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Received October 16, 1978.

Accepted for publication December 14, 1978.

Supported by Contract N01-CM-33743 from the Division of Cancer Treatment, National Cancer Institute, National Institutes of Health.

The authors thank Dr. Harry B. Wood and Mr. Robert B. Ing of the National Cancer Institute for their interest and encouragement.

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Conformation, Partition, and Drug Design

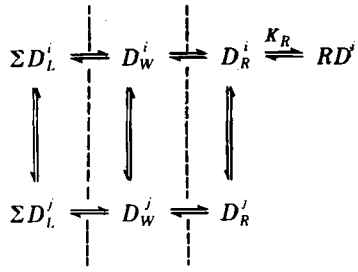
Keyphrases □ Conformations—drug, biological activity, fraction of conformer and partition coefficient □ Structure-activity relationships—drug conformers, biological activity, fraction of conformer and partition coefficient □ Partition coefficients—drug conformers, structure-activity relationships, biological activity

To the Editor:

Current interest in drug conformation rests on the postulate that a single preferred conformer binds to the receptor productively. If this conformer can be identified, it can then be fixed, or at least its population can be enhanced, by chemical means. In most areas of interest in drug design, however, drug–receptor complexes are not available for detailed molecular study, so the active conformation must be inferred. The usual procedure has been to seek correlations between conformation, determined experimentally or theoretically for a drug series, and biological response.

Until recently, the dominant conformer was assumed to be the biologically active agent (1). While there have been problems of agreement on the form of the dominant conformer (2), the widely variable responses that can occur even when the physical conformation is unambiguous (3) have encouraged the idea that a minor conformer may sometimes be responsible for activity (4–7). Thus, besides an interest in the nature of the active conformation, there is an interest in the fraction of active conformer in solution and in how it varies with chemical structure (5, 6).

An entirely different approach to drug design is based on multiparameter correlations of biological response with partition coefficients and other physical properties. This



Scheme I—Distribution of drug D *as active conformer* D^i *and inactive conformer(s)* D^j *between the aqueous phase* W, *the lipoidal loss phases* L, *the receptor phase* R, *and the receptor surface.*

quantitative structure–activity relationship approach (8) is used routinely by medicinal chemists in drug design (9). These two different approaches are almost invariably pursued in isolation. The purpose of this paper is to discuss the relation between them.

A flexible molecule behaves as many different molecules, depending on conformation. Different conformations have their own physical, chemical, biological, and thermodynamic properties. Of particular use is the concept of the micropartition coefficient, defined as the partition coefficient attaching to an individual conformer.

Consider a drug supplied as a single dose to a multiphase system (Scheme I). Regions of similar partition coefficient constitute a single phase even if anatomically separate. The model comprises an aqueous phase (volume V_W) and a receptor phase (volume V_R), together with N nonaqueous loss phases (devoid of receptors) with volumes V_L (L = 1–N). If biological activity resides in a single conformer D^i, its equilibrium concentrations in the various phases are $[D_W^i]$, $[D_R^i]$, and $[D_L^i]$, giving fractions of active conformer:

$$f_W^i = \frac{[D_W^i]}{[D_W]} \qquad \text{(Eq. 1a)}$$

$$f_R^i = \frac{[D_R^i]}{[D_R]} \qquad \text{(Eq. 1b)}$$

$$f_L^i = \frac{[D_L^i]}{[D_L]} \qquad \text{(Eq. 1c)}$$

Equilibration of the drug between the receptors and the receptor phase is defined by a binding constant:

$$K_R = \frac{[RD^i]}{[R][D_R^i]} \qquad \text{(Eq. 2)}$$

where $[R]$ and $[RD^i]$ are the concentrations of free receptors and productive drug–receptor complexes, respectively.

Suppose that drug distribution is much faster than degradation or elimination. Suppose also that the biological response is directly proportional to receptor coverage $[RD^i]$, that receptors are identical and independent, and that a negligible fraction of the total drug is bound to receptors. Receptor flexibility and the mechanism and kinetics of drug binding are outside the scope of this discussion. If the total dose is S, then:

$$S = V_W[D_W] + V_R[D_R] + \sum_{L=1}^{L=N} V_L[D_L] \qquad \text{(Eq. 3)}$$

$$S = [D_W]\left\{V_W + V_R P_R + \sum_{L=1}^{L=N} V_L P_L\right\} \qquad \text{(Eq. 4)}$$

where P_R and P_L are partition coefficients. The relationship $[D_W] = [D_R]/P_R$, taken with Eqs. 1 and 2, allows $[D_W]$ to be substituted, giving:

0022-3549/79/0300-0396$01.00/0

Table I—Conformer Populations in Furfuraldehyde

Medium	ϵ	$\Delta G_{cis} - \Delta G_{trans}$, kcal/mole	Ratio *trans/cis*	Reference
Vapor	1.0	1.0 (25°)	5	11
		2.0 (25°)	31	12
		2.0 (37°)	26	13
1,1-Difluoro-2,2-dichloroethylene	2.9	0.34 (37°)	1.7	13
Dimethyl sulfoxide	45	−0.84 (37°)	0.22	13

$$\frac{1}{S} = \frac{K_R[R]f^i_R P_R}{[RD^i]\left\{V_W + V_R P_R + \sum_{L=1}^{L=N} V_L P_L\right\}} \quad \text{(Eq. 5)}$$

For a constant biological response (*i.e.*, constant $[RD^i]$), $1/S$ is a measure of the potency of any drug within a series. If all nonaqueous loss phases can be considered collectively with P_N as a net coefficient for partition into phases of total volume $V_N = \Sigma_{L=1}^{L=N} V_L$, then:

$$\frac{1}{S} = \frac{K_R[R]f^i_R P_R}{[RD^i]\{V_W + V_R P_R + V_N P_N\}} \quad \text{(Eq. 6)}$$

Three special cases exist, depending on which phase is dominant (contains most of the drug).

Case 1—If $V_R P_R \gg V_W + V_N P_N$, then $1/S \propto K_R f^i_R$. Potency increases with the fraction of drug in the active conformation and with increasing affinity constant. This case is trivial.

Case 2—If $V_W \gg V_R P_R + V_N P_N$, then $1/S \propto K_R f^i_R P_R$. If most of the drug is lost in the aqueous phase, potency becomes a mixed function of partition coefficient and active conformer fraction; neither alone can be expected to correlate directly with biological data.

Case 3—If $V_N P_N \gg V_W + V_R P_R$, then $1/S \propto K_R f^i_R P_R / P_N$.

Attention concentrates on Case 2, which is simpler than Case 3 but demonstrates the main principles and is applicable equally to steady-state models (7).

The micropartition coefficient, P^i_R, for the active conformer may be defined by analogy with the overall or macropartition coefficient, P_R:

$$P^i_R = \frac{[D^i_R]}{[D^i_W]} P_R = \frac{[D_R]}{[D_W]} \quad \text{(Eq. 7)}$$

By combining Eqs. 1 and 7, it may be seen that:

$$f^i_R P_R = f^i_W P^i_R \quad \text{(Eq. 8)}$$

so an alternative form for Case 2 is $1/S \propto K_R f^i_W P^i_R$.

Equation 8 demonstrates a necessary interdependence between the conformer balance and partition coefficient. Variations in the active conformer fraction between phases must be accompanied by variations in macro- and micropartition coefficients. This result has consequence only to the extent that shifts in conformer balance actually occur. Conformer populations can vary substantially with solvent (10–14) (Tables I and II), and this must mean that micropartition coefficients can vary sharply with conformation. Further evidence comes from recent work on hydroxyureas (15). Similarly, the 4.3-fold increase in the octanol–water partition coefficient between *p*- and *ortho*-hydroxybenzoic acids is almost certainly due to internally hydrogen-bonded species in the latter having greater micropartition coefficients than the open forms (16).

In real tissues, drugs distribute themselves among the different biological phases in a complex manner. The two forms for Case 2 show the effects of partition and conformation to be complementary variables in any model of such behavior. In our idealized situation (Case 2), the biological potency is related to the usual macropartition coefficient, P, and the active conformer fraction in the receptor phase. Alternatively, a relation could be sought involving the active aqueous phase conformer fraction and the micropartition coefficient, P^i_R. Either relation in logarithmic form takes on a quantitative structure–activity relationship appearance (9). The choice between them is a matter of experimental convenience. The utility of $1/S \propto K_R f^i_W P^i_R$ is limited by experimental difficulties in determining the micropartition coefficient, P^i, but such values may become more accessible as methods for theoretical calculation improve. Some measure of the active conformer fraction will be required in any comprehensive study of the relation between structure and activity.

This complementary relationship has implications for toxicity and pharmacodynamics.

Table II—Conformer Populations in 1-Fluoro-2-chloroethane[a]

Medium	ϵ	$\Delta G_{gauche} - \Delta G_{trans}$, kcal/mole	Ratio *trans/gauche*	Reference
Vapor	1.0	0.90	2.3	14
Cyclohexane	2.0	0.31	0.85	14
Methyl iodide	7.0	−0.16	0.38	14
Acetone	20.7	−0.64	0.17	14
Pure liquid	21.1	−0.67	0.16	14

[a] These values assume that the intensity of the C—Cl stretching band is independent of conformation. The relative values of the *trans–gauche* ratio and $\delta\,\Delta G$ are unaffected by this assumption.

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Received July 31, 1978.
Accepted for publication December 6, 1978.