

# Hydrophobic-Lipophilic Interactions. Aggregation and Self-Coiling of Organic Molecules<sup>†</sup>

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Hydrophobic-lipophilic interactions (hereafter abbreviated HLI), together with Nature's other forces, create aggregates (Ag's), micelles, vesicles, and living cells from organic molecules in hydrophilic (or aggregating) media.<sup>1</sup> To understand life, we must try to understand HLI. Ag's of electrically neutral organic molecules are formed almost solely by HLI; thus they may serve as one of the simplest models for such studies. These considerations may be taken as a first good reason to investigate thoroughly the phenomena of aggregation and self-coiling (or hairpin looping of hydrocarbon chains), which form the two main themes of the present Account.

Menger first proposed the concept of intermolecular aggregation in order to explain the rate retardation of the hydrolysis of *p*-nitrophenyl dodecanoate (12-*p*-NO<sub>2</sub>) in water.<sup>2</sup> Knowles then suggested that self-coiling of long-chain molecules can also be a cause of such rate retardations.<sup>3</sup> Later, Murakami<sup>4</sup> and Guthrie<sup>5</sup> further extended the studies on aggregation and self-coiling.

In order to differentiate simple Ag's from assemblages of higher forms, such as micelles, we shall define an Ag formed in an aggregating medium as a cluster of a neutral organic species in equilibrium with its monomeric form, as well as with other clusters of differing aggregation numbers. An Ag containing more than one organic species will be referred to as a coaggregate (CoAg). Besides aqueous media, most aggregating media studied are aquiorganano (aqueous organic) binary systems.<sup>6</sup>

A second reason to study and understand aggregation and self-coiling is that it concerns all chemists; i.e., the chemical reactivity of the stuff in your test tube might be affected by aggregation and self-coiling in subtle ways. For instance: (1) Although it had been suggested that only monomeric esters are sufficiently reactive in hydrolysis,<sup>4</sup> this proposition might not be strictly valid.<sup>7</sup> (2) Under certain circumstances, the nature of the substituent effect may be hydrophobic, instead of electronic.<sup>7,8</sup> (3) The rate-enhancing "proximity effect" has been conceived of as the result of the juxtaposition of two reacting long-chain molecules under the influence of HLI, whereas actually it could have been the result of coaggregation.<sup>3,5,9-12</sup>

Third, the concept of HLI-enforced aggregation and self-coiling may have valuable applications in synthetic chemistry and other disciplines. Certainly, aggregation

and self-coiling can retard reactions, but they can also expedite both intermolecular and intramolecular reactions.<sup>13</sup> Of particular interest is its application to the formation of macrocyclic entities.<sup>14-16</sup> Tung has recently applied the HLI concept in his interesting photochemistry studies.<sup>17-21</sup>

Finally, knowing more about aggregation and self-coiling will be beneficial to all kinds of scientific workers, e.g., biochemists, biologists, pharmaceutical chemists, polymer chemists, physiologists, and even physicians, because Ag's are probably ubiquitous in living matter, e.g., in our cells and in our blood. To make up a case for illustration, we suggest that aggregation is possibly a first step toward arteriosclerosis.

Prior to 1984, there were about six lines of evidence for aggregation but no direct evidence for self-coiling.<sup>6</sup> Now there are about twenty lines of evidence,<sup>6-8,12,14-27</sup>

<sup>†</sup> Abbreviations: Ag, aggregate; CAgC, critical aggregate concentration; cmc, critical micelle concentration; *f*<sub>1</sub>, Rekker's hydrophobic fragmental constant, a measure of lipophilicity; HLI, hydrophobic-lipophilic interactions; *N*, average aggregation number; S, an organic species, a substrate or probe; SAgP, solvent aggregating power; *φ*, volume fraction of the organic component of an aqueous organic mixture.

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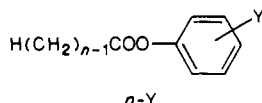
Xi-Kui Jiang (Stanley Hsi-Kwei Chiang), born in Shanghai in 1926, received his B.S. with Honors in 1947 from St. John's University (Shanghai) and his Ph.D. under the direction of Hyp J. Dauben, Jr., in 1952 from the University of Washington (Seattle). In 1978, he founded the Department of Physical Organic Chemistry at the Shanghai Institute of Organic Chemistry, where he is now a professor. His research interests include free radical chemistry; electron-transfer and halophilic reactions; fluoroorganic chemistry; solvent and microenvironmental effects; and the effects of hydrophobic-lipophilic interactions, aggregation, and self-coiling.

including some direct and cogent evidence for hairpin looping.<sup>14-16,21,23</sup>

### Some General Notions

Hansch's important and pioneering works have greatly boosted our understanding of HLL,<sup>28</sup> and we are also indebted to Rekker for his wonderful hydrophobic (or lipophilic) fragmental constants ( $f$ ), which, like Hansch's  $\pi$  constants, are calculated from partition coefficients.<sup>29</sup> For any organic compound, summation of the pertinent  $f$  values will yield a  $\Sigma f$  value that is a good indicator of the lipophilicity of this compound. In our works we have often used these  $\Sigma f$  values to evaluate the relative lipophilicities of not only substrates and solvents but also substituent groups.<sup>7,8,24</sup>

The molar concentration (usually a narrow region),  $[S]$ , of an organic species  $S$  (a substrate or probe) at the onset of aggregation is the critical aggregate concentration (CAGC) of  $S$ . It is generally accepted that below CAGC,  $S$  exists in its monomeric form.<sup>2-8,22,26,27</sup> If  $S$  is a long-chain ester, e.g.,  $n$ -Y, its CAGC values in different



Y = para and meta substituents, e.g., Y = NO<sub>2</sub>  
2-Y, n = 2; 8-Y, n = 8; 12-Y, n = 12; 16-Y, n = 16

media can be obtained from  $\log k$  vs  $[S]_i$  plots, where  $[S]_i$  is the initial substrate concentration, because the hydrolytic rates ( $k$ ) of  $S$  will decrease rather suddenly at the CAGC.<sup>2,4-6,26,27</sup> More recently, spectroscopic methods are available for the determination of CAGC.<sup>15,17,30</sup> All the known CAGC values of compounds with chain lengths greater than 8-10 carbons fall in the range  $10^{-5}$ - $10^{-7}$  M,<sup>2,4-6,8,15,17,30</sup> e.g., for 12- $p$ -NO<sub>2</sub>,  $1.2 \times 10^{-6}$  M.<sup>5b</sup> References 26 and 27 provide 35 CAGC values. It appears<sup>6,31</sup> that the CAGC of  $S$  is slightly smaller than the solubility of  $S$  (cf. ref 5). Therefore, in most cases  $S$  will probably precipitate out of the solution before it has a chance to form true micelles, because the critical micelle concentrations (cmc's) of typical ionic surfactants with longer than 10-carbon chains are in the range  $10^{-2}$ - $10^{-4}$  M.<sup>32</sup> Evidently, Ag's are not necessarily "premicelles".

Under a specific condition, the value of CAGC depends on structural factors; e.g., for esters such as  $n$ -Y, CAGCs will decrease with increasing chain length. For

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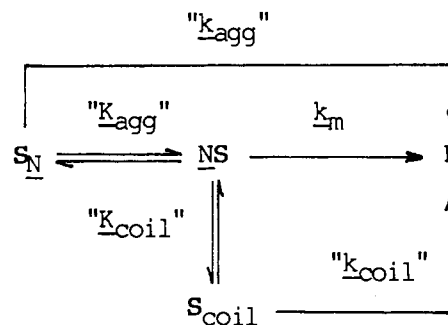
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Scheme I



a particular compound  $S$ , its CAGCs will decrease with increasing solvent aggregating power (SAGP), which usually parallels solvent hydrophilicity. If we designate the volume fraction of the organic component of an aquiorghano mixture by  $\phi$ , then for a particular binary system, the CAGCs of  $S$  will increase with increasing  $\phi$  (or decreasing SAGP). For mixtures with different organic components at the same  $\phi$  value, the SAGP will decrease with the increasing lipophilicities or deaggregating abilities of the organic components, which are estimable from the  $\Sigma f$  values.<sup>7,24,26,27,29</sup> This Account will show how useful is the concept of CAGC.<sup>33</sup>

There is no sharp line of demarcation between Ag's and micelles. Then why CAGC instead of just cmc? Because typical simple aggregates are different from typical micelles. In order to avoid future misunderstanding, we suggest the following criteria for differentiating typical (simple) Ag's from typical micelles: (1) Micelles are formed from ionic surfactants. They have structure; e.g., they have a Stern layer.<sup>32,34</sup> Ag's are formed from neutral molecules. They have much less structure and are more disordered and fluctuant;<sup>7</sup> e.g., they have no Stern layer. (2) As mentioned above, cmc's are usually orders of magnitude larger than CAGC's. (3) The average aggregation numbers  $N$  for micelles are usually  $>40$ ;<sup>32</sup> the  $N$  value for Ag's are smaller, probably  $<15-40$ . By using the method for the determination of  $N$  of micelles, Tung has reported that the  $N$  of dodecane in Me<sub>2</sub>SO-H<sub>2</sub>O ( $\phi = 0.50$ ) is 18.<sup>18</sup> (4) For micelle-forming molecules above cmc, most of them exist either in micelles or as monomers;<sup>1b,30,34,35</sup> for Ag-forming molecules above CAGC, the size distribution pattern is possibly quite different; e.g., if  $N = 10$ , then the amounts of 3-mers, 4-mers, —, 9-mers, 11-mers, — etc. are also appreciable. Naturally, the behavior of many species will lie somewhere inbetween the two aforesaid typical models.<sup>32b,36</sup> Admittedly, we are tempted to classify some previously designated "micelles" as Ag's.<sup>11b,37</sup>

### Solvent Effects of Aquiorghano Binary Solvents

The apparently simple hydrolysis reaction of a long-chain ester  $S$  to form the product  $P$  in an aggregating medium actually can be an exceedingly com-

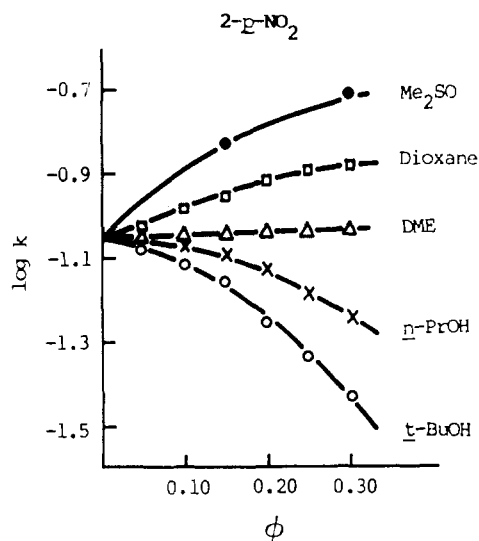
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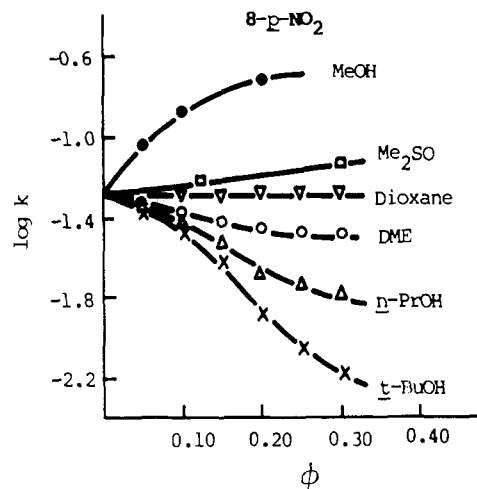
**Figure 1.**  $\log k$  vs  $\phi$  plots for 2-*p*-NO<sub>2</sub> in different aquiorgano solvents.

plicated process, as might be depicted by Scheme I.<sup>6,7,24-26</sup> In Scheme I, Ag's with different aggregation numbers are represented by a single symbol S<sub>N</sub>, and all coiling conformers that hydrolyze more slowly than S are represented as S<sub>coil</sub>. Only  $k_m$ , the rate constant of the monomeric species S, is a true constant; all the quotation-marked  $K$ 's and  $k$ 's are not. At each temperature, the relative importance of the different pathways depends not only on the chemical properties of the reacting species but also on HLI. If we use the expression "the degree of aggregation" to reflect both the  $N$  and the Ag concentration, then the degree of aggregation and coiling of S will increase with increasing SAgP. If S aggregates and coils up, it is not possible to calculate  $k_m$  from  $k_{\text{obsd}}$ , the observed rate constant.

Solvent effects of aquiorgano solvents may contain important contributions from HLI; thus one may want to compare the  $k_m$  values of esters with different chain lengths under identical conditions. Previously this could not be done because the pertinent CAgC values were not known. Therefore we have addressed this problem by first finding mediums with the proper SAgP in which the CAgC's can be measured and then comparing the  $k_{\text{obsd}}$ 's which are true  $k_m$ 's.

We measured 486 rate constants for the hydrolysis at 35 °C of four esters, i.e., 2-*p*-NO<sub>2</sub>, 8-*p*-NO<sub>2</sub>, 12-*p*-NO<sub>2</sub>, and 16-*p*-NO<sub>2</sub>, in six aquiorgano binaries in which the organic cosolvents were MeOH, Me<sub>2</sub>SO, 1,4-dioxane (DX), 1,2-dimethoxyethane (DME), *n*PrOH, and *t*BuOH at graded  $\phi$  values.<sup>26</sup> Some of our results are summarized in Figure 1 (for 2-*p*-NO<sub>2</sub>) and Figure 2 (for 8-*p*-NO<sub>2</sub>), in which  $\log k$  is plotted against  $\phi$  for the aforesaid solvents.

We reckoned that in addition to the other well-known contributors to solvent effects,<sup>26,38,39</sup> HLI could also be a contributor that would retard the rates by the following solvation effects: (1) a general selective or preferential solvation of the ester S by the organic cosolvent molecules brought about by HLI with the consequence that the solvent shell has a higher cosolvent/water ratio than does the bulk solution;<sup>26,38</sup> (2) a



**Figure 2.**  $\log k$  vs  $\phi$  plots for monomeric 8-*p*-NO<sub>2</sub> in different aquiorgano solvents.

specific solvation involving loose and short-lived S-cosolvent "complexes" that are formed as a result of the cooperation of three types of forces, i.e., dipole-dipole, H bonding, and HLI.<sup>26</sup> Thus if all other solvent effects were absent, the expected order of decreasing rates would correspond to an order of increasing HLI or cosolvent lipophilicity (parenthesized  $\sum f$  values), i.e., Me<sub>2</sub>SO (-1.35) > DX (-0.42) > DME (-0.15) > *n*PrOH (0.34) > *t*BuOH (0.37). Fortunately, for *n*PrOH and *t*BuOH, other solvent effects, i.e., the cosolvent-induced desolvation of the H-bonded HO<sup>-</sup> and pH change of the medium,<sup>26</sup> would lead to an ordering different from above, i.e., *t*BuOH > *n*PrOH. Thus the idea that HLI can play an important role in solvent effects is amenable to experimental test.

First, by just looking at the behavior of the acetate 2-*p*-NO<sub>2</sub> alone, we can already see something intriguing in Figure 1 that is implicative of HLI. As mentioned, if HLI as an opposing force were unimportant, then all the organic cosolvents would increase the rate, and we would expect *t*BuOH > *n*PrOH. But Figure 1 says this is not so, and we can find no good rationale other than the HLI hypothesis discussed above.

Now we present a more telling evidence, namely, a comparison of Figure 1 with Figure 2. If HLI were of little consequence, then Figure 2 would look rather similar to Figure 1. Yet all the curves in Figure 1 appear to have been pushed down (rate retarding) by some magic force. This force, we argue, could be none other than our HLI. Notably, the ordering of these curves happens to coincide with the expected order based on considerations of HLI discussed earlier. Furthermore, dozens of CAgC values for 8-*p*-NO<sub>2</sub> and 12-*p*-NO<sub>2</sub> also support our views (see ref 26). Therefore we conclude that HLI can play important roles in solvent effects too.

### Can Lipophilicity Sometimes Play Important Roles?

Lipophilic interaction, or attractive van der Waals interaction between hydrocarbon entities, is the less important component of HLI,<sup>26,40</sup> but we thought lipophilicity might sometimes play consequential or even indispensable roles. In an attempt to demonstrate this point, we used three pairs of fluorocarbon and hydro-

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carbon surfactants of similar chain lengths and examined their host-guest complexation behaviors with sodium (carboxymethyl)amylose (NaCMA), which can wrap up long-chain substrates,<sup>41-47</sup> as well as  $\alpha$ - and  $\beta$ -cyclodextrin.<sup>40</sup>

Our approach was based on the following considerations: (1) There is lipophilic interaction between the host molecules and hydrocarbon surfactants, but practically none between the host and fluorocarbon surfactants. (2) Cyclodextrins have preorganized cavities but NaCMA does not. For the latter to form helical inclusion complexes with straight-chain substrates it has to readjust its conformations from loose and extended helices with random coils to interrupted helices during the process of induced fit.<sup>41-46</sup> We thus hypothesized that this binding process might demand extra free energy requirements, and lipophilic interactions, although only playing a supporting role to hydrophobic forces, might provide this process with the extra and indispensable free energy. In other words, we speculated that NaCMA, although it can easily encapsulate hydrocarbon chains, would not be able to wrap up the fluorocarbon chains because there was no lipophilic interaction to help. Indeed, surface tension measurements demonstrated that all three fluorocarbon surfactants refused to be encapsulated by NaCMA.<sup>40</sup> Furthermore, it was found that hydrocarbon guests can displace iodine from the NaCMA-iodine complex, but the fluorocarbons cannot.

As another example,  $\beta$ -cyclodextrin binds the fluorocarbon surfactant  $\text{Cl}(\text{CF}_2)_8\text{CH}_2\text{CH}_2\text{N}^+\text{Me}_3\text{I}^-$  ( $K_d^* = 3.2 \times 10^{-5}$ , 35 °C) much more effectively than it binds  $\text{CH}_3(\text{CH}_2)_8\text{CH}_2\text{N}^+\text{Me}_3\text{I}^-$  ( $K_d^* = 1.1 \times 10^{-2}$ ). More interestingly, the binding of the former is entropy favored ( $\Delta G = -6.3 \text{ kcal mol}^{-1}$ ,  $\Delta H = -1.7 \text{ kcal mol}^{-1}$ ,  $\Delta S = +15 \text{ eu}$ ), whereas the binding of  $\text{C}_{12}\text{H}_{25}\text{N}^+\text{Me}_3\text{I}^-$  is enthalpy favored ( $\Delta G = -5.2 \text{ kcal mol}^{-1}$ ,  $\Delta H = -9.0 \text{ kcal mol}^{-1}$ ,  $\Delta S = -12 \text{ eu}$ ). We hope fellow chemists with all their novel and exotic host molecules will also use fluorocarbon substrates for their host-guest studies and find out whether the aforesaid result is generally true. It will also be interesting to see how the fluorocarbon guests behave in pure organic mediums in which hydrophobic forces do not exist.<sup>48</sup>

### Rate Ratio as a Measure of Solvent Aggregating Power (SAGP). Correlation of SAGP with Rekker's $f$ Constants

Aggregation and self-coiling affect chemical reactivity, and the degree to which it is affected depends on the degree of aggregation. For a particular compound S the degree of aggregation depends on [S] and the SAGP of

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the medium. Is it possible to relate reactivity quantitatively in terms of rate constants with SAGP?

A tremendous amount of work has been dedicated to the correlation of reactivity with some solvent property, such as viscosity, hydrogen-bonding ability, and, especially, "polarity", for which numerous empirical parameters have been successfully applied.<sup>38,39</sup> Yet there was one solvent attribute that had not been included, namely, SAGP. Obviously, we need a good probe or indicator for the degree of aggregation before we can begin to address this problem of basic and general interest.

The first such probe found was the  $k_8/k_{16}$  ratio, where  $k_8$  and  $k_{16}$  are the hydrolytic rate constants measured at 40 °C in ten aquiorghano binary solvents for 8-*p*-NO<sub>2</sub> and 16-*p*-NO<sub>2</sub>.<sup>24</sup> Arranged in order of increasing lipophilicity or deaggregating power according to the parenthesized  $\sum f$  values, the ten organic cosolvents used were HOCH<sub>2</sub>CH<sub>2</sub>OH (-1.92), Me<sub>2</sub>SO (-1.35), MeOCH<sub>2</sub>CH<sub>2</sub>OH (-1.30), DMF (-1.01), dioxane (-0.42), CH<sub>3</sub>CN (-0.36), acetone (-0.30), EtOH (-0.26), MeOCH<sub>2</sub>CH<sub>2</sub>OMe (-0.15), and *t*BuOH (+0.37). It was found that at  $\phi = 0.50$ , the  $k_8/k_{16}$  ratios for the last eight solvents all lie in the range 1.0-1.2, but in Me<sub>2</sub>SO-H<sub>2</sub>O,  $k_8/k_{16} = 24$ , and in HOCH<sub>2</sub>CH<sub>2</sub>OH,  $k_8/k_{16} = 68$ . Evidently, the 0.5 value of  $\phi$  is too high for differentiating the SAGP's of the ten solvents. At  $\phi = 0.30$ , however, the  $k_8/k_{16}$  values range all the way from 680 for HOCH<sub>2</sub>CH<sub>2</sub>OH-H<sub>2</sub>O to roughly unity for *t*BuOH-H<sub>2</sub>O. Attempts to correlate these ratios with various solvent polarity parameters all failed, but to our delight and some surprise we bumped into what was possibly one of the first quantitative correlations between HLI ( $\sum f$ ) and degree of aggregation or SAGP. The equation thus found is<sup>24,49</sup>

$$\log(k_8/k_{16}) = (-1.17 \pm 0.13)\sum f + (0.50 \pm 0.12)$$

$$n = 10, r = 0.953, \text{ confidence level } >99.9\%$$

This work argues for the necessity of setting up some empirical scale or parameters for SAGP in the future. It may also have practical applications. For example, in running a reaction in aqueous medium a chemist may want to solubilize an organic compound by adding an organic cosolvent; knowing now our ten-solvent order, he may pick *t*BuOH as his first choice instead of acetone or EtOH.

### Correlation of Hydrophobic Substituent Constants with Chemical Reactivity

By using the  $f$  constants, we have succeeded in establishing first examples<sup>7,8</sup> of correlation of hydrophobic-lipophilic substituent constants with chemical reactivity in terms of rate constants measured in the absence of enzymes or their models for substrates (16-Y, 12-Y; Y = *p*-NO<sub>2</sub>, *m*-NO<sub>2</sub>, *p*-CHO, *m*-Cl, *p*-Cl, *p*-Br, *p*-CO<sub>2</sub><sup>-</sup>, *p*-CH<sub>3</sub>, *m*-CH<sub>3</sub>, *p*-OMe, *p*-Ph, *p*-*t*-Bu) bearing a wide variety of substituents.

Initially, we were certain that in "good" or nonaggregating solvents, e.g., Me<sub>2</sub>SO-H<sub>2</sub>O with  $\phi > 0.70$ , the substituent effect of Y on hydrolytic rates of 16-Y should be electronic in nature, i.e.,  $\log(k/k_0) = \rho\sigma$ , where  $\sigma$  is a Hammett-type substituent constant. We

(49) In the original paper<sup>24</sup> the  $\sum f$  values used for dioxane, MeOCH<sub>2</sub>CH<sub>2</sub>OMe, and *t*BuOH were -0.49, -0.70, and +0.77, respectively, and  $r = 0.975$ .

**Table I**  
**Values of  $\rho$ ,  $h$ , and  $C$  of  $\log k = \rho\sigma + hf + C$  and Their Standard Deviations,<sup>a</sup>  $h/\rho$  Ratios,  $F$  Tests, and Explained SS's for Correlations with 11 or 12 Substrates in Media of Various  $\phi$  Values**

$\phi$	$\rho$	$h$	$C$	$-h/\rho$	$n^b$	$F^c$	explained SS, <sup>d</sup> %
0.55	0.34 (0.088)	-0.78 (0.049)	-3.10 (0.051)	2.29	11	222	98.2
0.60	1.12 (0.131)	-0.50 (0.074)	-3.04 (0.076)	0.45	11	119	96.7
0.65	1.14 (0.134)	-0.41 (0.064)	-2.64 (0.076)	0.36	12	132	96.7
0.70	1.11 (0.158)	-0.33 (0.075)	-2.57 (0.090)	0.30	12	77.8	94.5

<sup>a</sup>Standard deviation values listed in parentheses directly below the  $\rho$ ,  $h$ , or  $c$  values. <sup>b</sup>Number of substituents. <sup>c</sup>Goodness of fit. <sup>d</sup>Explained SS (sum of squares) as percent total.

could hardly dare to postulate, however, that in "poor" or aggregating solvents, e.g., Me<sub>2</sub>SO-H<sub>2</sub>O with  $\phi < 0.50$ , the substituent effect of Y would become hydrophobic in nature, i.e.,  $\log(k/k_0) = hf$ , where  $h$  is a constant that reflects the sensitivity of the reaction to HLI. This was because (1) the reaction is so complicated that any change in Y (substrate) or SAgP (medium) will change all the  $K$ 's and  $k$ 's (cf. Scheme I), and there is no step that is singularly rate determining, and (2) the Y groups are only small portions of big molecules (16-Y). Nevertheless, we bet on the possibility that the degree of aggregation and coiling of 16-Y is directly related to the  $\sum f$  values of Y and that it can express itself through the  $k$ 's. We then prepared 13 16-Y's and measured their  $k$ 's first in a "good" solvent ( $\phi = 0.70$ , Me<sub>2</sub>SO-H<sub>2</sub>O) and then in a "poor" solvent ( $\phi = 0.55$ ). As expected, in the first medium 16-Y follows the Hammett correlation. In the second medium, as it turned out, 16-Y follows a new correlation,  $\log(k/k_0) = -0.88f$  ( $r = 0.974$ ). So the nature of the substituent effect can be changed by changing the reaction medium!

As noted above, we believed that the size distribution of Ag's is different from that of the ionic surfactants; i.e., in the case of Ag's there is no sudden change in the concentrations of the successive oligomeric clusters. We also believed that under certain circumstances, Ag's with low  $N$  values, e.g., dimers and trimers, may abound, and that their " $k_{agg}$ " values are not negligible in comparison with  $k_m$ .<sup>4</sup> Therefore we speculated that (1) there should be circumstances under which all paths in Scheme I were open (in varying degrees), (2) under these circumstances all the " $K$ 's" and " $k$ 's" in Scheme I would express themselves in the observed  $k$ 's, and (3) these  $k$ 's might be correlatable by a two-parameter equation such as  $\log k = \rho\sigma + hf + C$ , where  $\rho\sigma$  and  $hf$  are defined above and  $C$  is a constant.

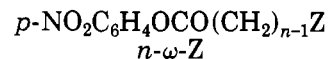
Since at a fixed [S]<sub>i</sub> the degree of aggregation depends on SAgP, the circumstances visualized above could correspond to a condition with the composition region inbetween  $\phi = 0.70$  and  $\phi = 0.55$ . We therefore measured the observed  $k$ 's at  $\phi = 0.65$  and  $\phi = 0.60$ . After treatment of our data, two well-behaved equations of the type  $\log k = \rho\sigma + hf + C$  emerged (see Table I). With this initial success, the treatment was extended to include the conditions with  $\phi = 0.70$  and 0.55. Again the  $k$ 's were well behaved, as shown in Table I. A noteworthy point is that the  $h/\rho$  values increase with decreasing  $\phi$ , signifying that HLI is playing more important roles as the SAgP increases. Results of a new approach to the correlation analysis involving  $hf$  and  $\rho\sigma$  indicate that there are roughly three [S] regions, i.e., monomer, Ag's with small  $N$ 's, and Ag's with "large"

$N$ 's, in accord with our notions on the size distribution of Ag's.<sup>8</sup>

### Let HLI Do Some Job: Formation of Macrocyclic Entities

One of the crudest and perhaps far-fetched ways to mimic some enzyme properties, e.g., self-folding and facilitation of some chemical reaction, could be the deliberate use of HLI to fold a long-chain molecule and make its terminal groups interact. A performance as such would also provide a direct and convincing evidence for hairpin looping. We realized this goal by three approaches, i.e., by using kinetics,<sup>14</sup> spectroscopy,<sup>15</sup> and photochemical reaction as tools.<sup>16</sup>

We used  $\omega$ -substituted carboxylic esters of various chain lengths ( $n$ - $\omega$ -Z) as substrates and measured their



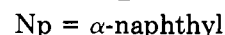
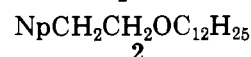
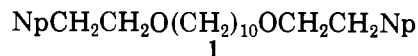
11- $\omega$ -Z,  $n = 11$ ; 13- $\omega$ -Z,  $n = 13$ ;

16- $\omega$ -Z,  $n = 16$ ; 17- $\omega$ -Z,  $n = 17$

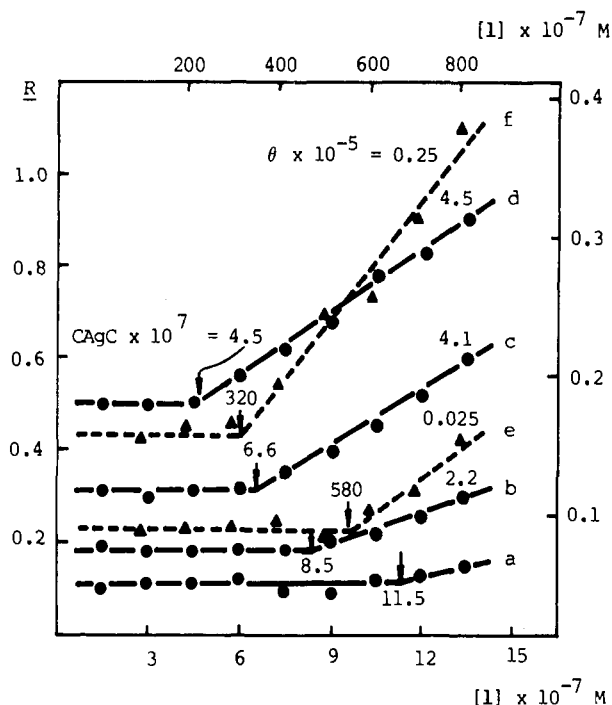
hydrolysis rates at 35 °C in Me<sub>2</sub>SO-H<sub>2</sub>O. Esters of medium chain lengths, i.e., 8- $\omega$ -H and 11- $\omega$ -H, which do not form Ag's under our experimental conditions, were used as standards of comparison with their longer chain analogues, 13- $\omega$ -Z, 16- $\omega$ -Z, and 17- $\omega$ -Z.<sup>14</sup>

For 16- $\omega$ -SH at [S]<sub>i</sub> =  $2 \times 10^{-5}$  M and  $\phi = 0.50$ , a rate-enhancing factor of at least six is effected by the HLI-driven 17-membered-ring "neighboring-group" participation involving the  $\omega$ -SH and the carbonyl group. Similarly, rate data of 11- $\omega$ -Z, 13- $\omega$ -Z, and 17- $\omega$ -Z (Z = H, SH, etc.) at  $\phi = 0.40, 0.45, 0.50$ , and 0.55 show that neighboring-group participations involving 14- and 18-membered rings are also quite effective, but 12-membered-ring participation, if existent, is not very effective. Thus the minimum length for effective hairpin looping to occur is around 10–12 carbons (cf. ref 4).

We used fluorescence spectrometry to monitor both the intra- and intermolecular excimer formation by the probes 1,16-bis( $\alpha$ -naphthyl)-3,14-dioxahexadecane (1) and 1-( $\alpha$ -naphthyl)-3-oxapentadecane (2).<sup>15</sup>



The fluorescence behaviors of 1 and 2 were studied at 15 °C in two solvent systems, i.e., Me<sub>2</sub>SO-H<sub>2</sub>O and

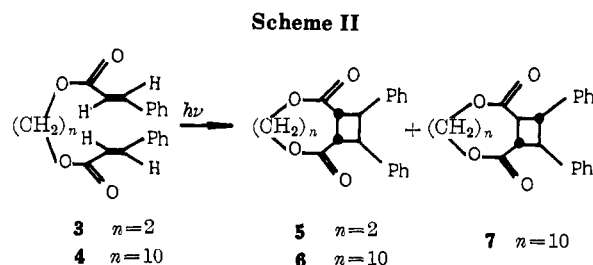


**Figure 3.**  $R$  (F-400/F-337) as a function of the concentration of **1** at different volume fractions ( $\phi$ ). Values on the left are for the  $\text{Me}_2\text{SO}-\text{H}_2\text{O}$  system, and values on the right are for the  $\text{DX}-\text{H}_2\text{O}$  system.  $\theta$  is the slope of the line. Solid lines a-d are for the  $\text{Me}_2\text{SO}-\text{H}_2\text{O}$  system, and dashed lines e and f are for  $\text{DX}-\text{H}_2\text{O}$ . Molar concentration units on the bottom are for the  $\text{Me}_2\text{SO}-\text{H}_2\text{O}$  system, and those on top are for  $\text{DX}-\text{H}_2\text{O}$ . The  $\phi$  values for the six curves are the following: a, 0.65; b, 0.60; c, 0.55; d, 0.50; e, 0.40; f, 0.30.

$\text{DX}-\text{H}_2\text{O}$ , with graded  $\phi$  values. Both **1** and **2** have fluorescence  $\lambda_{\text{max}}$  at 337 nm (naphthalene ring) and 400 nm (excimer); thus the ratio  $R = \text{F-400}/\text{F-337}$  was used to measure the relative amounts of excimers formed. The symbol  $R_m$  stands for the  $R$  value registered below  $\text{CAgC}$ , i.e., the  $R$  of the monomeric **1**. The main results are summarized in Figure 3, which is self-explanatory. Suffice it here to say that our results demonstrate not only that HLI can effectively bring about large-ring intramolecular excimer as well as intermolecular excimer formation but also that the population of the coiled-up conformers is quantitatively related to the magnitude of HLI because  $\log R_m = -4.18\phi + 1.79$  ( $n = 4$ ,  $r = 0.9989$ ) and  $\log \text{CAgC} = 2.66\phi - 7.67$  ( $n = 4$ ,  $r = 0.9966$ ). The  $\log R_m - \phi$  equation might be taken as a case of linear free energy ( $\Delta G$ ) relationship with  $\Delta G$  related to the equilibrium between the stretched-out conformers and properly coiled-up or preassociated conformers of **1**.

The formation of a macrocyclic ring from a flexible chain demands a formidable price in terms of entropy, and thus synthetic chemists have resorted to energetically highly favorable reactions between the end groups. We wanted to try a different approach, i.e., let HLI pay the entropy expense.<sup>16</sup>

The photochemical intramolecular cycloaddition of the 1,2-dicinnamoxyethane **3** ( $n = 2$ ) and the 1,10-dicinnamoxydecane **4** ( $n = 10$ ) to the  $\beta$ -truxinates (**5**,  $n = 2$ ; **6**,  $n = 10$ ) and the  $\delta$ -truxinate (**7**,  $n = 10$ ) is shown in Scheme II. Previously reported yields were good for



**5** (90%) but very poor for the macrocyclic products **6** + **7** (6–7%).<sup>50,51</sup> We have studied the effects of  $\text{SAGP}$  on the yields and rates of this intramolecular reaction in nine aquiorghano media with graded compositions.<sup>16</sup> Among other observations, we have found that the yield of **6** + **7** can be dramatically increased to 90% in  $\text{Me}_2\text{SO}-\text{H}_2\text{O}$  with  $\phi = 0.30$  and that self-coiling in an aggregating medium, just like aggregation, is mainly an entropy-driven process.

### Concluding Remarks

The main purpose of this Account is to arouse the interest of scientific workers of diverse disciplines, and we would like to raise more questions than to give answers. The following list illustrates the type of problems or tasks that are waiting to be addressed and explored: (1) the relationship of HLI to molecular volume;<sup>52</sup> (2) new or improved methodology for the study of aggregation and coiling, e.g., novel methods for studying the size distribution and structure of the simple Ag's; (3) investigation of that very large number of compounds whose behaviors lie inbetween typical simple Ag's and typical micelles;<sup>11b,32,36,37</sup> (4) behaviors of fluorocarbon media and substrates (probes); (5) aggregation in non-aqueous media;<sup>53</sup> (6) the setting up of empirical parameters or scales that reflect only the  $\text{SAGP}$  of all kinds of solvent systems; (7) kinetics of reactions that occur both inside and outside of  $\text{CoAg}$ 's; (8) temperature effects on aggregation; (9) structural effects on the tendencies toward aggregation, coaggregation, and hairpin looping; (10) applications of the concepts of aggregation and self-coiling to studies in other disciplines, e.g., biochemistry, photochemistry, pharmacy, etc.; (11) design of molecules that have abilities either to form  $\text{CoAg}$ 's or to break up Ag's (such studies might lead to useful drugs (e.g., ref 54); (12) the types and concentrations of aggregates existing in living matter (e.g., in blood, cells, etc.) and the connection between these Ag's and particular illnesses. We believe other workers will suggest additional problems, and we hope most of them will be studied in the near future.

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