explanation of the extraordinarily high affinity of various tricyclic and related compounds which have two aromatic rings at a certain angle to one another.

Experimental Section

Derivatives 1–4 were synthetized according to Smissman and Pazdernik,[8] and both they and (±)-amphetamine were tested as inhibitors of norepinephrine uptake in rat hypothalamic homogenates containing synaptosomes and as inhibitors of dopamine uptake in striatal homogenates. Details of the procedure have been published previously.[1] The brain tissue was homogenized and centrifuged at low speed to remove debris; then the supernatant which contained synaptosomes was incubated for 5 min in Krebs–Henseleit buffer at pH 7.4 with 10^{-8} M [^{3}H]norepinephrine (New England Nuclear, 6.5 Ci/mmol) or 10^{-7} M [^{3}H]dopamine (The Radiochemical Centre, 500 mCi/mmol), various concentrations of the inhibitor or solvent, 0.2 mg/ml of ascorbic acid, and 1.25×10^{-5} M nialamide. After incubation the particulate materials were separated with a membrane filter (Schleicher & Schüll, cellulose nitrate filter, 0.45-μm pore size) and washed with saline. The filter was transferred to a counting vial and the radioactivity accumulated in the tissue was measured by scintillation counting. The inhibition of uptake was calculated as a percentage of the uptake in control samples without an inhibitor. The percentage inhibition was transferred to probit, and the IC_{50} (concentration inhibiting 50% of uptake) was calculated by using semilogarithmic paper. The data obtained with different substrate concentrations were treated for use in double-reciprocal kinetic plots as previously described.[1] Student's t test was used to calculate the significance of the differences between two means.

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Partition Coefficients and Surface Areas of Some Alkylbenzenes

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The experimentally measured log P values (logarithms of partition coefficients) of a number of alkylbenzenes are shown to be quantitatively related to the hydrocarbon surface area HSA of the molecule by $\pi = 0.0275 \times \text{HSA} - 0.863$ (correlation coefficient = 0.996, standard deviation = 0.071). The use of surface area as a correlating parameter eliminates the need for correction factors to account for branching, cyclization, ring fusion, and "backfolding". Furthermore, surface area calculations provide a conceptual basis for understanding how conformation can effect partitioning.

The partition coefficient of a drug is commonly recognized as a key parameter in determining its biological activity. Unfortunately, this parameter cannot usually be determined for the appropriate biological system and we must settle for data obtained by some in vitro partitioning experiment. Octanol–water is by far the most frequently used system for such experiments and has served as an adequate model for correlation with biological data.

Since the pioneering work of Collander[1] there has been a great deal of interest in correlating partition coefficients or π values with chemical structure. The group contribution approach using the substituent constants compiled by Hansch[2] and Leo et al.[3] is probably the most accepted means of estimating log P values for organic compounds in the octanol–water system. While this approach is generally quite good, it cannot be consistently relied upon to give accurate values of log P especially for cyclic, condensed, or multiply branched or for coiled or folded molecules.

It is well known that an extended hydrocarbon will invariably have a higher partition coefficient than its branched isomers. In most cases, the differences can be accounted for by simple correction factors but in complex molecules this is often difficult. In any case, there is no clear-cut explanation for the effects due to isomerism or other structural features on partition coefficients.

Table I. Log P (Octanol–Water) and Total Surface Area (TSA) of Alkylbenzenes

Compound	Log P exptl	Log P calcd from eq 1	TSA, Å^2
Benzene	2.13	2.15	109.5
Toluene	2.69	2.62	126.5
Ethylbenzene	3.15	3.13	144.9
Propylbenzene	3.68	3.63	163.0
Isopropylbenzene	3.66	3.64	163.4
Indan	3.33	3.30	151.1
Tetralin	3.52[a]	3.63	163.0
tert-Butylbenzene	4.11	4.01	176.8
Cyclopentylbenzene	4.27[a]	4.20	183.7
Cyclohexylbenzene	4.64[a]	4.58	197.4
1-Adamantylbenzene	5.43[b]	5.53	232.0
o-Xylene	3.12	3.18	146.8
m-Xylene	3.20	3.28	150.3
p-Xylene	3.15	3.28	150.3

[a] Based on substituted phenoxyacetic acid data (see ref 6). [b] Based on adamantyl alcohol data (see ref 6).

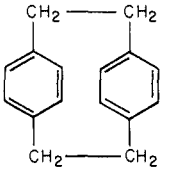
We propose that the differences observed in the partition coefficients of aliphatic and aromatic compounds having the same number of carbon atoms can be fully explained on the basis of differences in the surface areas

of the molecules and that surface area is the fundamental property that determines the magnitude of the partition coefficient of a hydrocarbon. In support of this contention, we have determined the molecular surface areas[4] of those alkylbenzenes for which Hansch et al.[5] have listed aromatic substituents π values. These total surface areas and log P values for several compounds are listed in Table I. For these molecules the total surface area values, TSA, are equivalent to their hydrocarbon surface area, HSA. The log P values here represent the logarithm of partition coefficients of the compounds between octanol and water and are the sum of the log P value of 2.13 for benzene and aromatic substituent π values.[5] An analysis of the data indicates that the relationship between hydrocarbon surface area HSA and log P is

$$\log P = 0.0275 \times \text{HSA} - 0.863 \quad (1)$$
$$\text{correlation coeff} = 0.996;$$
$$\text{std deviation} = 0.071$$

The significance of the excellent correlation between HSA and log P lies in the fact that no correction factors for branching or cyclization were used in the calculation of HSA. These features were completely accounted for by their effect on molecular surface area. Furthermore, the above slope (0.0275) is in excellent agreement with 0.0276, the value expected from the rather well-known π value of 0.5 for a methylene group in an extended chain and its group surface area of 18.1 Å^2.[5] The good fit of the adamantylbenzene provides a further indication of the correlation between surface area and π. It would be extremely difficult to obtain this log P value from group contributions of substituent atoms even with corrections for branching and ring formation.

We are not advocating that surface area calculations replace the group contribution approach for determining π values, but rather that an appreciation of the significance of the molecular surface area can provide a conceptual understanding of the role of structural modification in partitioning. In certain specific instances, surface area considerations can provide insight into apparent discrepancies of the group contribution approach. A classic example of such a discrepancy is paracyclophane (di-*p*-xylylene)



paracyclophane

which has an experimental log P value of 2.33.[6] By the group contribution approach, this compound would have a log P value of 6.30 (twice the value of *p*-xylene) which corresponds to an error of 10000-fold in estimating the partition coefficient. The surface area of paracyclophane is 196.6 Å^2 which is only slightly greater than that of *p*-xylene. By eq 1 this corresponds to an estimated log P value of 4.55 which is about 100 times closer than the group contribution value. The difference between the calculated and experimental values is now small enough to be explained by the increased polarizability of the stacked benzene rings.

It is tempting to try to develop a set of group contributions to surface area from which it would be possible to calculate molecular surface area. This trap must be avoided because the surface area of a particular group is highly dependent upon its neighbors. Nearest neighbors can be accounted for quite successfully by corrections for branching as in the Hansch system, but since non-nearest neighbors contribute toward the reduction of a particular group's surface area, this type of simplified approach is not justified in surface area estimations. The successful explanation of partition phenomena of alkylbenzenes is in full agreement with the recent work of Yalkowsky,[7] Amidon,[8] Valvani,[5] Harris,[9] Hermann,[10] and Reynolds,[11] all of which show agreement between surface area and solution thermodynamic properties of organic compounds.

We are presently in the process of relating the partition coefficients of a number of primary, secondary, and tertiary aliphatic alcohols to their hydroxyl group and hydrocarbon surface areas.

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