Shape and Aggregating Tendency. The Aggregating Behavior of Eight Esters of Eight-Carbon Carboxylic Acids

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Received April 24, 1995[⊗]

Abstract: The aggregating tendencies of eight *p*-nitrophenyl esters of eight-carbon carboxylic acids (**1**–**8**) and two *O*-octyl phosphonates (**10, 11**) have been evaluated by measuring their critical aggregate concentrations (CAgC's). Results show that (1) branching reduces aggregating tendency and (2) flexibility of the hydrocarbon chain favors aggregation. The behavior of a "spheroidal" molecule **8** shows that shape is undoubtedly an important factor that affects the aggregating tendency. This conclusion is unmistakably confirmed by the CAgC of an ester of the seven-carbon acid **9**.

1. Introduction

Many types of organic molecules with differing shapes and volumes form various kinds of molecular aggregates or assemblages in water, the most important solvent with solvent aggregating power (SAgP). Among Nature's forces, hydrophobic–lipophilic interaction (HLI) is one of the most important and essential driving forces for the formation of these assemblages, e.g., micelles, vesicles, biological membranes, and living cells.[1–3] One conspicuous feature of life is that a living cell has to be separated from its environment by a biological membrane, and one conspicuous feature of the biological membrane is that it has long methylene chains as one of its basic building blocks.[1a,b] Since long methylene hydrocarbon chains are shaped like a rope or thread, perhaps the rope-like shape is the most "effective" shape for the most simple HLI-driven process of aggregation, i.e., formation of simple aggregates (Ag's), while other shapes are most effective for more complicated supramolecular interactions. If the above-mentioned proposition were correct, then it would be evident that the effect of molecular shape on the aggregating tendency of simple aggregators (Agr's), i.e., molecules that form simple Ag's under the influence of HLI,[3c,4] should be studied in order to gain insights for understanding more complicated biological processes at the molecular level.

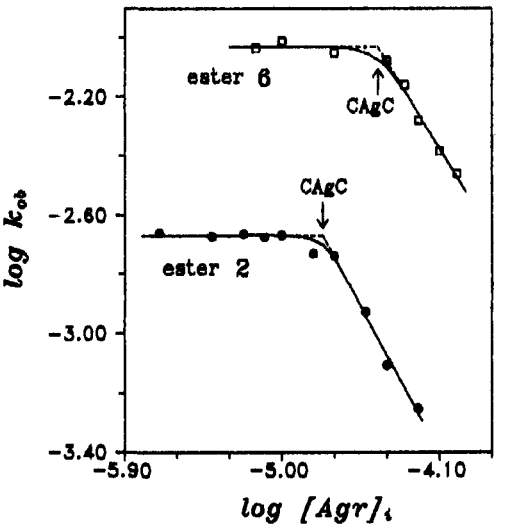

Figure 1. Plots of log k_{ob} vs log $[Agr]_i$ for the evaluation of CAgC values of esters **2** and **6**.

Structure effects on aggregating tendency may be briefly summarized as follows:[3b,c] (1) In the absence of other complicating factors, the hydrophobicity (or lipophilicity) of an Agr can be roughly evaluated by Rekker's Σf value or Hansch's π constants.[5] If similar types of Agr's are compared, then Agr's with larger Σf values will have greater aggregating tendencies. (2) Flat molecules without a side chain may not readily undergo HLI-driven aggregation.[6] (3) There is a "linked-up effect", i.e., if equal-length chains are compared, then each of the two or three linked-up chains will have a greater aggregating tendency than each of the two or three free chains.[3c,7a] (4) There is a "neighboring-moiety-assisted chain-foldability effect",[7] i.e., a long methylene chain can simultaneously fold on itself and interact with the other part of the same molecule, thereby greatly reducing the aggregating tendency of that molecule. This effect might be directly responsible for the fact that the composition of the arterial plague is[8] cholesteryl stearate (2.0%), oleate

[⊗] Abstract published in *Advance ACS Abstracts,* December 1, 1995.

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(5) Rekker's f values or hydrophobic fragmental constants are calculated from octanol–water partition coefficients. The total hydrophobicity of an organic molecule can be roughly estimated from a summation of the f values of all the "fragments" of that molecule. For illustration, the parenthesized f values are given by Rekker for the following fragments: CH_3 (0.701), CH_2 (0.519), CH (0.337), C (0.155), H (0.182), CH_2=CH (0.856), COO (−1.251), C_6H_4 (1.658), NO_2 (−0.053). See: (a) Rekker, R. F. *The Hydrophobic Fragmental Constants;* Elsevier: Amsterdam, 1977; Vol. 1. (b) Rekker, R. F.; de Kort, H. M. *Eur. J. Med. Chem.* **1979,** *14,* 479–488. (c) Hansch, C.; Leo, A. *Substituent Constants for Correlation Analysis in Chemistry and Biology;* Wiley: New York, 1979.

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0002-7863/95/1517-12679$09.00/0

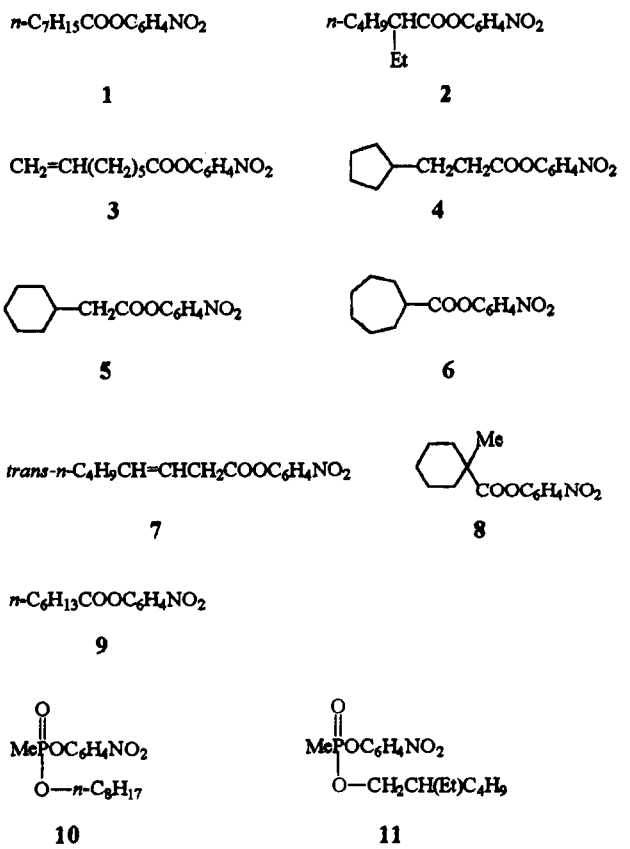
Table 1. Dependence of Saponification Rate Constants, k_{ob} (10^{-3} s^{-1}), of Agr's **1**–**11** on the Initial Agr Concentration, $[Agr]_i$ (10^{-5} M), in Aqueous Solution at 35.0 °C

1	$[Agr]_i$	0.20	0.40	0.60	1.0	1.5	2.0	3.0	4.0	6.0	10.0
	k_{ob}	38.0	37.8	39.0	36.4	31.1	21.7	12.3	8.27	5.44	3.47
2	$[Agr]_i$	0.20	0.40	0.60	0.80	1.0	1.5	2.0	3.0	4.0	6.0
	k_{ob}	2.19	2.13	2.17	2.12	2.15	1.86	1.83	1.18	0.779	0.557
3	$[Agr]_i$	0.50	1.0	1.5	2.0	3.0	4.0	5.0	6.0	7.0	8.0
	k_{ob}	44.5	44.8	45.5	45.5	42.4	32.1	26.5	21.5	18.3	14.9
4	$[Agr]_i$	0.50	1.0	2.0	3.0	4.0	5.0	6.0	10.0		
	k_{ob}	17.5	16.6	16.7	16.0	14.5	9.30	7.89	4.91		
5	$[Agr]_i$	0.50	1.0	2.0	4.0	6.0	8.0	10.0	15.0		
	k_{ob}	9.21	8.28	9.11	8.71	5.87	4.45	3.43	2.38		
6	$[Agr]_i$	0.70	1.0	2.0	4.0	5.0	6.0	8.0	10.0		
	k_{ob}	9.21	9.71	8.91	8.35	6.91	5.24	4.13	3.46		
7	$[Agr]_i$	1.0	2.0	2.7	3.5	4.6	5.0	6.0	8.0	9.0	10.0
	k_{ob}	100	100	105	101	92	90	73	42.4	39.0	34.8
8	$[Agr]_i$	0.70	2.0	3.0	4.0	5.0	6.0	10.0	12.0	14.0	16.0
	k_{ob}	5.47	5.90	5.72	5.51	5.46	5.55	4.93	4.35	4.06	3.86
9	$[Agr]_i$	1.0	1.5	2.0	3.0	4.0	5.0	6.0	7.0	8.0	9.0
	k_{ob}	129	132	131	130	120	107	95	85.7	73.6	63.9
10[a]	$[Agr]_i$	0.20	0.50	1.0	2.0	3.0	4.0	5.0	6.0	7.9	9.9
	k_{ob}	8.04	8.05	8.17	7.91	7.98	7.43	6.95	6.09	5.18	4.55
11	$[Agr]_i$	0.20	0.51	1.0	2.0	4.1	5.1	8.2	10.2		
	k_{ob}	0.448	0.445	0.470	0.450	0.452	0.449	0.446	0.451		

[a] k_{ob} in units of 10^{-4} s^{-1}.

(32.3%), linoleate (34.9%), because one or two double bonds in the middle of the 18-carbon chain will retard folding of the chain.

None of the above-mentioned structural effects, however, can be properly coined as shape or geometry effects. In order to study the shape factor, we opted to use the following substrates as simple models. They are the *p*-nitrophenyl esters of *n*-octanoic acid (**1**), 2-ethylhexanoic acid (**2**), 7-octenoic acid (**3**), 3-cyclopentanepropanoic acid (**4**), cyclohexaneacetic acid (**5**), cycloheptanecarboxylic acid (**6**), *trans*-3-octenoic acid (**7**), 1-methyl cyclohexanecarboxylic acid (**8**), *n*-heptanoic acid (**9**), *O*-*n*-octyl methylphosphonic acid (**10**), and *O*-2-ethylhexyl methylphosphonic acid (**11**). The first eight models were chosen because they are all eight-carbon acids with $\sum f$ values of roughly comparable magnitudes, namely, for **1** and **2**, $\sum f = 4.17$, and for **3**–**6**, $\sum f = 3.81$. The $\sum f$ for ester **9** is 3.65. [5] Saponification rate constants (k_{ob}) of these esters (cf. Table 1) were measured in order to evaluate the critical aggregate concentrations (CAgC's) of these model substrates (cf. the Experimental Section and Figure 1).



In recent years, critical aggregate concentration (CAgC) or critical coaggregate concentration (CoCAgC) has been firmly established as the most reliable indicator of the aggregating tendency of an Agr.[3,9] Actually, quite a few linear correlations have been established between CAgC's or CoCAgC's and some other variable, e.g., temperature, substrate concentration, chain length, SAgP, and concentration of the salt additive.[9-12] One of the best methods used for the evaluation of CAgC is that of plotting the observed saponification rate constant of a substrate, usually an ester Agr, against its initial concentration $[Agr]_i$,[3,9,11,13,14] as illustrated by Figure 1 (and by the data summarized in Table 1). This method is therefore the method of choice for the present study, with the target molecules **1**–**11** serving as substrates for kinetic measurements.[9] Under identical experimental conditions, a smaller CAgC value signifies a greater aggregating tendency.

2. Experimental Section

Apparatus. Boiling points were not corrected. Mass spectra were obtained by using an HP 5989A spectrometer at an ionization potential of 70 eV. ^1H NMR spectra were taken on a Varian EM 360 or EM 390 spectrometer with TMS as the external standard, and ^{31}P NMR on a Varian FX-90Q spectrometer with 85% H_3PO_4 as the external standard, but determination of *cis* or *trans* configuration of 3-octenoic acid 4-nitrophenyl ester (**7**) was performed on a Bruker AM 300 spectrometer. Infrared spectra were recorded by using a Shimadzu IR 440 spectrophotometer.

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Materials. *n*-Octanoic acid (chemical-pure grade, Shanghai Chemical), 2-ethylhexanoic acid (chemical-pure grade, Shanghai Chemical), 3-cyclopentanepropanoic acid (Aldrich), cyclohexaneacetic acid (Tokyo Kasei), cycloheptanecarboxylic acid (Aldrich), *n*-heptanoic acid (chemical-pure grade, Shanghai Chemical), *n*-octanol (analytical-reagent grade, Shanghai Chemical), and *p*-nitrophenol (chemical-pure grade, Shanghai Chemical) were commercially available and were used without purification. 2-Ethylhexanol was reagent grade and purified by distillation *in vacuo*. 1-Methylcyclohexanecarboxylic acid, 3- and 7-octenoic acid, and methylphosphonic dichloride were prepared according to refs 15, 16, 17, and 18, respectively. Boiling points of acids prepared in our laboratory were as follows: 3-octenoic acid, 125−130 °C/15 Torr (lit.[19] 92 °C/1.4 Torr); 1-methylcyclohexanecarboxylic acid, 84−88 °C/4 Torr (lit.[15] 79−81 °C/0.5 Torr). 7-Octenoic acid was not distilled and was used directly for the next step because it polymerized during our first attempt to distill it. The above-mentioned three carboxylic acids were further identified by ^{1}H NMR spectroscopy. All the nine carboxylic acids were converted to the corresponding acid chlorides by reaction with thionyl chloride and subsequently to the 4-nitrophenyl esters by reaction with 4-nitrophenol.[20,21] The esters were purified on silica gel column with petroleum−acetone as eluent, and their purity was further established by elemental analysis. Alkyl *p*-nitrophenyl methylphosphonates, **10** and **11**, were obtained as follows: methylphosphonic dichloride was first half-esterified by the action of alkanol in the presence of triethylamine in benzene at 40 °C, then followed by addition of the mixture of nitrophenol and triethylamine in benzene. Compound **10** was mentioned by Aaviksaar,[22] but no analytical and spectral data were given.

Compounds **2**, **3**, **6**, **7**, **8**, and **11** are new. Their spectral and analytical data, including those of **10**, are reported below.

2-Ethylhexanoic Acid *p*-Nitrophenyl Ester (2). MS: *m/z* 266 (MH^+), 180, 140, 127, 99, 57. ^{1}H NMR (60 MHz, CCl_4): δ 0.5−1.9 (14H, m), 2.0−2.5 (1H, m, >C*H*COO−), 6.8−7.2 (2H) and 7.8−8.2 (2H) (AA′BB′ pattern, Ar-*H*). IR (film): 2970, 2870, 1770, 1620, 1600, 1530, 1495, 1353, 1210, 1160, 1100, 862, 747 cm^{-1}. Anal. Calcd for $C_{14}H_{19}NO_4$: C, 63.38; H, 7.22; N, 5.28. Found: C, 63.33; H, 7.47; N, 5.48.

7-Octenoic Acid *p*-Nitrophenyl Ester (3). MS: *m/z* 264 (MH^+), 180, 140, 125, 107, 97, 81. ^{1}H NMR (90 MHz, CCl_4): δ 1.1−2.2 (8H, m, =CHCH_2CH_2CH_2CH_2−), 2.44 (2H, t, J = 4.8 Hz, −CH_2-COO−), 4.7−5.0 (2H, m, CH_2=), 5.4−5.9 (1H, m, =C*H*−), 7.0−7.2 (2H) and 8.0−8.2 (2H) (AA′BB′ pattern, Ar-*H*). IR (film): 3060, 2920, 2850, 1770, 1640, 1614, 1595, 1526, 1491, 1350, 1210, 1161, 1108, 910, 863, 746 cm^{-1}. Anal. Calcd for $C_{14}H_{17}NO_4$: C, 63.87; H, 6.51; N, 5.32. Found: C, 63.92; H, 6.44; N, 5.31.

Cycloheptanecarboxylic Acid *p*-Nitrophenyl Ester (6). MS: *m/z* 264 (MH^+). ^{1}H NMR (60 MHz, CCl_4): δ 0.8−2.6 (13H, m), 6.6−6.9 (2H) and 7.7−8.0 (2H) (AA′BB′ pattern, Ar-*H*). Anal. Calcd for $C_{14}H_{17}NO_4$: C, 63.87; H, 6.51. Found: C, 63.79; H, 6.35.

***trans*-3-Octenoic Acid *p*-Nitrophenyl Ester (7).** MS: *m/z* 264 (MH^+), 207, 187, 181, 159, 125, 97, 81, 55. ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.91 (3H, t, J = 7.0 Hz, CH_3−), 1.25−1.48 (4H, m, $CH_3CH_2CH_2$−), 2.02−2.15 (2H, m, −CH_2CH=), 3.31 (2H, d, J = 6.6 Hz, −CH_2COO−), 5.53−5.78 (2H, m, −C*H*=C*H*−), 7.21−7.35 (2H) and 8.2−8.32 (2H) (AA′BB′ pattern, Ar-*H*). IR (film): 2940, 2860, 1770, 1618, 1599, 1530, 1495, 1352, 1213, 1115, 970, 865 cm^{-1}. Anal. Calcd for $C_{14}H_{17}NO_4$: C, 63.87; H, 6.51; N, 5.32. Found: C, 63.61; H, 6.56; N, 5.34.

Table 2. CAgC Values of Esters **1**−**11**

compd	CAgC (10^{-5} M)	compd	CAgC (10^{-5} M)
1	1.2 ± 0.1	**7**	4.6 ± 0.3
2	1.7 ± 0.1	**8**	7.6 ± 0.5
3	3.0 ± 0.2	**9**	4.1 ± 0.3
4	3.2 ± 0.3	**10**	3.9 ± 0.3
6	3.5 ± 0.4	**11**	>10
5	3.9 ± 0.4		

The coupling constant of the two protons of the double bond (−C*H*=C*H*−) was determined to be 15.4 Hz by the decoupling method; therefore, the double bond possessed a *trans* configuration.[23]

1-Methylcyclohexanecarboxylic Acid *p*-Nitrophenyl Ester (8). MS: *m/z* 264 (MH^+). ^{1}H NMR (60 MHz, CCl_4): δ 1.2−2.7 (13H, m), 7.2−7.5 (2H) and 8.4−8.7 (2H) (AA′BB′ pattern, Ar-*H*). Anal. Calcd for $C_{14}H_{17}NO_4$: C, 63.87; H, 6.51. Found: C, 64.05; H, 6.53.

Octyl *p*-Nitrophenyl Methylphosphonate (10). MS: *m/z* 330 (MH^+), 218, 209. ^{1}H NMR (90 MHz, $CDCl_3$): δ 0.86 (3H, t, J = 5.4 Hz), 1.1−1.5 (12H, m), 1.70 (3H, d, J_{P-H} = 17.9 Hz), 3.8−4.3 (2H, m), 7.2−7.5 (2H) and 8.1−8.4 (2H) (AA′BB′ pattern, Ar-*H*). ^{31}P{^{1}H} NMR (36 MHz, $CDCl_3$): δ 28.24. IR (film): 1245 (P=O), 1010 (P−O−C) cm^{-1}. Anal. Calcd for $C_{15}H_{24}NO_5P$: C, 54.70; H, 7.34; N, 4.25; P, 9.40. Found: C, 54.71; H, 7.77; N, 3.88; P, 9.47.

2-Ethylhexyl *p*-Nitrophenyl Methylphosphonate (11). MS: *m/z* 330 (MH^+), 218, 201. ^{1}H NMR (90 MHz, $CDCl_3$): δ 0.88 (6H, t, J = 6.0 Hz), 1.1−1.5 (8H, m), 1.56 (1H, br), 1.71 (3H, d, J_{P-H} = 17.8 Hz), 3.9−4.2 (2H, m), 7.3−7.5 (2H) and 8.1−8.3 (2H) (AA′BB′ pattern, Ar-*H*). ^{31}P{^{1}H} NMR (36 MHz, $CDCl_3$): δ 28.20. IR (film): 1247 (P=O), 1015 (P−O−C) cm^{-1}. Anal. Calcd for $C_{15}H_{24}NO_5P$: C, 54.70; H, 7.34; N, 4.25; P, 9.40. Found: C, 54.97; H, 7.12; N, 4.22; P, 9.22.

Kinetics. Dioxane was purified according to a standard procedure.[24] Water was distilled twice. Analytical reagent grades of NaOH, $NaHCO_3$, and NaCl were used for preparing the buffer solution. Kinetic measurements were made by using a Perkin-Elmer Lambda 5 UV−vis spectrophotometer equipped with a thermostat. A solution with a specified concentration of the substrate (2.0×10^{-6} to 1.6×10^{-4} M, cf. Table 2) was prepared by first dissolving an accurately weighed sample (ca. 20−30 mg) in 10 mL of dioxane. This stock solution (ca. 10^{-2} M) was then diluted (from 100 to 1000 times) to the desired specified concentration mentioned above (cf. Table 2). All kinetic experiments were performed at 35.0 ± 0.2 °C in aqueous NaOH−$NaHCO_3$ (0.014 and 0.010 M, respectively) buffer solution containing 0.35 M NaCl (pH 11.70 at 18 °C) by the standard procedure described previously.[3a,4,9,10,14] The experimental uncertainty for the k_{ob} values was ±5%. As done in all previous works and illustrated by Figure 1,[3,9,10,14] log k_{ob} was plotted against log $[Agr]_i$, and the crossing point of the horizontal line and the sloping line was taken as the CAgC. Values of CAgC for the 11 target molecules (**1**−**11**) are summarized in Table 2.

3. Results and Discussions

The crude and approximate evaluation of the hydrophobicity of an organic molecule by its Σf value will be referred to as the "Σf factor" in this work.[5] Strictly speaking, in order to reveal structural effects other than the Σf factor on the aggregating tendency of an Agr, only Agr's with the same Σf value should be compared. It is noteworthy, however, that a small difference in the Σf value is not necessarily a deciding or important factor. For instance, the order of increasing aggregating tendency of the *p*-nitrophenyl esters of four 18-carbon acids is oleic (Σf = 9.86) < elaidic (Σf = 9.86) < stearic (Σf = 10.23) < stearolic (Σf = 9.48).[14c] Nonetheless, we will analyze our data by a rigorous criterion, i.e., compounds with the same Σf value will be compared.

A look at the CAgC values of the two saturated esters **1** and **2** (Table 2), both with the same Σf value, immediately reveals an important structure effect, namely, branching of the chain reduces the aggregating tendency. The aforesaid tentative

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conclusion is supported by our observation (Table 2) that the aggregating tendency of the phosphonate **10** is much larger than that of its branch-chained isomer **11**. If this conclusion is true in general, then it is not surprising that relatively long methylene chains are among the main building blocks of biological membranes.[1a,b]

The $\sum f$ factor for the unsaturated and cyclic esters **3**−**8** is also the same, but their CAgC values are certainly not. The aggregating tendencies of **3, 4,** and **6** are not greatly different from each other, while that of **7** seems to be distinctly smaller, with that of **5** lying in between. A point of special interest is that two olefinic compounds (**3** and **7**) are occupying the two end positions of the aforesaid "quintet spectrum". Therefore, it would not be possible to generalize whether a C−C double bond or a cyclane structure would be more effective in reducing the aggregating tendency, although a comparison of CAgC's of **1** and **2** with those of the quintet **3**−**7** does confirm the expected effect of the $\sum f$ factor on aggregating tendency.

An observation of true significance here is that the aggregating tendency of a terminal olefin (ester **3**) is much larger than the aggregating tendency of an internal olefin (ester **7**). Apparently, this is caused by a "flexibility effect". In other words, an internal double bond will reduce the flexibility of a hydrocarbon chain, and before the phenomenon of self-coiling sets in, flexibility of a straight hydrocarbon chain is expected to favor aggregation because simple Ag's are composed of many conformers of hydrocarbon chains in dynamic equilibrium. This flexibility factor may be operating also in cyclic compounds, such as **4**, **5**, and **6**, although we are unable to discuss them on the basis of our data.

The most significant observation that stands out from Table 2 is that a "spheroidal" molecule (ester **8**) possesses a very much smaller tendency toward aggregation. This observed result is certainly a consequence of the shape or geometry effect discussed in our introduction. Although our observed shape effect could be expected if the effective contact area between two Agr molecules were considered, any experimental confirmation of this shape factor should still be a valuable addition to our knowledge of structural effects on the ease of HLI-driven aggregation. The great difference between the CAgC of **8** and those of the other seven eight-carbon substrates (**1**−**7**) suggests that the shape factor is one of the most important and basic factors that affect the ease of aggregation of organic molecules.

Finally, we note that a comparison of the CAgC of **8** with that of **9** can serve as yet another piece of cogent evidence for the importance of the shape factor because the former is derived from an eight-carbon acid, and the latter, from a seven-carbon acid. To our knowledge, in the absence of complications of self-coiling,[3] if similar types of molecules are compared, the molecule with one more carbon "should" always possess greater aggregating tendency than those with one less carbon. But here the conventional rule is unmistakably broken. Indeed, sometimes shape not only is an important factor but also may become a predominant factor that affects the aggregating tendency of an organic molecule.

Acknowledgment. We thank the National Natural Science Foundation of China and the Postdoctoral Foundation of China for financial support.

JA9512992