tions. This establishes the configurations of all compounds in Scheme I and thus the stereochemistry of the transformations of (+)-V to (−)-VII-HBr and (+)-VIII under von Braun conditions.

It is known that the conversion of (+)-VIII to XIV proceeds stereospecifically with retention of configuration and that the rest of the reactions of Scheme I do not affect the original center of asymmetry (3–7). Accordingly, the fact that (+)-V and (+)-VIII afford antipodal X-*p*-toluenesulfonates proves that they have the same configuration. The conversion of (−)-VII-HBr to (+)-VIII establishes that it, too, has the same configuration as (+)-V and (+)-VIII. This proves that the conversion of (+)-V to (−)-VII-HBr and (+)-VIII proceeds with retention of configuration. Within the limits of experimental error, the rotations of the *p*-toluenesulfonates indicate that the reaction is stereospecific (90 ± 10%).

If cyanogen bromide attacks at nitrogen to give XII, the only *direct* route to a 3-bromo analog must involve XVI, which would result in inversion of configuration. The less direct route through XVII and XII is also untenable on stereochemical grounds. Thus, the mechanism of the reaction must involve initial attack of cyanogen bromide on the hydroxyl to give IX (*cf.*, 2). Displacement of cyanate by bromide is consistent with both the chemistry of alkyl cyanates (9–14) and the formation of (+)-V from (−)-I *via* a closed ion-pair (XVII) with 15% retention of configuration under *quasi*-Favorskii conditions (4, 5, 8). Accordingly, VII is the precursor of VIII.

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ACKNOWLEDGMENTS AND ADDRESSES

Received May 17, 1973, from the *Laboratory of Medicinal Chemistry, Division of Organic Chemistry, College of Pharmaceutical Sciences in the City of New York, Columbia University, New York, NY 10023*

Accepted for publication August 31, 1973.

Abstracted from a dissertation submitted by J. R. Soares to Columbia University in partial fulfillment of the Doctor of Philosophy degree requirements.

Supported by Grant NB-03593, National Institutes of Health, U.S. Public Health Service, and in part by a grant from the University of Connecticut Research Foundation.

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COMMUNICATIONS

General Influence of Physicochemical Properties on Drug–Receptor Combination

Keyphrases □ Drug–receptor combinations—influence of physicochemical properties □ Structure–activity relationships—influence of physicochemical properties on drug-receptor combinations □ Receptor sites—influence of physicochemical properties on interaction with drugs

Sir:

Previous publications (1–10) showed how the physicochemical properties of chemically and structurally related compounds, particularly homologs, can be the principal determinant of the structure–biological activity "parabolic" profile for a congeneric family by reason of the influence of the physicochemical properties on relative rates of transport. There are, of course, circumstances that preclude involvement of transport in the determination of activity profiles. Even in the absence of a significant or identifiable transport component, so-called "parabolic" dependencies are generally still observed for compounds chemically similar in polar functionality but widely dissimilar in hydrophobic property (11). Again, models founded on fundamental physicochemical relationships have been proposed to explain some of these data (12, 13), the most sophisticated treatment being that of Higuchi and Davis (13) in which the relative degree of receptor site occupation is computed using a quasiequilibrium distributional model. Among other things, the Higuchi and Davis model assumes the net receptor interaction or "occu-

pancy" at a given concentration to be a summation of: *(a)* interactions with the receptor of specific functional groups having specific positional placements, the "lock and key" effect; and *(b)* interactions influenced by the gross structure of the molecules, which in a general and often predictable manner contribute to the receptor site–receptor environment equilibrium.

The present communication suggests another mechanism whereby physicochemical properties can determine or influence structure–activity profiles. The principles outlined here apply to binding in two-dimensional phases (interfaces, surfaces, and protein surfaces) generally, but the particulars are directed to drug–receptor interactions. The concepts presented are based on relative receptor site occupation by homologs. The receptor is viewed as a homogeneous two-dimensional phase obeying a Langmuir-type isotherm, which is a common idealization of a receptor phase. Thus, the receptor "compartment" is considered to have a finite, limiting capacity, *i.e.*, full occupancy, for the active compounds.

Langmuir's isotherm can be expressed in the following form:

$$f = \frac{(k_1/k_{-1})C}{1 + (k_1/k_{-1})C} \qquad \text{(Eq. 1)}$$

where f is the fractional occupation of available sites ($1 > f > 0$); (k_1/k_{-1}) is the ratio of the adsorptive rate constant, k_1, to the desorptive rate constant, k_{-1}; and C is an arbitrarily chosen and fixed bulk equilibrium concentration. Here we are assuming that C is constant after equilibrium is established, a condition that can be obtained by titrating to a fixed C at equilibrium or by using a large bulk phase reservoir so that C_0 and C_∞ are not appreciably different. As formulated, the isotherm has f in lieu of the more standard "amount adsorbed per unit weight of adsorbent." Thus, the limiting capacity term, often designated as A, does not appear explicitly in the equation, since the limiting capacity in terms of fractional site occupation is obviously unity.

In addition to the assumptions of Higuchi and Davis, two commonly accepted assumptions regarding the relationship of biological response to receptor occupation are incorporated in the thoughts presented; namely, the biological response is proportional to the fractional occupation of receptor sites and, due to analytical sensitivity or other similar constraints, there is a finite value of f, f^*, below which response is uncertain. The f^* value is the threshold for measurable pharmacological activity. Collectively, these assumptions and Eq. 1 imply that as f approaches unity, the response approaches a maximum. Moreover, at low values of f, a linear dependency between response and concentration exists. It is tacitly assumed that the receptor environment is aqueous in nature.

To understand better the relationship between pharmacological response (or f) and the physicochemical properties of the compounds in question, it is necessary first to define physicochemical relationships related to structure for each parameter (k_1, k_{-1}, and, possibly, C) in Eq. 1. Fortunately, simple and reasonably general mathematical relationships can be drawn for such properties if the discussion is limited to homologs. It cannot be stressed too strongly that the concepts (but not the simple equations) also apply to less regularly behaving structural modifications.

Within an homologous series, relative values of the adsorption rate constant/desorption rate constant ratio are known generally to follow Traube's rule (14–16) or to conform to the mathematical relationship:

$$K_n = (k_1/k_{-1})_n = (k_1/k_{-1})_0 10^{\epsilon n} \qquad \text{(Eq. 2}a\text{)}$$

or alternatively:

$$\log (k_1/k_{-1})_n = \log (k_1/k_{-1})_0 + \epsilon n \qquad \text{(Eq. 2}b\text{)}$$

where $(k_1/k_{-1})_n$ is the adsorptive equilibrium constant at chain length n, $(k_1/k_{-1})_0$ is the Y intercept of the adsorptive equilibrium constants (K_n values) plotted semilogarithmically against chain length n (corresponding to the adsorptive equilibrium constant of the hypothetical zero chain length compound), and ϵ is the slope of the plot.

Combination of Eqs. 1 and 2a yields for fractional occupation by a given homolog, f_n, at a given concentration:

$$f_n = \frac{(k_1/k_{-1})_0 10^{\epsilon n} C}{1 + (k_1/k_{-1})_0 10^{\epsilon n} C} \qquad \text{(Eq. 3)}$$

If we arbitrarily choose and fix a value of C such that, at small n, $f_n << 1$ [alternatively, $(k_1/k_{-1})_0 10^{\epsilon n} << 1$], this equation predicts:

1. As chain length is extended from small values to intermediate values of n, the fractional occupation of the receptor phase grows exponentially.

2. Considering the exponential nature of the function, $10^{\epsilon n}$, at some value of n, the condition $(k_1/k_{-1})_0 10^{\epsilon n} C >> 1$ will develop. The fractional occupation thus will asymptotically approach 1. This is true regardless of the choice of C and may even be true for small n if C is sufficiently large. Providing there are no limitations on C, maximal response (full receptor occupation) will occur at some chain length and will be maintained thereafter with further increases in n.

There are, of course, definite limitations on concentration dictated by the solubilities of the respective homologs in the series. It has been shown that, in water, homolog solubilities generally obey the relationship (17, 18):

$$S_n = S_0 10^{-\delta n} \qquad \text{(Eq. 4}a\text{)}$$

or, alternatively:

$$\log S_n = \log S_0 - \delta n \qquad \text{(Eq. 4}b\text{)}$$

where S_n is the solubility of the homolog of chain length n, S_0 is the Y intercept (zero chain length value) of a plot of log (solubility) against chain length, and δ is the absolute value of the slope of the function as described in Eq. 4b. Equation 3 may be

reformulated for the case where adsorption from saturated solutions of the respective homologs is solely considered by incorporation of the solubility relationship for C, *i.e.*:

$$(f_n)_s = \frac{(k_1/k_{-1})_0 S_0 10^{(\epsilon-\delta)n}}{1 + (k_1/k_{-1})_0 S_0 10^{(\epsilon-\delta)n}} \qquad \text{(Eq. 5)}$$

It is obvious from Eq. 5 that the fractional occupation of sites from saturated solutions for a given homolog, $(f_n)_s$, is responsive to the extrapolated adsorptive equilibrium and solubility of the hypothetical zero chain length homolog and the relative magnitudes of ϵ and δ, which appear in exponential form as a difference. Clearly, if $\epsilon > \delta$, the fractional occupation will approach the maximum value of 1 as alkyl chain length is extended when dealing with saturated solutions. But if $\delta > \epsilon$, the reverse will ultimately be true; that is, occupancy will tend to zero with lengthening of the alkyl chain.

It is our contention that the latter situation, $\delta > \epsilon$, is invariably true. Values of the function δ were previously organized by Saracco and Marchetti (17). They analyzed data for the aqueous solubilities of a large and diverse number of homologous series and found that δ values ranged from 0.43 to about 0.75, with an average value in excess of 0.6 (the values stated here are in terms of base$_{10}$ logs). Values of ϵ have not been similarly organized, but some idea of the magnitude of ϵ can be garnered from literature data (14–16, 19–32). These data indicate that the incremental increase in the adsorptive constant (or other related adsorptive property) per methylene unit for adsorption of homologs from a water onto a solid surface has an upper limit of about 3 and ranges down to values less than 1.5. This translates into an ϵ value range of roughly 0.15–0.5. These data do not lend themselves to simple tabulation because several adsorption isotherms are involved, adsorptive capacities and adsorptive constants have generally not been factored, and, in some cases, only single-point (single-concentration) determinations have been made. It is clear, however, that δ values are larger than ϵ values.

With all of the limiting assumptions in mind, particularly the rather idealized assumption that we are dealing with a homogeneous two-dimensional phase, we can proceed in the analysis of the impact of incrementally increasing adsorptive constants and decrementally decreasing solubilities on "occupancy" profiles. Equation 5 can be restated in the following logarithmic form:

$$\log (f_n)_s = \log[(k_1/k_{-1})_0 S_0] + (\epsilon - \delta)n - \log[1 + (k_1/k_{-1})_0 S_0 10^{(\epsilon-\delta)n}] \qquad \text{(Eq. 6)}$$

Two subcases of Eq. 6 are evident. When $(k_1/k_{-1})_0 S_0 10^{(\epsilon-\delta)n} >> 1$, Eq. 6 becomes:

$$\log (f_n)_s = 0 \qquad \text{(Eq. 7a)}$$

and

$$(f_n)_s = 1 \qquad \text{(Eq. 7b)}$$

Considering that $(\epsilon - \delta)$ is less than zero, this condition will only result at small n values, if at all. In other words, the product of the solubility-determined concentration[1] and the equilibrium constant is greater at short chain lengths and diminishes as chain length is extended. Due to the diminishing solubility–adsorptive constant product, at some chain length the condition $1 >> (k_1/k_{-1})_0 S_0 10^{(\epsilon-\delta)n}$ ensues which leads to the second case:

$$\log (f_n)_s = \log[(k_1/k_{-1})_0 S_0] - (\delta - \epsilon)n \qquad \text{(Eq. 8)}$$

Since the term $\log [(k_1/k_{-1})_0 S_0]$ is constant, the log (occupancy fraction) drops by $(\delta - \epsilon)$ for each additional methylene unit added. When using hypothetical values of 0.6 and 0.3 for δ and ϵ, respectively, this corresponds to a twofold decrease in the fraction of sites occupied per unit increase in chain length in this region of the profile.

The general situation at short chain lengths is that practical experimental concentrations lie considerably under the solubility curve and adsorptivities may, in fact, be studied over the short chain length range at a fixed equilibrium concentration, C. Thus, Eq. 3 may initially describe the adsorptive trend.

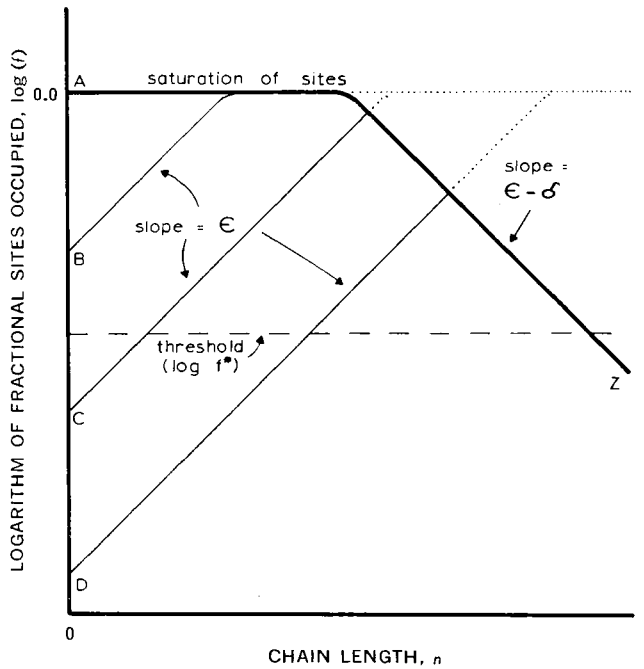


Figure 1—*Theoretical curves for the fractional occupancy of a perfect Langmuirian receptor phase as a function of alkyl chain length under the condition that* $S_0(k_1/k_{-1})_0 >> 1$. *The heavy line, line A–Z, is the expected trend for saturated solutions. Profiles initiating at points B, C, and D are idealized profiles obtained using fixed concentrations* C_1, C_2, *and* C_3, *respectively, where* $S_0 > C_1 > C_2 > C_3$. *In such cases, log* (f) *increases linearly with chain length until the saturation limitation is obtained. Thereafter, the profiles are superimposed on the saturation profile. The dotted lines represent the continuing trends expected, neglecting the solubility restriction. "Parabolic" curves can be generated at a fixed concentration. The apex of the "parabola," the chain length of maximal activity, can be flat or broad, depending on concentration. Its position on the chain length axis is also concentration dependent.*

[1] Here we assume that saturation of all homologs is at concentrations much less than those that would change the solvent character from water to that of a mixed solvent.

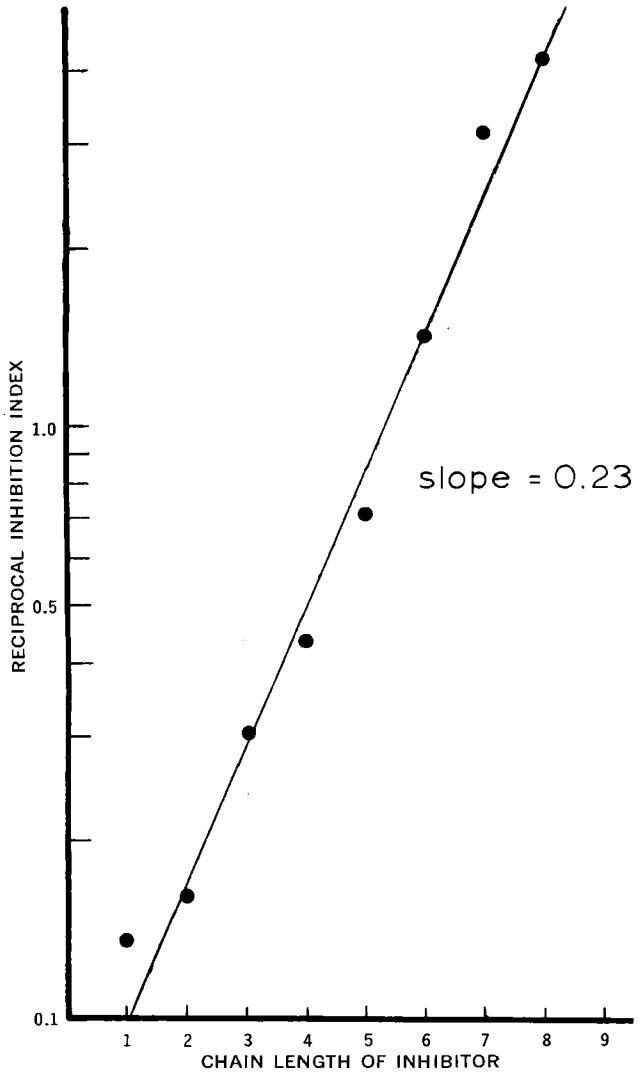


Figure 2—*Data of Schaeffer (41) for the inhibition of adenosine deaminase. The slope of the plot, 0.23, is a measure of ϵ in the system in question. Despite the exponentially increasing efficiency of inhibition, the C_9 and C_{10} compounds proved too insoluble for measurement of inhibition.*

However, irrespective of the choice of C, at some chain length the solubility limitation must enter the picture due to the exponential declivity of the solubility function; thereafter, Eq. 5 or 6 describes the adsorptive pattern. The possible homolog profiles generated by Eqs. 3 and 6 are collectively presented in Fig. 1 in terms of log (f_n) *versus* n.

To put the concepts into perspective, it seems necessary now to answer several basic questions regarding this analysis. What underlying energetic phenomena make the gross generalizations of the treatment sound or at least possible? And, considering the complexities of biological systems, are there actual instances where the presumed phenomena might be demonstrated or observed?

With regard to the first question, the adsorptive equilibrium constant, $(k_1/k_{-1})_n$, is a thermodynamically controlled parameter. It reflects a summation of all enthalpic and entropic contributions to the free energy of adsorptive binding. In other words, the adsorptive equilibrium constant is responsive to the free energy differential experienced when a homolog leaves the bulk phase and occupies an adsorption site. For active compounds, it can be assumed that the enthalpic exchange in this process is significantly large and mainly attributable to the specific "lock and key" receptor interaction. This free energy input is assumed constant throughout a homologous series. There also is a slight "binding unfavorable" entropic effect derived from pinning of the molecule to the receptor. As chain length is extended, there is enthalpic contribution to the free energy of binding which are derived from the differential of van der Waal's forces experienced in the bulk phase less those experienced on the adsorptive surface. Based on the arguments of Nemethy and Sheraga (33) and other water structure experts (34, 35), the magnitude of this enthalpic input would be small and the sign indeterminant. In other words, this effect is not of great magnitude, and it plays a small role in the free energetic scheme of events.

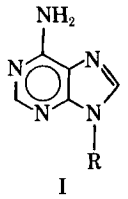
The principal effect of extending chain length is attributable to water structuring at nonpolar surfaces. A large, negative entropic contribution to free energy results when a hydrocarbon or any other low energy surface is exposed to water (33–35). This entropic factor is proportional to the net molecular surface area, which is incrementally increased as methylene units are added to the chain. Any process or factor that conserves surface area exposed to water diminishes the absolute magnitude of the hydrophobic, entropic free energy. Since the molecular surfaces of interest, particularly the peptide backbones of proteins, are relatively nonpolar (36), a low energy surface is conserved as the homolog lays itself down onto the biopolymer and a significant net increase in entropy (net decrease in free energy) proportional to the length of the hydrocarbon chain is obtained. In other words, there is less total surface exposed to the aqueous solvent in the bound situation than in the dissociated situation.

The molal free energy of binding for compound of chain length n at equilibrium follows the usual relationship $\Delta G_n = -RT \ln K_n$; thus, considering Eq. 2*b*:

$$\Delta G_n = \frac{-RT}{2.303}[\log(k_1/k_{-1})_0 + \epsilon n] \qquad \text{(Eq. 9)}$$

which highlights the linearity of the free energy relationship. The general conclusion is that there should be a linearly decreasing, free energy of site occupation with chain length extension as factors other than hydrophobic bonding are either constant or only slightly changing compared to the entropy gained in surface area conservation. Since the conservation of low energy surface area is less in an adsorption situation than in partitioning where the molecule completely escapes the aqueous phase, the effect of general hydrophobic interaction on adsorption should be less than that experienced in partitioning, and this is as observed (37–39).

In what systems might the general trends predicted here actually be observed? It is apparent upon studying the extensive review of Hansch and Coats



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(40) that these conditions can be approached in a test tube using pure enzyme, its substrate, and a homologous series of competitive inhibitors[2]. Apparently the enzyme provides, to a good approximation, the homogeneous two-dimensional phase; and its interactions with homologous competitive inhibitors follow patterns of behavior that have been outlined here, presuming, of course, that there is a true split in specific and nonspecific binding. One interesting literature case can be cited to substantiate this view. Schaeffer (41) studied the influence of homologous inhibitors on the deamination of adenosine mediated by adenosine deaminase. For inhibitors of the type indicated by Structure I, where R varied from CH_3 to CH_3—$(CH_2)_7$, the inhibition index decreased exponentially. The inhibition index as defined by Schaeffer is reciprocally related to K_n, and his observations are thus synonymous with an exponentially increasing adsorptive equilibrium. As can be seen in Fig. 2, the free energy relationship is reasonably linear over the full chain length range and the deviations appear quite random. The value of ϵ is the slope of this plot of the logarithm of the reciprocal of the inhibition index against n and is roughly 0.23 in this system. Thus, the inhibition at a given concentration apparently increases by a factor of about 1.7/methylene unit.

In apparent paradox, considering the exponentially increasing efficiency of inhibition, the 9-*n*-nonyl and 9-*n*-decyl adenines were found to be inactive. This finding was attributed to insufficient solubility by the author (41) and is the expected case considering the small magnitude of ϵ (0.23), assuming a typical magnitude for δ of about 0.6. In other words, Schaeffer's (41) results strongly suggest that the product of K_nS_n for the C_9 and C_{10} compounds is below that necessary for a threshold response. This paper thus highlights the fact that relative activities based on response data normalized to a given fixed concentration can be, and generally are, very misleading in that the normalized concentration is usually an impractical or unobtainable concentration for the compounds in question in a real or usage situation. In the last analysis, relative rates of transport (1), relative amounts distributed to various biophases in the pseudosteady state (13), and relative receptor site occupation are all functions of a phenomenological constant times a concentration term. Limitations on the magnitude of either the phenomenological constant or concentration can be the source of biological inactivity, and it is necessary when characterizing relative biological activities to consider the product term as well as its component part, the phenomenological constant.

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Received July 2, 1973.
Accepted for publication October 19, 1973.

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[2] Data concerning the influence of alkyl substituents on protein binding or enzyme inhibition are found in Refs. 16, 17, 23, 26, 30, 46, 48, 49, 50-52, and 57 of the Hansch and Coats (40) review. These data support the formulations of Eqs. 2 and 9 found in this communication.