.06)	−0.575 (±0.11)	37	0.985	0.225					
Methyl isobutyl ketone	XV	950	1.094 (±0.07)	+0.050 (±0.11)	17	0.993	0.184					
Ethyl acetate	XVI	1620	0.932 (±0.21)	+0.052 (±0.18)	9	0.969	0.202					
Octanol	XVII	2300	0.0	+1.00								
Cyclohexanone	XVIII	4490	1.035 (±0.20)	+0.896 (±0.30)	10	0.972	0.340					
Primary pentanols	XIX	5000	0.808 (±0.07)	+0.0271 (±0.09)	19	0.987	0.161					
sec- and *tert*-pentanols	XX	5320	0.892 (±0.06)	+0.288 (±0.06)	11	0.996	0.091					
2-Butanone	XXI	5460	0.493 (±0.07)	+0.315 (±0.07)	9	0.987	0.093					
Cyclohexanol	XXII	6510	0.745 (±0.09)	+0.866 (±0.14)	12	0.985	0.100					
Primary butanols	XXIII	9440	0.697 (±0.02)	+0.381 (±0.03)	57	0.993	0.123					

[a] These tables are included in the microfilm edition of this paper. [b] The values in parentheses are the 95% confidence intervals.
[c] The "N" equation is

$$\log P_{CCl_4} = \underset{(\pm 0.60)}{0.862} \log P_{octanol} - \underset{(\pm 0.70)}{0.626} \qquad \overset{n}{6} \qquad \overset{r}{0.809} \qquad \overset{s}{0.462}$$

[d] The "N" equation is

$$\log P_{CHCl_3} = \underset{(\pm 0.12)}{1.10} \log P_{octanol} - \underset{(\pm 0.18)}{0.649} \qquad 23 \qquad 0.971 \qquad 0.292$$

It is clearly evident from Smith's data[6] that, when the nonpolar phases of the partitioning systems differ widely, and especially when the solute sets contain molecules which cannot hydrogen bond along with those which can, eq 1 does *not* give a good correlation. For example, in comparing benzene–water with octanol–water, one needs at least two equations to relate a wide variety of solute molecules with a correlation coefficient greater than 0.85. The simplest way to make such a separation is to take the values from a single equation and separate all the "minus deviants" into one category and the "plus deviants" into another. After one has done this for several solvent systems, one finds that the strong hydrogen-bond donors are the "minus deviants" and the hydrogen-bond acceptors are the "plus deviants." The ether–water system is exceptional, for, while it also segregates the donors from acceptors, the deviations are reversed.

Since the importance of the role of hydrogen bonding in solvent–solute interactions has been appreciated for some time,[9-11] it seemed reasonable to try to assign a specific order to the H-bonding properties of both the solutes and the organic solvents used in the partitioning

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(9) J. H. Hildebrand, "Solubility," 2nd ed, Reinhold, New York, N. Y., 1936, p 166.

(10) G. F. Zellhoeffer, M. J. Copley, and C. S. Marvel, *J. Amer. Chem. Soc.*, **60**, 1337 (1938).

(11) R. Ewell, J. Harrison, and L. Berg, *Ind. Eng. Chem.*, **36**, 871 (1944).

TABLE II

SOLUTES UNCLASSIFIED

Solvent	*a*	*b*	*n*	*r*	*s*
Cyclohexane	0.872 (±0.28)	−1.241 (±0.55)	56	0.649	1.015
Heptane	1.566 (±0.70)	−2.661 (±1.45)	21	0.731	1.354
CCl_4	1.307 (±0.32)	−1.592 (±0.42)	41	0.797	0.937
Xylene	1.033 (±0.20)	−1.180 (±0.34)	40	0.862	0.661
Toluene	1.328 (±0.28)	−1.560 (±0.46)	36	0.852	0.664
Benzene	0.979 (±0.20)	−1.005 (±0.24)	52	0.815	0.555
$CHCl_3$	1.012 (±0.17)	−0.512 (±0.27)	72	0.811	0.734
Oils	1.096 (±0.08)	−1.147 (±0.15)	79	0.945	0.470
Ether	1.184 (±0.09)	−0.474 (±0.10)	103	0.929	0.477

systems. However, at the present time there is not enough applicable data to carry out such a task. Higuchi, *et al.*,[12] have been able to assign a relative H-donor capacity to a series of substituted phenols, and Taft, *et al.*,[13] have measured the H-acceptor capacity of a series of 55 bases of widely different structures. However, from these data it is not possible to assign an H-bonding parameter to more than a small fraction of the solutes common to partitioning work. Furthermore, there appears to be little agreement on the relative H-bonding ability of each of the common functional groups, except the well-known rules based on the electronegativity and size of the two atoms bound by the hydrogen atom.[14] Undoubtedly the sizable variations within any such functional group category has tended to discourage such efforts.[15a] Nevertheless, with the deviations from the regression equations relating the partition coefficients as a guide, we ordered some common functional groups into general solute classes. These appear in Chart I. The numbers which appear on the left are primarily for the purpose of identifying each class in the tables which follow and are not necessarily the order of H-bonding ability *within* each of the three groups. This matter is covered in greater detail in the supplementary material for microfilm edition.[15b]

The classification scheme shown in Chart I has been followed as closely as possible in assigning every solute appearing in Tables III through XXIII[15b] to the proper equation group. We have labeled the equations which correlate acidic solutes (H donors) as "A," and those correlating the basic solutes (H acceptors) as "B." In the case of $CHCl_3$ and CCl_4 we felt that a third equation was needed to give a good correlation for solutes having both donor and acceptor ability; these equations are labeled "N."

CHART I

GENERAL SOLUTE CLASSES

Always "A"	1.	Acids
	2.	Phenols
Usually "A" Sometimes "N"	3.	Barbiturates
	4.	Alcohols
	5.	Amides (negatively substituted, but not di-N-substituted)
	6.	Sulfonamides
	7.	Nitriles
	8.	Imides
	9.[a]	Aromatic amines (not di-N-substituted)
	10.[a]	Amides
Always "B"	11.	Aliphatic amines and imines
	12.	Tertiary amines, including ring N compounds
	13.	Ketones
	14.	Ethers
	15.	Esters
	16.	Compounds with intramolecular H bonds (*e.g.*, *o*-nitrophenol)
	17.	Aromatic hydrocarbons
	18.	Miscellaneous acceptors

[a] Classes 9 and 10 must be reversed when considering the ether and oil solvent systems.

It will be noted that a special H-acceptor classification (16) was assigned to groups which normally are H donors but which can satisfy this tendency by an intramolecular bond.

Whenever a solute molecule contained two or more noninteracting functional groups, each of which would require classification as "A" and "B," we have placed it in the class which gave the best fit with that particular equation. It was felt that the best fit of the data would serve to categorize the dominant solvation forces in such cases. For example, *p*-methoxybenzoic acid is both an acid (class 1) and an ether (class 14). Equation "A" is clearly the one of choice in the solvent systems: benzene, toluene, and xylene (see Tables VIII, VII, and VI).[15b] This suggests that the H-donor ability of the carboxyl group is dominating in placing *p*-methoxybenzoic acid in the most poorly accommodated category when these solvents are compared to octanol. In the $CHCl_3$–water system, however, *p*-methoxybenzoic acid is not so poorly accommodated (again in relation to the standard reference system), and actually the "N" equation fits it as well as the "A" (see Table IX).[15b] This suggests that the weak H-donor capability of the solvent, $CHCl_3$, increases the accommodation of this solute by interacting with the etherial oxygen.

There were not enough examples available to assign classes 7 and 8 with a satisfactory degree of confidence. The one value for acetonitrile in ether–water clearly places it in the "A" equation, but Taft's value for the formation constant of the complex with *p*-fluorophenol would indicate that it can act as an H acceptor to the same degree as does acetophenone. Of course, dipole forces *other* than hydrogen bonding may be involved in the partitioning process, and the —C≡N group may

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(12) T. Higuchi, J. Richards, S. Davis, A. Kamada, J. Hou, M. Nakano, N. Nakano, and I. Pitman, *J. Pharm. Sci.*, **58**, 661 (1969).

(13) R. W. Taft, D. Gurka, L. Joris, P. v. R. Schleyer, and J. W. Rakshys, *J. Amer. Chem. Soc.*, **91**, 4794, 4801 (1969).

(14) G. Pimentel and A. McClellan, "The Hydrogen Bond," Reinhold, New York, N. Y., 1960, p 229 ff.

(15) (a) For example, Taft's K_f values for substituted pyridine varies from 2.30 for 2,4,6-trimethylpyridine to 0.75 for 3,5-dichloropyridine, while the parent compound has a K_f of 1.88. (b) Tables containing the partition coefficient data for each of the solute molecules used to derive the 20 regression equations and further discussion of their application appear following these pages in the microfilm edition of this volume of the journal. Single copies may be obtained from the Reprint Department, ACS Publications, 1155 Sixteenth St., N.W., Washington, D. C. 20036, by referring to author, title of article, volume, and page number. Remit $9.00 for photocopy or $2.00 for microfilm.

retain its classification within the intermediate group as more partitioning values become available.

Phthalimide provides the only example of a true imide for which other solvent system values could be found (ether and $CHCl_3$). However, classification in this case is not so difficult because the imide group is known to be acidic. If saccharin is included under this heading, many other values also establish this classification.

In establishing a scale for *solvents*, and for purposes where hydrogen bonding is *not* a dominant factor, a scale based on either dipole moment, dielectric constant, or solubility parameter can be useful and informative. For comparing a wide variety of partitioning solvents, however, none of these parameters are suitable, even when corrected for the water content at saturation.[16,17]

A useful and certainly a simple scheme for classification of partitioning solvent systems is to arrange them according to the amount of water each contains in the saturated state. This quantity was measured in each of the solvents appearing in this study by the Karl Fischer titration procedure (see Experimental Section). The values appear in the second column of Table I in (moles of H_2O per liter of solvent) $\times 10^3$. Of course, using the solubility of water in the solvent to index solvent character is ambivalent. In one sense it is a measure of the affinity of the functional group in the solvent for water molecules; in another sense (for partitioning work) it is a measure of the character of the solvent phase itself.

The balance of Table I is comprised of the regression equation data for each solute group arranged in order of decreasing H-donor capability: "A," "N," "B." Table II contains the single regression equations prior to segregation of the solutes into classes.

The usefulness of the equations in Tables I and II lies in the fact that the parameters "*a*" (slope) and "*b*" (intercept) can be an indication of the solute–solvent interaction as compared to the standard solute–octanol interaction. Considering the *slope* value first, we can see that it is a measure of the solvent system's sensitivity to changes in lipophilicity of solutes. The solvent system with the lowest sensitivity is butanol–water, as expected. When this pair is saturated with one another, they are about as much alike as possible and still remain as separate phases. Since log *P* measures the difference in transfer energy between the two, changes in solute character will register as only small differences when compared to octanol.

As the hydrocarbon chain length in the solvent alcohol is increased, the alcohol–water phases become more and more unlike, and the sensitivity to solute changes increases. Apparently a maximum sensitivity is reached at octanol, for the slope in the oleyl alcohol equation is also 1.0.

It should be borne in mind that the kind of solute molecules comprising a set can have considerable influence on the slope and that for some of the sets a "normal" distribution of solutes is lacking. As expected, only the very lipophilic solvents such as CCl_4, benzene, toluene, and oils have slopes greater than 1.0. One might expect that xylene should be included in this group and indeed, with a better selection of solutes, the slope might be appreciably greater.

There is some basis for the postulate that the partition process, outside of hydrogen bonding, is the same for solutes in each system, and therefore, if hydrogen bonding were accounted for separately, the slopes of all the equations in Tables I and II would be 1.0. Some of the results reported by Higuchi and his coworkers[12] can be interpreted in this manner. They have used the cyclohexane–water system, where the organic phase has a minimum of hydrogen-bonding ability, and to it have added a small amount of tributyl phosphate (TBP) or isopropoxymethyl phosphoryl fluoride (sarin) as H-bond acceptors. By partitioning a set of substituted phenols between the two phases, they have calculated an equilibrium constant for the solute–TBP complex. From their data and log P_{octanol} values for the phenols, eq 2 and 3 have been formulated. The

$$\log P_{\text{octanol}} = 0.50 \log P_{\text{cyclohexane}} + 2.43 \quad \begin{array}{ccc} n & r & s \\ 9 & 0.791 & 0.391 \end{array} \qquad (2)$$

$$\log P_{\text{octanol}} = 1.00 \log P_{\text{cyclohexane}} + 1.20 \log K_{\text{HB}} + 2.35 \quad 9 \quad 0.979 \quad 0.140 \qquad (3)$$

correlation between partition coefficients in octanol and cyclohexane is poor, as shown by eq 2. However, when correction is made for the hydrogen-bonding ability of the phenols by adding a term in log K_{HB}, a good correlation is obtained with eq 3. Moreover, the coefficient with log $P_{\text{cyclohexane}}$ is 1.00, indicating that in a rough sense the desolvation processes are the same for each system. As more hydrogen-bonding constants become available, it should be possible to construct a broadly based set of correlation equations relating free energies of transfer of solutes in many systems. If this objective can be realized, then the above procedure can be reversed and eq 3 can be used to calculate the relative hydrogen bonding constants.

The *intercept* value for each of the regression equations in Table I can be used as a measure of the lipophilicity of the solvent in a slightly different fashion. It is apparent that the intercept for a given solvent system is the log *P* for any solute which is distributed equally between water and octanol; *i.e.*, $\log P_{\text{octanol}} = 0$. Thus a negative intercept for any equation indicates that the solvent is more lipophilic than octanol, and a positive intercept indicates that it is more hydrophilic. This is more readily apparent if one examines a homologous series of solutes, for example, the carboxylic acids. The octanol log *P* values begin at −0.54 for formic and rise to −0.17 for acetic and to +0.33 for propionic. Therefore, it takes between two and three lipophilic methylene groups to balance the hydrophilic carboxyl group and allow the octanol to share the solute equally with water.

In the oleyl alcohol–water system it takes one *additional* methylene group before a carboxylic acid becomes lipophilic enough to be equally shared; *i.e.*, $\log P_{\text{oleyl alc}} = 0$ between propionic and butyric. Similarly, it is noted that in nitrobenzene–water it takes two *additional* methylenes, in benzene–water it takes three, and in CCl_4–water it takes about 4.5 additional groups

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[16] H. Mottola and H. Freiser, *Talanta*, **13**, 55 (1966).

[17] M. Chertkoff and A. Martin, *J. Pharm. Sci.*, **49**, 444 (1960).

to bring the solute to an equal lipophilic level with the organic phase.[18]

Using the intercept values from either the "A" or "sole" equations as a measure of a solvent's lipophilicity, we see that there is a very good correlation between these values and the water content at saturation. The

$$\log [\mathrm{H_2O}] = 1.077[\text{intercept}] + 0.249 \qquad \begin{matrix} n & r & s \\ 17 & 0.979 & 0.217 \end{matrix} \qquad (4)$$

values for isopentyl acetate and cyclohexanone were not considered in deriving eq 4. This relationship is seen in graphic form in Figure 1.

Experimental Section

The water content at saturation in each of the partitioning solvents listed in Tables I and II was measured at 25.0° using Karl Fischer reagent and standard procedures.[19,20] A dual buret apparatus capable of measuring water contents over the range of 1 ppm to 100% water was used. The end point is indicated with this instrument by a conductance-type meter using platinum electrodes.

Each of the solvents was shaken vigorously for 1 min before being placed in a constant temperature bath at 25.0 ± 0.1° for 48 hr. Each container was shaken twice again for 30 sec during this period and then centrifuged at 10,000 RCF for 20 min. During centrifuging and prior to actual titration, the temperature was maintained at 25.0 ± 1°.

Anhydrous methanol was used as the titration solvent for the alcohols and esters. A 3:1 pyridine–methanol mixture was used for the ketones to reduce any tendency to form acetals or iodo compounds,[21] and a 1:1 mixture of methanol–dichloromethane was used for the hydrocarbons, chlorinated hydrocarbons, and olive oil. In this way a one-phase system was maintained throughout each titration, and the K-F end point, once attained for 30 sec, could always be regained with the addition of no more than 0.1 ml of reagent even after the equipment was left standing for 30 min.

Some differences in water content were observed when the saturation procedures were varied. For instance, when octanol was freshly shaken with water at 20° and allowed to separate by gravity for 30 min, a slight haziness was still apparent and the water content was measured as 2.36 mol. After centrifuging at 15,000 RCF for 10 min, it was water-clear and gave a value of 2.27 mol of water. After being allowed to stand over water in a 2-l. bottle for several weeks (with a temperature variation of ±3°), the water content was 2.02 mol, which perhaps indicates that it is not safe to assume that all water in excess of saturation can be removed by a large centrifugal force acting during a relatively short time.

Discussion

As pointed out earlier, a single equation is sufficient to give an excellent correlation ($r \geqq 0.97$) with the octanol reference system even if the solute types vary widely, as long as the solvent in question has both H-donor and H-acceptor functional groups (see ref 24 in the microfilm edition of this paper). The R–OH group in the alcohol series provides both donor and acceptor capability, and, in the case of the low molecular weight esters and ketones, these solvents evidently dissolve sufficient water to also act effectively in both capacities. It appears quite likely that any organic solvent containing 1 mol of water at saturation can act both as an H donor and H acceptor in partitioning work if the solute concentration is 0.1 mol or less.

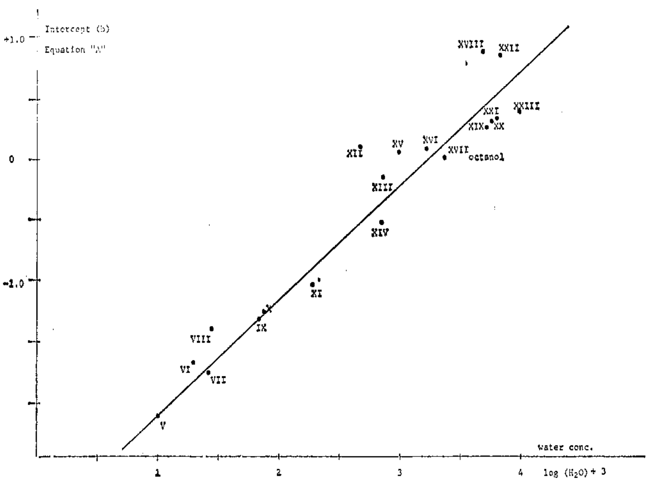

Figure 1.

From Tables III, IV, Vc, VIb, VIIb, VIIIb, IXc, and XIIIb[15b] it is seen that solute classes 10 through 18 consistently fall into eq "B." It should be noted, however, that there is some ambivalence in the two functional groups, aromatic amines and amides. In the least polar solvents (cyclohexane, heptane, CCl_4, benzene, toluene, and xylene), the aromatic amines are better fitted if placed with the H acceptors and thus are assigned class 10. In the more polar solvents which still require two or more equations (ether and oils), the aromatic amines are better fitted in the H-donor category and are assigned class 9.

On the opposite end of the scale, acids and phenols are clearly to be placed in the category of the strongest H donors. The large negative intercepts for most of the equations of type "A" means that H-donor solutes are relatively less easily accommodated by all the solvents except ether (again when octanol is the reference for comparison).

In the case of chloroform, the need for a third equation to fill the gap between classes 2 and 10 seems real, and it appears safe to conclude that the H-donor capabilities of these groups are also intermediate. The exact order within the classes 3–8 and 11–18 cannot be determined from the present data, but, if a sufficient number of new solute values are measured, a further degree of order may be possible. For example, if it develops that most of the barbiturates in the $CHCl_3$ regression eq "X" show negative deviations from the calculated value while most imides show positive deviations, this would mean the barbiturates are more closely aligned with type "A" solutes while imides are more like type "B" solutes, and the difference in H-donor ability between classes 3 and 8 would be real.

Taft's system of measuring the formation constant in CCl_4 of the hydrogen-bonded complex between a set of acceptors and a standard fluorophenol donor[13] is well suited to establish the order within the group "B" of Table I. Based on his K_f values, ethers as a class should be the weakest acceptors (average of 5 K_f = 0.876), followed by pyrimidine (1.05), esters (ethyl acetate = 1.08), and ketones (average of 4 K_f = 1.12). Aliphatic amines are much stronger acceptors on this scale (average of 7 K_f = 1.63). Compounds with ni-

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(18) It should be remembered that this direct comparison can only be strictly applied over a wide range of solutes when the slope value for the equation is nearly unity; otherwise, it applies only in the range of solutes where log P = 0.

(19) J. Mitchell, Jr., and D. M. Smith, "Aquametry," Interscience, New York, N. Y., 1948.

(20) I. Kolthoff and P. Elvining, "Treatise on Analytical Chemistry," Part II, Vol. 1, Wiley, New York, N. Y., Section A, pp 69–165.

(21) J. Mitchell, Jr., *Anal. Chem.*, **23**, 1069 (1951).

trogen in an aromatic ring are, as expected, greatly influenced by the polar nature of any substituents, but the K_f value for pyridine (1.88) places them, as a group, among the most capable H acceptors.

It is quite obvious that, in collecting data from hundreds of different laboratories where a variety of techniques were used over a span of 90 years, a sizable number of erroneous values are to be expected in Tables III–XXIII.[15b] However, these "random errors" are certainly as likely in the butanol–water system as in any other, and yet the correlation between it and octanol–water is remarkably good ($r = 0.993$). We must conclude, therefore, that the majority of the deviations noted, for example in the $CHCl_3$–water system, are real and are subject to interpretation on the basis of how the solvent–solute forces differ from the reference system.

Accumulation of partition coefficient data is continuing, and future compilations of more accurate values should place the structural interpretations on an even firmer basis.

Registry No.—Cyclohexane, 110-82-7; heptane, 142-82-5; CCl_4, 56-23-5; xylene, 1330-20-7; toluene, 108-88-3; benzene, 71-43-2; $CHCl_3$, 67-66-3; nitrobenzene, 98-95-3; isopentyl acetate, 123-92-2; oleyl alcohol, 143-28-2; methyl isobutyl ketone, 108-10-1; ethyl acetate, 141-78-6; octanol, 111-87-5; cyclohexanone, 108-94-1; 2-butanone, 78-93-3; cyclohexanol, 108-93-0.

Intermediates in Nucleophilic Aromatic Substitution. IX.[1,2] Kinetic and Proton Magnetic Resonance Investigations of the Interaction of Lyate Ions with *N*-*tert*-Butyl-2,4,6-trinitrobenzamide

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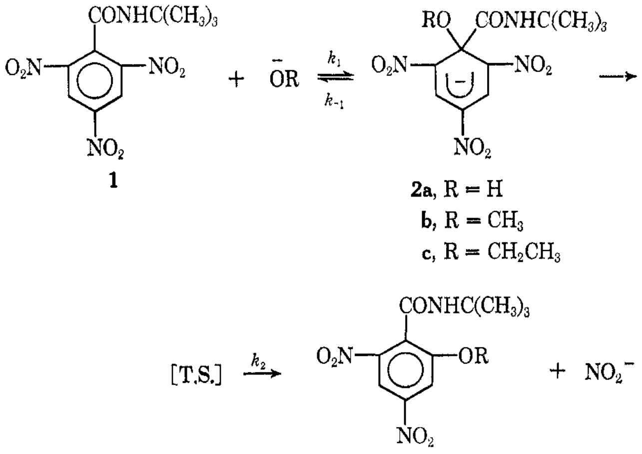
Received October 2, 1970

The interaction of hydroxide and methoxide ions with *N*-*tert*-butyl-2,4,6-trinitrobenzamide (**1**) in water and in methanol, respectively, results in the equilibrium formation of the 1-OH- (or -OCH_3-) 1-$CONHC(CH_3)_3$-2,4,6-$(NO_2)_3C_6H_2$ Meisenheimer complex and the formation of nitrite ions. Rate constants for the formation, k_1, and decomposition, k_{-1}, of these complexes as well as those for nitrite ion production, k_2, have been determined. At 25.00° for hydroxide ion interaction with **1** in water, $k_1 = 17.6$ l. mol^{-1} sec^{-1}, $k_{-1} = 0.0156$ sec^{-1}, and $k_2 = 1.43 \times 10^{-5}$ sec^{-1}, and for the methoxide ion interaction with **1** in methanol, $k_1 = 1.13 \times 10^3$ l. mol$^-$ sec^{-1}, $k_{-1} = 0.46$ sec^{-1}, and $k_2 = 6.7 \times 10^{-5}$ sec^{-1}. Equilibrium constants ($K = k_1/k_{-1}$) have been determined from kinetic measurements of the attainment of equilibrium for complex formation, from those of nitrite ion elimination, and from linear Benesi–Hildebrand plots. Excellent agreement among the three independently determined K values has been found. Structures of the hydroxy, methoxy, and ethoxy Meisenheimer complexes of **1** have been substantiated by pmr measurements of the isolated and *in situ* generated complexes.

N-*tert*-Butyl-2,4,6-trinitrobenzamide (**1**) was reported to undergo nucleophilic substitution with "hydroxide ion" in aqueous methanol (50/50 v/v) producing nitrite ions.[4] The formation of a red color upon the addition of the base to **1** led to the postulation of the presence of a complex.[4] The nature of these experiments, however, precluded the quantitative assessment of all the kinetic steps involved. The replacement of a nitro group on the aromatic ring by lyate ions as well as the relative steric, inductive, and resonance effects of the *tert*-butylamido group on the equilibrium constant for complex formation render the detailed kinetic investigation of this system particularly important. We have obtained data for the attainment of the equilibrium for the formation of the hydroxy and methoxy adducts of **1**, in pure water and in pure methanol, respectively, and for the formation of nitrite ions at different lyate ion concentrations. Using these data the rate constants k_1, k_{-1}, and k_2 in



2a, R = H
b, R = CH_3
c, R = CH_2CH_3

have been obtained. Additionally we have elucidated the structures of **2a**, **2b**, and **2c** using proton magnetic resonance spectroscopy both for the isolated and the *in situ* generated complexes.

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