charcoal (3). A rather small amount of charcoal also would be less likely to come into rapid and complete contact with drug in the GI fluids than would a larger amount of the adsorbent and a larger dose of drug. In a sense, this represents a mass law effect under dynamic conditions where competitive processes (mainly absorption) are operative.

Andersen (13) showed that the *in vivo* inhibitory effect of charcoal on drug absorption is quantitatively different in the rabbit and dog, possibly due to differences in rates of GI residence time. Similar quantitative differences are likely to exist between man and laboratory animals in general. It would seem, therefore, that *in vitro* adsorption studies, particularly when combined with desorption rate determinations using not only simple aqueous media but gastric and intestinal fluids, should be as useful in many instances as animal experiments for obtaining an estimate of the likely relative antidotal efficacy of activated charcoal for drugs and other potential poisons. Rigorously controlled studies *in man*, as described in the previous report in this series (3), are mandatory for a quantitative assessment of the antidotal efficacy of activated charcoal with respect to the many drugs for which it may be used.

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Relationship between Lipophilic Character and Anesthetic Activity

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Abstract □ The structure–activity relationships in the anesthetic action of a set of 26 aliphatic ethers were found to be parabolic functions of their octanol–water partition coefficients. The results obtained with the gaseous anesthetics were compared with correlations obtained for various hypnotics acting from solution. It was found that optimum lipophilic character (defined as log P_0 from the octanol–water system) is about 2.0 for general anesthetics, which is the same as that found for barbiturates, ureas, alcohols, *etc.*

Keyphrases □ Lipophilicity of aliphatic ethers—related to anesthetic activity, correlated with hypnotics in solution □ Anesthetic activity of aliphatic ethers—related to lipophilicity, correlated with hypnotics in solution □ Structure–activity relationships—lipophilicity and anesthetic activity, aliphatic ethers

The Meyer–Overton theory of the mode of action of anesthetics postulated a linear relationship between anesthetic potency and oil–water partition coefficients of the inert, nonspecific, general anesthetics as well as simple narcotics such as alcohols and esters (1). Despite the fact that linearity cannot hold indefinitely, relatively little thought was given until recently (2–5) to explaining the departures from linearity in such relationships. The efforts of Ferguson (6) stand out as an exception. The evidence is now quite clear that the linear relationship between biological response (usually defined as log $1/C$, where C is the molar concentration of applied drug) and lipophilic character (defined as log P) is not linear in the general sense, but is rather well approximated (7) by Eq. 1:

$$\log 1/C = -k_1 (\log P)^2 + k_2 \log P + k_3 \qquad \text{(Eq. 1)}$$

In Eq. 1, k_1–k_3 are parameters evaluated by the method of least squares using an IBM 360/40 computer. The apex of the parabola defined by Eq. 1 can be obtained by setting the derivative, $(d \log 1/C)/(d \log P)$, equal to zero and solving for log P. This constant of a given system has been termed log P_0. It represents the optimum lipophilic character for a set of congeners acting on a given system. It is a most useful reference point to determine early in any drug modification study, since it represents the maximum activity that can be obtained for a set of drugs simply by manipulation of the lipophilic quality.

In a study of the structure–activity relationships of 16 sets of hypnotics, eight of which were different sets of barbiturates and eight of which were other hypnotics, a mean log P_0 of 1.98 ± 0.35 was found (8). For these different sets of drugs acting on different kinds of animals, log P_0 was obtained from experiments in which the drugs were given by injection (mostly intraperi-

toneal) in aqueous solution. One assumes that the drugs move by a random-walk process to the receptor sites in the CNS. Thus, log P_0 of 2.0 ± 0.3 can be said to be the ideal lipophilic character to design into a *neutral* molecule for *passive* penetration into the CNS. This observation finds support from the work of Soloway *et al.* (9) who injected solutions of benzeneboronic acids into mice and, after 15 min., analyzed for the concentration of boron in the mouse brain. For this situation, we found (8) log P_0 = 2.3. For this example, log P_0 is found directly by chemical analysis and not inferentially by observation of a biological response.

It is of interest to know whether the mode of introduction *via* the lungs or by intraperitoneal injection plays any part in setting the value of log P_0. Using the extrathermodynamic approach, employing numerical constants and regression analysis, one can compare the gaseous anesthetics with the barbiturates, carbamates, alcohols, *etc.*

RESULTS AND DISCUSSION

While many studies have been made of sets of gaseous anesthetics, the literature is lacking in examples where rather lipophilic molecules were employed. The only good example is the study on aliphatic ethers by Marsh and Leake (10). By using their results obtained with mice and the partition coefficients of Table I, Eqs. 2 and 3 were derived:

$$\log 1/C = 0.440(\pm 0.09)\log P + 2.443(\pm 0.15) \quad n\ 26\ r\ 0.894\ s\ 0.171 \quad \text{(Eq. 2)}$$

$$\log 1/C = -0.221(\pm 0.07)(\log P)^2 + 1.038(\pm 0.19)\log P + 2.161(\pm 0.12) \quad n\ 26\ r\ 0.966\ s\ 0.101 \quad \text{(Eq. 3)}$$

Equation 3 is a significant improvement over Eq. 2 ($F_{1,23}$ = 46.2; $F_{1,23\ \alpha.005}$ = 9.6). However, of most interest is the value of 2.35 (2.10–2.81) found for log P_0. The figures in parentheses are the 95% confidence intervals on this parameter (8). The value of log P_0 found for administration of anesthetics in vapor form is close to the mean value of that found for a wide variety of nonvolatile drugs given by injection in aqueous solution (8). The similarity of action of the volatile anesthetics to other hypnotics which probably act *via* membrane perturbation is indicated by the coefficient of 1.04 with the log P term of Eq. 3. This is quite close to the mean value of 1.01 ± 0.13 found for 57 other similar processes involving narcosis or membrane perturbation (11, 12).

The intercept of Eq. 1 is a useful index for comparing different sets of congeners, either acting on the same system or on different systems. In comparing intercepts, comparison is being made of isolipophilic molecules where P = 1 or log P = 0. The value of the intercept is a function of the test system and of the intrinsic pharmacophoric character of a given set of congeners. Since activity has been defined by the reciprocal ($1/C$), the larger the intercept, the more active is the drug. The value of the intercept for any given system depends, of course, on the kind of response demanded by the investigator. For example, an ED_{100} yields a smaller intercept than an ED_{50}.

The intercept of Eq. 3 is much higher than those found for nonspecific narcotics acting in aqueous solution. For example, Eq. 4 correlates (13, 14) the narcosis of tadpoles by miscellaneous *neutral* compounds:

$$\log 1/C = 0.94(\pm 0.07)\log P + 0.87(\pm 0.12) \quad n\ 51\ r\ 0.971\ s\ 0.280 \quad \text{(Eq. 4)}$$

In the case of the tadpoles, log P_0 is higher than 2. In deriving Eq. 4, data on a fair number of molecules having log $P > 2.4$ were used. However, adding a term in $(\log P)^2$ to Eq. 4 does not result in an improvement in the correlation. While the linear terms in Eqs. 3 and 4 are, for practical purposes, identical, the point of departure from linearity in the two cases is higher for the tadpoles. The interpretation of this is that there is a simpler random walk to the sites of action for the drugs in the tadpoles than in the mouse or other mammals. Narcosis in the tadpole is defined as a lack of movement of the tadpole when swimming in an aqueous solution of the narcotic. This difference in narcosis of tadpoles might be due to inhibition of oxygen uptake by the gills or a general blocking of the neuromuscular junction. In this latter connection, it is of interest to consider Eqs. 5 and 6:

$$\log 1/C = 0.85(\pm 0.14)\log P + 0.70(\pm 0.23) \quad n\ 28\ r\ 0.927\ s\ 0.369 \quad \text{(Eq. 5)}$$

$$\log 1/C = 1.05(\pm 0.10)\log P + 0.28(\pm 0.20) \quad n\ 8\ r\ 0.995\ s\ 0.141 \quad \text{(Eq. 6)}$$

correlating nerve block by miscellaneous organic compounds on the frog sartorius muscle (15) and aliphatic alcohols (ROH) on the frog sciatic nerve (12), respectively.

In Eq. 5, the data were collected by simultaneously impaling single fibers with two micropipets for stimulating and recording potential changes. The criterion used to determine minimum blocking concentration was failure to excite 5–10 cells, whose resting potential was greater than 80 mv., with depolarizing pulses of 50–70 mv. Not all of the data used to formulate Eq. 5 were from the same laboratory, and this may, at least in part, account for the somewhat high standard deviation of Eq. 5. Most of the data are from the work of Agin *et al.* (15). Equations 4 and 5 are about as close to being identical as one could expect.

The data upon which Eq. 6 is based were obtained in a similar but less precisely defined manner (16). Equation 6 is also very close in form to Eqs. 4 and 5. Thus, it seems that Eq. 1 and its simpler linear form can be used to help make decisions about the mode of action of drugs acting on different systems. Anesthetics and narcotics, when injected into or inhaled by animals, show the same linear dependence on log P; however, the linear relation does not hold over such a wide range with the mammals as it does with tadpoles. This suggests that effects on the CNS of mammals may be rate controlling in anesthesia or narcosis, while tadpole movement is rate controlled more by the blocking of the neuromuscular junc-

Table I—ED_{50} for Anesthesia of Mice by Aliphatic Ethers

	Compound	log P[a]	log 1/C Obs.[b]	log 1/C Calc.[c]	|Δ log 1/C|
1	Dimethyl	−0.23	1.85	1.91	0.06
2	Methyl ethyl	0.27	2.22	2.42	0.21
3	Divinyl[d]		2.82		
4	Ethyl vinyl[d]	1.04[e]	2.82	3.00	0.18
5	Methyl cyclopropyl	0.48	2.85	2.61	0.24
6	Methyl isopropyl	0.57	2.70	2.68	0.02
7	Diethyl	0.77[e]	2.75	2.83	0.08
8	Methyl propyl	0.77	2.90	2.83	0.07
9	Ethyl cyclopropyl	0.98	3.10	2.97	0.13
10	Ethyl isopropyl	1.07	3.00	3.02	0.02
11	Methyl *tert*-butyl	0.80	3.00	2.85	0.15
12	Methyl *sec*-butyl	1.04	3.04	3.00	0.04
13	Methyl isobutyl	1.08	3.00	3.02	0.02
14	Ethyl propyl	1.27	3.10	3.12	0.02
15	Methyl butyl	1.27	3.15	3.12	0.03
16	Diisopropyl	1.63	3.15	3.27	0.12
17	Ethyl *tert*-butyl	1.56	3.15	3.24	0.09
18	Ethyl *sec*-butyl	1.80	3.22	3.32	0.10
19	Ethyl isobutyl	1.83	3.22	3.32	0.10
20	Propyl isopropyl	1.83	3.26	3.32	0.06
21	Methyl amyl	2.03	3.40	3.36	0.04
22	Dipropyl	2.03[e]	3.40	3.36	0.04
23	Ethyl butyl	2.03[e]	3.30	3.36	0.06
24	Ethyl *tert*-amyl	2.08	3.40	3.37	0.03
25	Ethyl isoamyl	2.35	3.45	3.38	0.07
26	Ethyl amyl	2.53	3.45	3.38	0.07
27	Di-*sec*-butyl	2.57	3.45	3.37	0.08
28	Diisobutyl	2.64	3.30	3.36	0.06

[a] P is from the octanol–water system. [b] From *Reference 10*. [c] Calculated using Eq. 3. [d] These compounds not used in deriving Eq. 3. The log P for ethyl vinyl ether was measured, and it does fit Eq. 3 rather well; however, because of experimental difficulties in the measurement of this compound, this value is not believed to be as reliable as the others of Table I. No attempt was made to determine log P for divinyl ether. [e] These values were determined experimentally; see text for the method used in calculating the other values.

Table II—Intrinsic Narcotic Activity of Neutral Isolipophilic Compounds to Various Systems

Type of Compound	Biological Activity	Intercept
ROH	5-mv. decrease in rest potential of lobster axon	−0.10 (±0.10)
Miscellaneous	Narcosis frog heart	0.11 (±0.10)
ROH	I_{50} lung O_2 consumption	0.16 (±0.11)
ROH	Inhibition bacterial luminescence	0.22 (±0.10)
ROH	Inhibition paramecium mobility	0.33 (±0.08)
Miscellaneous	I_{50} rabbit cervical ganglion O_2 consumption	0.56 (±0.66)
Miscellaneous	Colchicine-mitosis onion root tip	0.56 (±0.19)
ROH	Narcosis barnacle larvae	0.59 (±0.12)
Miscellaneous	I_{50} rabbit cervical ganglion postsynaptic pulse	0.82 (±0.52)
ROH	LD_{50} cat	0.81 (±0.44)

tion. In the one example (17) where quite lipophilic alcohols were used to narcotize tadpoles, a log P_0 of 7.6 (5.3–24) was found. While the 95% confidence intervals on this figure are high, there is no doubt that log P_0 is at least three orders of magnitude higher than for anesthetic or hypnotic action of drugs on mammals.

The narcotic effect of the type represented in Eqs. 4–6 is much less sensitive than that of Eq. 3. It is similar to that of other nonspecific processes, as illustrated by the intercepts of similar linear equations (*with slopes* near 1) in Table II. The intercept of Eq. 4 resembles those of Table II, while that of Eq. 3 is about 1.3 log units higher (about 20-fold). This indicates the much greater sensitivity of the mouse CNS to the nonspecific action of the chemically inert ethers.

Another way to obtain information on the validity of log P_0 of approximately 2 for general anesthetics is to measure the values for some of the most potent of the known drugs. Table III lists several examples. After so many years of searching for general anesthetics, it is interesting to note that the most potent drugs so far discovered have log P_0 values near 2.

From a practical point of view, it is important to be aware of the fact that log P_0 is about 2. Why this is so for general anesthetics adiminstered *via* the lungs and hypnotics given intraperitoneally is not completely clear.

With the injected hypnotics such as the barbiturates, it seems reasonable to assume a nonequilibrium situation and that the effective concentration of drug on the receptors is limited by a random-walk process. This idea has been shown (3, 4, 13) to be a reasonable way to account for log P_0. In addition to the "kinetic" explanation for log P_0, Higuchi and Davis (5) offered what might be termed a "thermodynamic" explanation for log P_0. Their mechanisms assume equilibrium (or something close to it) between the drug in the various compartments of the system. It has often been assumed that, in general anesthesia, one is working with a system near equilibrium. If this is true, then log P_0 would be "thermodynamically" determined; if not, one would be forced to assume "kinetic" determination of this parameter.

METHOD

Partition coefficients were not measured for every molecule and, except for diethyl ether, dipropyl ether, and ethyl butyl ether, were calculated by means of additivity principles (13, 18). Diethyl ether was used as the standard for calculating log P of ethers 1–15. Dipropyl ether and ethyl butyl ether were used as standards for calculating log P of ethers 16–28.

It has been found that each CH_2 in a homologous series increases log P by about 0.5. Thus, log P for dimethyl ether was calculated from log P for diethyl ether:

$$\log P_{\text{diethyl ether}} - 2(CH_2) = 0.77 - 1.00 = -0.23 \quad \text{(Eq. 7)}$$

A branched chain near a functional group usually decreases log P by 0.2. Hence:

$$\log P_{\text{isopropyl alcohol}} = \log P_{\text{propyl alcohol}} - 0.2 = 0.14 \quad \text{(Eq. 8)}$$

Thus, log P for methyl isopropyl ether was calculated from $\pi_{\text{isopropyl}}$ and π_{CH_3O}:

$$0.14 - \pi_{OH} = 0.14 - (-1.16) = \pi_{\text{isopropyl}} = 1.30 \quad \text{(Eq. 9)}$$

and:

$$\pi_{CH_3O} = \log P_{\text{dimethyl ether}} - 0.5 = -0.23 - 0.5 = -0.73 \quad \text{(Eq. 10)}$$

$$\log P_{\text{methyl isopropyl ether}} = 1.30 - 0.73 = 0.57 \quad \text{(Eq. 11)}$$

Table III—Octanol–Water Partition Coefficients of Potent Anesthetics

Compound		log P
Trichloroethylene	$Cl_2C{=}CHCl$	2.29
Methoxyflurane	$CH_3OCF_2CHCl_2$	2.21
Chloroform	$CHCl_3$	1.97
Halothane	$CF_3CHBrCl$	1.81

To calculate the log P of ethyl *tert*-butyl ether, ethyl butyl ether was used as the standard. Hence:

$$\log P_{\text{ethyl butyl ether}} - \pi_{Bu} = 2.03 - 2.00 = \pi_{C_2H_5O} = 0.03 \quad \text{(Eq. 12)}$$

$$\log P_{\text{ethyl } tert\text{-butyl ether}} = \pi_{C_2H_5O} + \pi_{tert\text{-Bu}} = 0.03 + 1.53 \text{ (obtained from } tert\text{-butyl alcohol)} = 1.56 \quad \text{(Eq. 13)}$$

Log P for methyl cyclopropyl ether was calculated as follows:

$$\log P_{\text{4-cyclopropyl-2-butanone}} - \log P_{\text{2-butanone}} = 1.50 - 0.29 = \pi_{\text{cyclopropyl}} = 1.21 \quad \text{(Eq. 14)}$$

$$\log P_{\text{methyl cyclopropyl ether}} = \pi_{\text{cyclopropyl}} + \pi_{CH_3O} = 1.21 - 0.73 = 0.48 \quad \text{(Eq. 15)}$$

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