sieve adsorbent to influence the course of an organic reaction was due to Dr. Z. Valenta (Department of Chemistry, U.N.B.) to whom we are also grateful for several helpful discussions during the course of this work.

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Molecular Tweezers: A Simple Model of Bifunctional Intercalation

Sir:

We have synthesized several bifunctional derivatives of caffeine[1-7] and wish to report here that they appear to show the expected exponential increase in association constants anticipated for formation of "sandwich" π-system hydrophobic complexes (eq 1). We refer to these molecules as "molecular
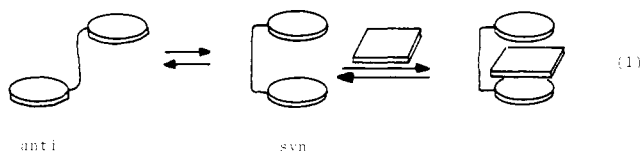
tweezers". These molecules, **1-3**, possess two of the three characteristics expected to enhance complexation of aromatic molecules in aqueous solution. (1) The rigid diyne unit prevents self-association[8] of the two caffeine moieties. (2) The caffeine–caffeine distance in the syn conformation, ~ 7 Å, is proper for insertion of a π system between the rings. The third structural feature, a rigid syn conformation, is not met.

1, $n = m = 1$
2, $n = 1; m = 2$
3, $n = m = 2$
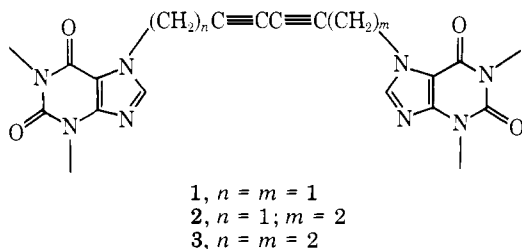
Association constants were determined by phase partitioning[9] of the tweezer ($\sim 10^{-4}$ M) between ethylene dichloride (EDC) and aqueous pH 7 potassium phosphate buffer containing varying concentrations of 2,6-dihydroxybenzoate (DHBA) or 1,3-dihydroxy-2-naphthoate[10] (DHNA). From EDC-buffer partition coefficients of the tweezers and the above experiment one may calculate an "apparent" association constant

$$K_A^{app} = [\text{bound tweezer}]/[\text{acid}][\text{free tweezer}]$$

One may then relate K_A^{app} algebraically to various possible binding schemes as a function of the concentration of the
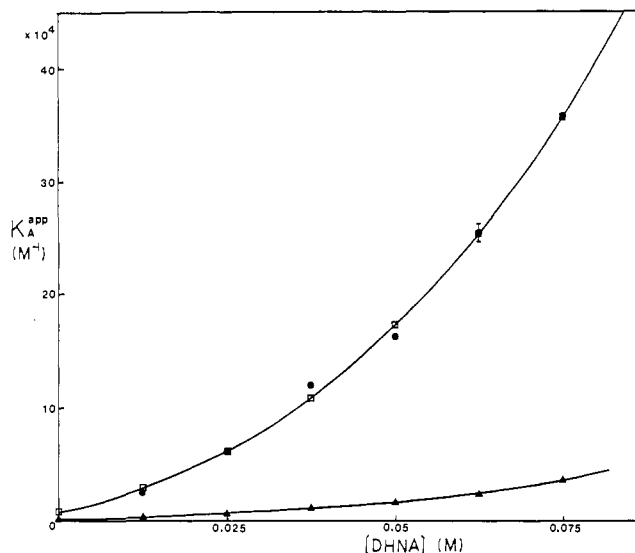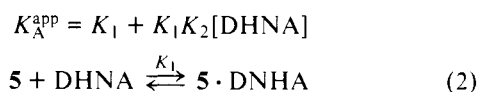
Figure 1. Calculated and experimental K_A^{app} vs. [DHNA] plot for **3** and potassium 1,3-dihydroxy-2-naphthoate in pH 7 phosphate buffer: ●, experimental points; ▲, calculated using $K_1 = 296$ M^{-1}, $K_2 = 16.7$ M^{-1}, $K_3 = 0$; □, calculated using $K_1 = 296$ M^{-1}, $K_2 = 47.5$ M^{-1}, $K_3 = 10\,400$ M^{-1} (see Table II).

DHBA or DHNA salt and the various association constants. From the behavior of theophylline derivatives **4** and **5** one may calculate a best fit association constant (K_3 below) for the formation of a stacking complexes. We use the necessity of invocation of a large K_3 as evidence *pro* or *con* for the hypothesis.

Complexation of the simple theophylline derivative **4** and **5** with DHNA follows eq 2 closely (correlation coefficient >0.99):

$$K_A^{app} = K_1 + K_1 K_2 [\text{DHNA}]$$

$$\mathbf{5} + \text{DHNA} \underset{}{\overset{K_1}{\rightleftharpoons}} \mathbf{5} \cdot \text{DNHA} \qquad (2)$$

$$\mathbf{5} \cdot \text{DNHA} + \text{DNHA} \overset{K_2}{\rightleftharpoons} \mathbf{5} \cdot (\text{DHNA})_2$$

Values of K_1 and K_2 for **4** and **5** complexing with several acids are in Table I and are consistent with literature values.[3] For tweezers **1-3** one may relate K_A^{app} to K_1, K_2, K_3, and [DHNA] by the equation

$$K_A^{app} = 2K_1 + (2K_1 K_2 + K_1)^2 [\text{C}] + 2K_1^2 K_2 [\text{C}]^2 + K_1^2 K_2^2 [\text{C}]^3 + K_3 (1 + K_2 [\text{C}])^2 \quad (3)$$

Here K_1 and K_2 are as defined above and represent single and
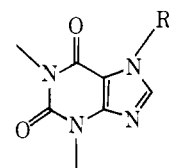
4, R = CH$_2$C≡CH
5, R = CH$_2$CH$_2$C≡CH
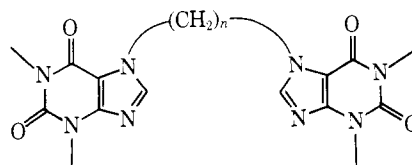
6, $n = 8$
7, $n = 10$

Table I. Association Constants (See Eq 2) of Alkyl Theophyllines

theophylline derivative	complexors	K_1, M^{-1}	K_2, M^{-1}
caffeine	DHNA^a	432	28.2
4	DHNA	365	25.7
5	DHNA	296	16.7
7-butyltheophylline	DHNA	350	15.7
4	DHBA^a	45.2	6.7
5	DHBA	36.9	4.7
7-butyltheophylline	DHBA	53.3	4.0

^{a} DHNA = potassium 1,3-dihydroxy-2-naphthoate in pH 7 phosphate buffer. DHBA = 2,6-dihydroxybenzoate in phosphate buffer.

Table II. Best Fit Sandwich Association Constant (K_3) Calculated According to Various Assumptions.

tweezer	entry	K_1, M^{-1}	K_2, M^{-1}	K_3, M^{-1}	$\Sigma\sigma^2$ $\times 10^{-7}$
1	a	365	25.7	21 830	161
	b	365	45	10 410	3.3
	c	693	26	10 470	4.4
	d	477	37	10 880	4.2
2	a	330	21	10 420	31.9
	b	330	35	5 200	0.9
	c	535	21	4 730	0.9
	d	416	28.5	5 160	0.8
3	a	296	16.7	47 400	1190
	b	296	47.5	10 400	27.4
	c	896	16.7	9 400	27.4
	d	464	33.5	12 570	28.8
6	a	350	16	12 140	108
	b	350	29.8	2 800	5.0
	c	587	15.7	330	6.2
	d	472	21	1 920	5.3
7	a	350	16	8 900	40
	b	350	24	2 420	6.0
	c	494	16	268	6.4
	d	409	20	1 860	6.1

^{a} K_1 and K_2 fixed at values found for monomers **4** or **5**, or for mean of **4** and **5** for **2**. ^{b} K_1 fixed at monomer value; K_2 allowed to vary. Value of K_2 shown is that one giving best fit of data. ^{c} K_2 fixed at monomer value; K_1 allowed to vary. ^{d} Both K_1 and K_2 allowed to vary, $\sim 100 \leq K_1 \leq \sim 1000$, $\sim 10 \leq K_2 \leq \sim 100$.

double complexation of the *independently* acting caffeine rings, K_3 is the association constant for sandwich complexation (eq 1), and [C] is concentration of the water-soluble complexors. A typical plot of K_A^{app} vs. [C] for **3** is shown in Figure 1.

For a given K_1, K_2, and set of K_A^{app}:[C] pairs, the method of least squares permits calculation of a best fit K_3. Data such as that in Figure 1 may be analyzed several ways as is shown in Table II. The following conclusions may be derived from these data. (1) The data are not explained by the assumption of independently acting rings with K_1 and K_2 values the same as those of the monomers. Complexation is too strong. (2) The data are satisfactorily accounted for by invocation of K_3, the sandwich π-complex association constant, under several analyses of the data. Even here though (entry a), best fit requires that either K_1 (entry c), K_2 (entry b), or both (entry d) be somewhat higher than that for the monomer. For tweezer **3** a remarkably constant value of K_3, 10^4 M^{-1}, is obtained under the three methods of analysis. Similar results are seen for 1,1 and 1,2 tweezers. (3) Similar but substantially diminished results are seen for **6** and **7**, lacking the rigid diyne spacer. While best fit results are presented in Table II, it was noted that there were very broad error minima and that values of K_1 and K_2 for which the best $K_3 = 0$ had similar errors. Most accurately one can say that K_3 is "small" for **6** and **7**. It is clear that the diyne spacer plays an important role. Similar results are obtained with DHBA as complexor. (4) It is not crucial that the two caffeine rings be able to assume a parallel conformation. Tweezer **1**, wherein the two ring cannot close to an angle of less than $\sim 30°$, also yields a K_3 of 10^4 M^{-1} for interaction with DHNA.

We consider the fact that a large K_3 is necessary for explanation of our data to be strong support for the formation of tweezer-like complexes as in eq 1. In this respect it is fascinating that the potent intercalator echinomycin[11] possesses a rigid tweezer-like structure. One may surmise that the rigid bicyclo peptide structure of this and related molecules plays an important role in its function. One may also suggest from our work that bifunctional intercalators[12,13] should perhaps be constructed with a rigid rather than floppy connecting chain.[14]

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