TABLE III

DIMETHYLNITROPHENYLSULFONIUM AND -SELENONIUM METHYL SULFATE SALTS

Compound	Yield, %	Mp, °C	Formula	Carbon, % Calcd	Carbon, % Found	Hydrogen, % Calcd	Hydrogen, % Found
Dimethyl-*o*-nitrophenylsulfonium methyl sulfate	85	160–162[a]	$C_9H_{13}NS_2O_6$	36.60	...	4.44	...
Dimethyl-*m*-nitrophenylsulfonium methyl sulfate	78	142–143[b]	$C_9H_{13}NS_2O_6$	36.60	36.85	4.44	4.62
Dimethyl-*p*-nitrophenylsulfonium methyl sulfate	92	157–158[c]	$C_9H_{13}NS_2O_6$	36.60	...	4.44	...
Dimethyl-*o*-nitrophenylselenonium methyl sulfate	63	156–158	$C_9H_{13}NSSeO_6$	31.58	31.38	3.83	3.83
Dimethyl-*m*-nitrophenylselenonium methyl sulfate	83	153–157	$C_9H_{13}NSSeO_6$	31.58	31.56	3.83	4.00
Dimethyl-*p*-nitrophenylselenonium methyl sulfate	93	163–165	$C_9H_{13}NSSeO_6$	31.58	31.72	3.83	4.00

[a] Lit. mp 155–157°, K. Brand and O. Stallmann, *Ber.*, **B54**, 1578 (1921). [b] Lit. mp 140–141°, K. Brand and H. W. Leyerzapf, *ibid.*, **B70**, 284 (1937). [c] Lit. mp 157–158.5°, F. G. Bordwell and P. J. Boutan, *J. Am. Chem. Soc.*, **78**, 87 (1956).

concentrated H_2SO_4 and 2 ml of concentrated HNO_3 at room temperature. As soon as a homogeneous solution was obtained, the solution was analyzed in the normal fashion. Gas chromatographic analysis indicated methyl phenyl sulfide and a trace of methyl *m*-nitrophenyl sulfide (<0.5%). The selenonium salt **2** was treated in a similar manner except that the reaction mixture had to be cooled in Dry Ice since, at room temperature, a considerable amount of substitution occurred even with a short reaction time. Only methyl phenyl selenide was observed with a trace of methyl *m*-nitrophenyl selenide (<0.5%). This indicated that there was essentially no substitution occurring during work-up of the reaction mixture.

The nitration of **1** and **2** was carried out in the normal fashion except that 0.3 g of methyl phenyl sulfide and methyl phenyl selenide, rspectively, were added to the reaction mixture. Analysis of the reaction mixture indicated no change in isomer distribution. Nitration of methyl phenyl sulfide and selenide under the nitration conditions of **1** and **2** yielded no methyl nitrophenyl sulfides or methyl nitrophenyl selenides.

Each individual dimethylnitrophenylsulfonium methyl sulfate (**3**, **4**, **5**) (0.5 g) and dimethylnitrophenylselenonium methyl sulfate (**6**, **7**, **8**) (0.5 g) was subjected to the normal nitration and analysis procedure. In all cases, only the corresponding methyl nitrophenyl sulfide or selenide was observed, indicating that there was no rearrangement under the conditions of the reaction and analysis. Two different known concentrations of the dimethylnitrophenylsulfonium methyl sulfate salts (**3**, **4**, **5**) were subjected to the normal nitration and analysis procedure. The results given in Table II indicate good agreement between the calculated and the actural percentages found. No dinitration was observed.

Registry No.—**1**, 6203-16-3; **2**, 13118-29-1; **3**, 13118-30-4; **4**, 13118-31-5; **5**, 13118-32-6; **6**, 13118-33-7; **7**, 13118-34-8; **8**, 13118-35-9.

The Effect of Intramolecular Hydrophobic Bonding on Partition Coefficients

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The 1-octanol–water partition coefficients are presented for 54 organic compounds. The additive–constitutive nature of the logarithm of partition coefficients is considered. It is postulated that intramolecular hydrophobic bonding can result in lower than expected values for partition coefficients in certain types of compounds.

Relatively few partition coefficients have been determined for simple neutral aliphatic compounds. While many studies have been made on simple aliphatic acids and bases, the difficulties involved in the problems of analysis of small concentrations of neutral molecules has not invited work in this area. The largest collection of such constants, although admittedly not very accurate, is that of Collander.[3]

In extending[4–7] the classical studies of Meyer and Overton on the use of partition coefficients for structure–activity correlations, we have used a relative constant π defined as $\pi = \log P_X - \log P_H$. P_H is the partition coefficient of the parent compound in a congeneric series and P_X is that of a derivative. We have shown that π and log P are additive–constitutive constants[8,9] and this property has now been confirmed by others.[10]

In our first studies[8] using aromatic compounds, we found the ultraviolet spectrophotometer to be a convenient tool for the determination of concentrations of the partitioned compounds. For the sake of analytical convenience, we decided to take advantage of the additive character of log P and π to obtain log P for aliphatic compounds. The approach given in eq 1 was used.

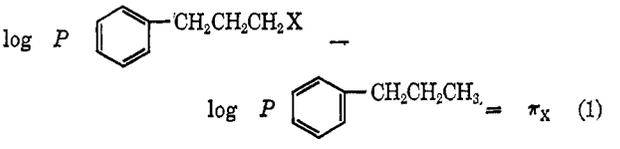

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TABLE I

LOG P FOR 1-OCTANOL–WATER PARTITION COEFFICIENTS

Compound	Registry no.	Log P[a]	No. of determinations[b]
1. Nitromethane	75-52-5	−0.33 + 0.02	7[c]
2. Nitroethane	79-24-3	0.18 ± 0.02	3[c]
3. 1-Nitropropane	108-03-2	0.65 ± 0.03	4[c]
4. Acetonitrile	75-05-8	−0.34 ± 0.03	2[d]
5. Propionitrile	107-12-0	0.16 ± 0.02	2[d]
6. Ethyl acetate	141-78-6	0.73 ± 0.03	2[d]
7. Ethyl propionate	105-37-3	1.21 ± 0.02	2[d]
8. Methanol	67-56-1	−0.66 ± 0.02	2[d]
9. 1-Propanol	71-23-8	0.34 ± 0.02	3[d]
10. 2-Butanol	78-92-2	0.61 ± 0.01	2[d]
11. *t*-Butyl alcohol	75-65-0	0.37 ± 0.03	4[d]
12. *t*-Amyl alcohol	75-85-4	0.89 ± 0.01	2[d]
13. Neopentyl alcohol	75-84-3	1.36 ± 0.03	6[d]
14. Cyclohexanol	108-93-0	1.23 ± 0.03	4[d]
15. 1-Fluoropentane	592-50-7	2.33 ± 0.01	4[d]
16. 1-Chlorobutane	109-69-3	2.39 ± 0.03	5[d]
17. 1-Bromopropane	106-94-5	2.10 ± 0.06	6[d]
18. Iodoethane	75-03-6	2.00 ± 0.10	6[d]
19. Chloroform	67-66-3	1.97 ± 0.04	5[d]
20. 2-Butanone[e]	78-93-3	0.29 ± 0.02	7[c,d]
21. Butyl ethyl ether	628-81-9	2.03 ± 0.03	3[d]
22. Diethyl sulfide	352-93-2	1.95 ± 0.02	4[d]
23. 1-Pentyne	627-19-0	1.98 ± 0.03	6[d]
24. N-Phenyl ethyl carbamate	101-99-5	2.30 ± 0.03	4[c]
25. N-Methyl phenyl carbamate	1943-79-9	1.24 ± 0.02	2[c]
26. Pyrrole	109-97-7	0.75 ± 0.01	3[c]
27. Quinine	130-95-0	1.73 ± 0.02	4[c]
28. Isoquinoline	119-65-3	2.08 ± 0.02	4[c]
29. Picric acid	88-89-1	1.34 ± 0.06	8[c]
30. Sulfanilamide	63-74-1	−0.78 ± 0.02	7[c]
31. 3,4-Methylenedioxybenzyl alcohol	495-76-1	1.05 ± 0.01	4[c]
32. 2,5-Dinitrophenol	329-71-5	1.75 ± 0.05	14[c]
33. 2,6-Dinitrophenol	573-56-8	1.25 ± 0.02	4[c]
34. DL-Camphorquinone	10373-78-1	1.52 ± 0.01	4[c]
35. 4-Trimethylsilylphenol	13132-25-7	3.56 ± 0.01	3[c]
36. 1-Naphthol	90-15-3	2.98 ± 0.01	2[c]
37. 2-Naphthol	135-19-3	2.84 ± 0.01	2[c]
38. Benzothiazole	95-16-9	2.01 ± 0.01	3[c]
39. Antipyrin	60-80-0	0.23 ± 0.01	4[c]
40. Methyl phenyl sulfone	3112-85-4	0.47 ± 0.01	2[c]
41. Salicylamide	65-45-2	1.26 ± 0.01	2[c]
42. 2-Nitroaniline	88-74-4	1.79 ± 0.01	2[c]
43. Acetylsalicylic acid	50-78-2	1.23 ± 0.01	4[c]
44. 4-Ethoxyacetanilide	62-44-2	1.58 ± 0.01	2[c]
45. Thymol	89-83-8	3.30 ± 0.01	2[c]
46. Morphine	57-27-2	0.76 ± 0.02	4[c]
47. Diphenyl sulfone	127-63-9	2.40 ± 0.01	2[c]
48. Benzotriazole	95-14-7	1.34 ± 0.01	2[c]
49. 1,3-Methylphenylurea	1007-36-9	0.42 ± 0.02	3[c]
50. 1,3-Methylphenylthiourea	2724-69-8	0.85 ± 0.01	2[c]
51. N,N-Dimethyl-N′-phenylurea	101-42-8	0.98 ± 0.02	2[c]
52. Indole[f]	120-72-9	2.14 ± 0.01	2[c]
53. Salicylic acid	69-72-7	2.26 ± 0.03	6[c]
54. Butyramide	541-35-5	−0.21 ± 0.02	4[g]

[a] Log P values are given with the standard derivation for the indicated numbers of determinations. The partition coefficient was calculated for the undissociated molecule[8] in the case of acids and bases. [b] Log P is the average of the indicated number of determinations. [c] Analysis made using a Cary Model 14 spectrophotometer. [d] Analysis made using vapor phase chromatography. [e] This value for 2-butanone is more reliable than our previously reported[9] figure of 0.32. The sign of value for 2-butanone in eq 4 of our previous report should be negative. The discovery of this error triggered the work reported in this paper. [f] Our previously reported value for this compound is in error because of a typographical mistake. [g] Determined using Nessler's method of nitrogen determination.

In this way the benzene ring served as a useful analytical marker. The π values obtained for functions such as OH, CN, halogen, etc., could then be added to π (0.5) for methyl and methylene groups to obtain log P for a great variety of aliphatic compounds. For example, log P for ethyl alcohol could be calculated according to eq 2. While this procedure gives a good self-consistent

$$\pi_{CH_3CH_2} + \pi_{OH} = \log P_{CH_3CH_2OH} = 1.0 - 1.8 = -0.8 \quad (2)$$

set of π and log P values of aliphatic compounds which yielded[9] an excellent structure–activity correlation with Overton's data, further work has now revealed an interaction between the aromatic ring and the side chain of the phenylpropyl derivatives which affects the absolute value of π or log P. We have now measured the 1-octanol–water partition coefficients for a variety of aliphatic molecules directly, using vapor phase chromatography as the analytical tool. These values are shown in Table I. Table I also contains a group of miscellaneous log P values which we have measured for various structure–activity studies. Table II shows the difference in π values for aliphatic functions obtained in these different ways. The values for π_1 were obtained[9] *via* eq 1 and those for π_2 were obtained similarly using $C_6H_5CH_2X$ and $C_6H_5CH_3$. Values for

TABLE II

COMPARISON OF DIRECTLY AND INDIRECTLY DETERMINED π VALUES

Function	π_1[a]	π_2[b]	π_3[c]	$\pi_1 - \pi_3$	$\pi_2 - \pi_3$
OH	−1.80	−1.59	−1.16	0.64	0.43
F	−0.73		−0.17	0.56	
Cl	−0.13		0.39	0.52	
Br	0.04		0.60	0.56	
$COOCH_3$	−0.91	−0.86	−0.27	0.64	0.59
$COCH_3$	−1.26	−1.25	−0.71	0.55	0.54
CN	−1.47	−1.13	−0.84	0.63	0.29
OCH_3	−0.98		−0.47	0.51	
$CONH_2$	−2.28	−2.24	−1.71	0.57	0.53

[a] Found[9] using eq 1. [b] Found analogously to π_1 using $C_6H_5CH_2X$ and $C_6H_5CH_3$. [c] Found from the data in Table I. The reference molecules for π_3 are 1-propanol, 1-fluoropentane, 1-chlorobutane, 1-bromopropane, ethyl acetate, 2-butanone, propionitrile, butyl ethyl ether, and butyramide. For each methylene or methyl group a value of 0.5 is assigned.

π_3 were obtained from the data in Table I, as illustrated for F in eq 3.

$$\log P_{C_5H_{11}F} - \pi_{C_5H_{11}} = \pi_F = 2.33 - 2.50 = -0.17 \quad (3)$$

Experimental Section

To determine partition coefficients for compounds not absorbing in the range covered by the Cary spectrophotometer, analysis was carried out using vapor phase chromatography. The Loenco

Model 70 gas chromatograph with hydrogen flame detector was used. The general method for purifying the octanol and partitioning has been described.[8] In our previous work, partitioning was done in centrifuge bottles with rubber stoppers. For our present work, partitioning was done in specially made centrifuge bottles having ground-glass stoppers. For the more volatile compounds, care was taken to use enough of the solvents so that the bottles were almost full; in this way partitioning with air could be neglected.[8] Care must be excercised with acidic or basic compounds to exclude carbon dioxide. Carbon dioxide free water and a nitrogen atmosphere were employed in these experiments.

The concentration was measured in either the octanol or water phase, most commonly the water phase. The concentrations were usually about 10^{-3} M. The amount of octanol used varied from 5 to 175 ml and the amount of water varied from 200 to 25 ml depending on the solubility characteristics of the compound being examined. These variations were made in order to keep the errors resulting from dividing small numbers into large numbers to a minimum.

A weighed portion of compound was usually dissolved in a specific amount of water to form a standard solution. Quantities (1 μl) of this standard were injected into the chromatograph. Usually five repetitions were made for each concentration of the standard. The desired amount of octanol was then added to each standard and the solutions were shaken and centrifuged. A 1-μl portion of the water (or octanol) phase was then chromatographed. The area of each peak was obtained by Xeroxing the graph (to get heavier paper), cutting out the peak, and weighing this piece of paper. The weight was proportional to the concentration of the compound in the solution which was proportional to the weight of sample used. The weight in the octanol layer was obtained by subtracting the weight of the peak of the partitioned solution from the weight of the standard peak.

$$P = \frac{\text{wt of standard peak} - \text{wt of partitioned peak}}{\text{wt of partitioned peak}} \times \frac{\text{vol. of } H_2O}{\text{vol. of octanol}}$$

Discussion

The most striking point in Table II is the essentially constant difference between π_1 and π_3. The agreement is especially good when one considers that π_1 values were obtained by one worker using the ultraviolet spectrophotometer for analysis and π_3 values were obtained 1 year later by another worker using vapor-phase chromatography as the analytical tool. The average standard deviation on the values of $\pi_2 - \pi_1$ is approximately 0.05. Our first thought was that this difference must be a result of an error in the determination of log $P_{C_6H_5CH_2CH_2CH_3}$ since this is a constant factor in the determination of π_1. However, log P for propylbenzene and benzene was determined by three different workers, each separated by about 1 year in time, and good agreement was obtained. Log P for benzene was measured using both the ultraviolet and vpc techniques and found to be the same by each method. The difference between log P for benzene and log P for propylbenzene is 1.56, which gives an average value of 0.52 for each CH_2 unit. This is in good agreement with what we have found in many other instances. Thus, the value for propylbenzene must be reasonably good. By no means can it be off anything near the amount of $\pi_1 - \pi_3$. This leaves us with the conclusion that there must be an interaction between the phenyl ring and the side chain in $C_6H_5CH_2CH_2CH_2X$ not present in propylbenzene. Also, this interaction appears to be essentially independent of the nature of X. It seems likely to us that an interaction of the side-chain dipole with the π electrons of the aromatic ring could result in a folding together of these two protions of the molecules. The electronic force is postulated because the effect is not present in propylbenzene. We would expect the electronic force to be weak but reinforced by intramolecular hydrophobic bonding. The net result is a more compact structure for $C_6H_5CH_2CH_2CH_2X$ and hence when it is placed in water, less perturbation of the water structure results and therefore greater than expected water solubility might be observed. This is what we find comparing π_1 and π_3; the greater negative value for π_1 means higher water solubility. Such effects are to be expected[11] and in fact have been observed. Currie, *et al.*,[10] have suggested that such folding results in a lower than expected log P for vitamin K_1. This, it would seem that the study of the difference between additively calculated partition coefficients and experimentally determined values could shed light on the conformations of complex molecules in aqueous solution. The study of such hydrophobic interactions aided by hydrogen bonding and/or dipolar interactions has been shown to play an important role in protein structure.[12,13]

Shortening the length of the side chain in eq 1 between the aromatic ring and X, one would expect the effect on π to decrease and even to disappear. This effect can be observed in Table II in the column $\pi_2 - \pi_3$. However, even in the benzyl derivatives there appears to be enough interaction between the side chain and the ring to seriously disrupt the normal envelope of water which one would expect[11] to be loosely held around the ring in aqueous solution. The values for $\pi_2 - \pi_3$ are smaller and more varied than $\pi_1 - \pi_3$. Presumably in the case of the benzyl derivatives less than complete shielding of one side of the aromatic ring occurs, while in the case of the phenylpropyl derivatives one side of the benzene ring is likely to be completely shielded from water interaction. In calculating partition coefficients for mixed aliphatic–aromatic compounds, our previously reported[9] values for π will be quite useful. However, when folding can occur and especially when it can be promoted by dipolar interactions or hydrogen bonding, caution must be used in additively combining π and log P values.

A point of concern to us has been the possible effect of a very polar group on π for an apolar moiety such as a methyl or methylene unit. Early work[8] showed that the electronic effect of substituents on a lone pair of electrons could have a pronounced effect on log P. Such an effect seems to be small for methyl and methylene groups. For example, the Δlog P increment in going from nitromethane to nitroethane is 0.52 and in going from nitroethane to nitropropane it is 0.47. The difference between acetonitrile and propionitrile is 0.50. The difference between ethyl acetate and ethyl propionate is 0.48. The difference between *t*-butyl and *t*-amyl alcohols is 0.52. The average value for CH_3 found on 15 different aromatic nuclei[8] is 0.505. It thus appears that polarizing effects of neighboring electronegative atoms on the carbon–hydrogen bond do not greatly affect log P.

In summary, one can say that π and log P values appear to be additive whenever there are no new effects

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in the summation not present in the constituent parts. Such intramolecular interactions which we have so far observed are electronic, hydrogen bonding, and the shielding effects considered in this report. The shielding may be of two kinds. For example, when two apolar groups are adjacent (*e.g., ortho*) to each other, they will not have the same number of structured water molecules around them as when separated (*e.g., para*). The other type of shielding occurs from folding in nonrigid molecules. In this type one can expect an important role for intramolecular hydrophobic bonding.

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The Reaction of Some Quaternary Hydrazones with Grignard Reagents[1]

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Quaternary hydrazones of the type $Ar_2C{=}NN^+R_3I^-$ were prepared by treating various benzophenone dialkylhydrazones with methyl iodide. They reacted exothermically with Grignard reagents to form substances from which the quaternary hydrazone could be recovered on mild hydrolysis. Upon refluxing in tetrahydrofuran, further reaction took place, involving N–N cleavage, leading to tertiary amine, benzophenonimine, N-substituted benzophenonimine, and biaryl (or bialkyl) (eq 3 and 4). A small part of the N-substituted imines corresponded to C to N migration of a C-aryl group, to account for which an amine N-imide intermediate is proposed (eq 5). However, the ratios of the N-attached groups from experiments in which the group in the Grignard reagent and those on the azomethine carbon were different are not consistent with known migration aptitudes and indicate that the major proportion of N-substituted imine arises by direct substitution on the nitrogen. *p*-Chlorobenzaldehyde quaternary hydrazone reacted with *p*-tolylmagnesium bromide to give *p*-methyl-*p'*-chlorobenzophenonimine, which may have arisen through initial base-catalyzed elimination to *p*-chlorobenzonitrile.

It is well known[2] that the azomethine system is less reactive than the carbonyl system toward addition of organometallic reagents, a consequence presumably of greater electronic symmetry. Although aldimines undergo conventional addition of Grignard reagents more or less readily, ketimines may undergo a competing base-catalyzed aldol-type condensation instead,[3] even to the complete exclusion of addition. In such cases, the ketimine acts as a source of active hydrogen and destroys the Grignard reagent (eq 1). Benzo-

$$\begin{matrix} PhC{=}NPh \\ | \\ CH_3 \end{matrix} + RMgX \rightarrow RH + \begin{matrix} PhC{=}CHC{=}NPh \\ | \quad\quad | \\ CH_3 \quad Ph \end{matrix} + PhNHMgX \qquad (1)$$

phenone anil reacts exothermically with phenylmagnesium bromide to form a complex, from which the anil may be recovered unchanged by hydrolysis.[3] When forcing conditions are used, 1,4 addition occurs, giving N-*o*-phenylbenzhydrylaniline.[4] Phenyllithium, however, adds conventionally to give N-triphenylmethylaniline.[5]

Hydrazones behave somewhat analogously to imines. Some aldehyde phenylhydrazones add Grignard reagents, but the NH proton destroys 1 mole of reagent and the reactions are accompanied by N–N cleavage and are not clean.[2] Benzophenone phenylhydrazone does not undergo addition at all.[4] Some dimethylhydrazones have been reported to undergo normal addition of butyllithium or phenyllithium to give trisubstituted hydrazines,[2] but many examples failed altogether and the highest yield reported was only 32%. The reaction of quaternary hydrazonium salts $R_2C{=}NN^+R_3X^-$ with organometallic reagents has not been reported before and is the subject of this paper. The sluggishness of the carbon–nitrogen double bond of imines toward addition of Grignard reagents is largely overcome in immonium salts, $R_2C{=}N^+R_2\ X^-$, which give good yields of tertiary amines.[6] In view of this, we expected that the inductive effect of the positive charge of quaternary hydrazonium salts would activate the azomethine system toward addition reactions. However, this expectation was not realized; this exploratory paper charts the principal types of reaction that actually take place.

Results

Quaternary hydrazonium iodides of benzophenone, *p,p'*-dichlorobenzophenone, *p,p'*-dimethoxybenzophenone, and *p*-chlorobenzaldehyde were prepared by treating the corresponding dimethylhydrazones or pentamethylenehydrazones with methyl iodide.[7]

Treatment of benzophenone trimethylhydrazonium iodide with phenylmagnesium bromide, methylmagnesium iodide, or methyllithium in ether resulted in marked heat evolution, but quaternary hydrazonium salt could be recovered upon hydrolysis, nearly quantitatively in the case of the Grignard reagents. Only when a threefold excess of Grignard reagent and a reaction time of 10 hr in refluxing ether were used was extensive further reaction observed with phenylmagnesium bromide. Hydrolysis led to the recovery

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