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New concepts for studying and understanding the aggregation, co-aggregation, de-aggregation and self-coiling of organic molecules. Why are cholesterols and triglycerides culprits of arteriosclerosis?

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Abstract - Recently proposed and studied new concepts of relevance to the phenomena of aggregation and self-coiling are reviewed. Ideas and studies on ESAg (electrostatically stabilized aggregate) and deAgr (deaggregator) are described. Measurement of coaggregating tendencies of the culprits of arteriosclerosis has led to the discovery of a neighboring-moiety-assisted chain-foldability effect.

In response to hydrophobic-lipophilic interactions (HLI), neutral organic molecules which possess at least one hydrocarbon chain with more than seven or eight carbons tend to form simple aggregates (Ag's) or co-aggregates (CoAg's) in solvents with "solvent aggregating power (SAgP)" (1). If this HLI-driven force for aggregate formation (together with Nature's other forces) were nonexistent, life would never have appeared in our universe.

If we call the above-mentioned neutral organic molecules " aggregators (Agr's) ", then we may say that in general aggregation occurs in the aggregator-concentration ([Agr]) domain of 10^{-7}-10^{-6} M. Higher concentrations most likely will result in the phase separation of the uncharged Agr from the solvent, unless the solution becomes supersaturated. The phenomena of aggregation brought about by HLI have been studied mostly in aqueous or aquiorgano solvents. The volume fraction of the organic component of an aquiorgano mixture is represented by the symbol φ. Naturally, for any particular binary aquiorgano system, its SAgP increases with its decreasing φ values. In non-supersaturated solutions, the average aggregate number (N) of simple Ag's or CoAg's is probably rather small, perhaps smaller than 5-15 (1, 2). Thus Ag's are both smaller and structurally simpler than typical micelles made up of ionic surfactants (1, 3). It has been very recently found (2a), that in the region of increasing degree of aggregation, it is mainly the average aggregate number (N), and not the number of aggregates, that is increasing in parallel with the aggregator concentration.

In solvents with SAgP, flexible hydrocarbon chains with more than

about twelve CH_2's tend to fold on itself like a hairpin (1, 4). This phenomenon is usually described as self-coiling or hairpin looping. It is also a phenomenon of profound significance in chemistry and possibly also in other disciplines related to the understanding of life and health (5, 6, 7). Recently, we have found that higher temperatures will reduce the aggregating tendency of Agr's (6b). It is particularly noteworthy that Tung has recently demonstrated that lipophobicity can also bring about aggregation and self-coiling of hydrophilic chains made up of CH_2CH_2O units (8). Recently, both the concepts of HLI-driven aggregation and of self-coiling have been successfully applied to synthetic chemistry, photochemistry (5d, 9, 10) and other disciplines, e. g., Cao's studies of LB films of porphyrin-viologen-carbazole triad compounds and electron donor-acceptor compounds (11). The present article will briefly review some new concepts as well as experimental results of relevance to these concepts obtained in our lab since 1988 (1).

Structure and Medium Effects

A general discussion of ' conventional ' structure and medium effects on aggregating and coiling tendencies has been given in an Account article (1). Here, we would like to emphasize that, for practical reasons, we are only talking about HLI-driven processes. In other words, e. g., aggregation or preassociation of two or more pyrene molecules in a dilute ([pyrene] $> 5 \times 10^{-6}$ M) hydrocarbon solvent (12) will not be included in either our discussion or our consideration. The word aggregation in this paper always refers to the HLI-driven process of simple Ag (and CoAg) formation, unless otherwise specified, as in the discussion of ESAg formation (vide infra).

The first simple conventional wisdom on this topic might be: The greater the hydrophobicity (or lipophilicity) of that particular molecule, as evaluated by the Rekker's $\sum f$ value (13), the greater will be its aggregating tendency. On the basis of this crude generalization, we would expect, e. g., that molecules with longer chains and less number of OH groups will have a higher aggregating (and coiling) tendency. This article, however, will not dwell on experimental observations expected from the aforesaid common knowledge, but will briefly describe how we speculated and established that there are other more subtle and interesting structural effects.

1. Do flat molecules need a side-chain ?

We speculated that at very low concentrations, flat molecules without a side chain might not readily undergo aggregation (14). This proposition has been supported by the fact that pyrene molecules do not form excimers even in supersaturated solutions ([pyrene] = 3 to 6 $\times 10^{-6}$ M) with relatively high SAgP, i. e., φ = 0. 15 EtOH-H_2O and φ = 0. 20 MeOH-H_2O mixtures, whereas addition of γ-cyclodextrin (CD) will immediately bring about the formation of excimers as a consequence of 1 : 2 host/guest complex formation. Similarly, anthracene-N, N-diethylaniline (DEA) or naphthalene-DEA will not form exciplexes in φ = 0. 15 EtOH-H_2O, while γ-CD will make them do so. (14)

2. The expected ' linked-up effect '.

If equal-length chains are compared, we expect each of the two or three linked-up chains to have a greater tendency toward coaggregation than each of the two or three free chains. In other words, if we compare the carboxylic esters, with chain length n, of ethanol (Et-n), glycol (EG-n) and glycerol (TG-n) at the molar concentration ratio of 3 : 3/2 : 1 in the dioxane (DX) -H_2O mixture, then we should observe an increasing coaggregating tendency order of Et-n < EG-n < TG-n. This expectation had been verified by sets of experimental data, e. g., the order of Et-12 < Et-16 < EG-12 < TG-12 (φ = 0. 45), but a surprising violation of the order was observed, i. e., TG-12 < EG-12 (φ = 0. 30)! At the same time, another violation (of the conventional wisdom on chain-length effect) was also found, i. e., TG-12 < TG-8 (φ = 0. 30) and TG-18 < TG-12 (φ = 0. 45). These unexpected observations led to the discovery of the " neighboring-moiety-assisted chain-foldability effect " (vide infra) (6).

3. The geometry or shape factor.

We reckoned that even molecules of approximately equal hydrophobicity ($\sum$ f values) might possess different inherent aggregating tendencies because of their differing geometry or shape. This expectation has now been verified by comparing the CAgC (critical aggregate concentration) values of various octanoic esters (15). It appears that the more a molecule approaches a " sphere " in shape, the smaller will be its aggregating tendency. The multiple-bond and cis/trans effects have also been studied (16), and the order of increasing aggregating tendency for the p-nitrophenyl esters of the 18-carbon acids is: oleic < elaidic < stearic < stearolic. This study also indicates that the chain-foldability effect can operate only with the assistance or participation (HLI-driven) of a neighboring moiety.

4. The intriguing chain-foldability effect.

As mentioned, some unexpected behaviors of TG-n and EG-n suggest that there is an interesting and important effect, the " neighboring-moiety-assisted chain-foldability effect ". This concept is now convincingly supported by some surprising coaggregating behaviors of cholesteryl acylates CE-n (n = number of carbons of the acyl group), oleate CE-ol and linoleate CE-ln, and of the 3-octanoyl, 3-dodecanoyl, 3-octadecanoyl and 3-oleyl derivatives of cholic acid methyl ester, i. e., BL-8, BL-12, BL-18 and BL-ol. Briefly speaking, this concept says, that by virtue of HLI, a methylene chain of more than 12 carbons can simultaneously fold on itself and interact with the other part (or moiety) of the same molecule, consequently, the inherent coaggregating tendency of that molecule is reduced because of the intramolecular self-satisfaction of HLI and of the reduced " arm-stretch " of the methylene chain. This useful concept may provide insights for understanding some life processes at the molecular level (vide infra).

5. Solvent effect and two types of salt effects.

Solvent aggregating power (SAgP) has been proposed to be yet another inherent solvent property which deserves our attention and study (1), and

the concept of SAgP is applied here only to the formation of Ag's or CoAg's from *neutral* Agr's. By our definition, for a particular Agr probe, e.g., p-nitrophenyl hexadecanoate (C16), in a particular aquiorgano solvent system, the SAgP of this system should be directly related to the degree of aggregation of the Agr C16. If it has been demonstrated that another kinetic probe, e.g., p-nitrophenyl octanoate (C8), is not an Agr, i.e., it is monomeric in the same solvent, then their hydrolytic rate constant ratio k_a/k_{1a} can be taken as an indicator of the degree of aggregation of C16. On the basis of these measured k_a/k_{1a} ratios, we have established that there is a linear dependence of the degree of aggregation on SAgP (φvalues) for five aquiorgano solvents, i.e., dioxane (DX)-H_2O, dimethylsulfoxide (DMSO)-H_2O, 2-methoxyethanol-H_2O, n-PrOH-H_2O and t-BuOH-H_2O, each within a certain range of φ values (17). Interestingly, this type of study can help us to answer the following type of question: If we want to use acetone instead of DMSO as the cosolvent of an aquiorgano mixture, how to roughly estimate the φ value of the acetone-H_2O system which has the same SAgP as the DMSO-H_2O system at a specified degree of aggregation (e.g., with $\log(k_a/k_{1a}) = 1.20$ or 1.60) of a certain probe C16?

A systematic study of the hydrolytic behaviors of the aforesaid kinetic probes C8, C12 and C16 in four solvent systems, i.e., H_2O, DMSO-H_2O, DX-H_2O and t-BuOH-H_2O, in the presence of the flexible host NaCMA (sodium carboxymethylamylose) has again confirmed that aggregation and host-guest interaction are competing processes (18).

For aquiorgano binary mixtures, the medium with the highest SAgP is that one with $\varphi = 0$, i.e., pure H_2O. However, the SAgP of an aqueous solution can also be raised or reduced by the addition of various salts. Our very recent systematic study shows that there are two types of salt effects, one for the formation of simple Ag's, and the other for the formation of ESAg's (vide infra) (15).

Is There a Measurable Inherent Property Common to the Culprits of Arteriosclerosis, Cholesterols and Triglycerides?

Even though the dreaded ailment arteriosclerosis is caused by a dauntingly complicated combination of interacting factors and causes, a chemist may still ask the following simple question: " Is there a measurable inherent property common to the culprits of arteriosclerosis, cholesterols and triglycerides? " Our hypothetical answer is: " Yes, perhaps. The common inherent property could be their coaggregating tendency. In other words, many culprit molecules may possess relatively high tendencies toward co-aggregation with other molecules carrying methylene chains (6). " We visualize that in our blood there exist trully complicated dynamic equilibria among all kinds of molecular assemblages, viz., from simple CoAg's to chylomicrons, VLDL, LDL and HDL, etc. Fatty substances, including the aforesaid culprit molecules, are getting in and out of these assemblages all the time. But in every elementary step of entering and leaving, one inherent property is involved or is of relevance, i.e., the coaggregating tendency of that particular molecule. Therefore, we should develop the methodology and then measure the relative coaggregating tendencies of these culprit molecules as well as other important substances related to life, e.g., phosopholipids and esters of multi-unsaturated acids. Coaggregating tendencies of the triglycerides TG-n as well as those of EG-n and Et-n have

already been briefly described (vide supra).

We have already succeeded in developing the methodology for measuring the coaggregating tendencies of the target molecules (including both the previously mentioned culprit molecules CE-n and non-culprit molecules BL-n), CE-0 (cholesterol itself), CE-n, CE-ol, CE-ln, BL-0, BL-n and BL-ol, kinetically in terms of $\Delta CAgC$ values (6), and spectroscopically in terms of average aggregate numbers (N_{ag}), fluorescence decay modes and life times of the CoAg's of a naphthalene fluorescence probe with a target molecule (2). All data obtained in the φ = 0.40 DX-H_2O system (for kinetic data, also in φ = 0.44 DX-H_2O) at 35 ℃ reveal or are consistent with the following orders of decreasing coaggregating tendencies: (1) CE-ol, CE-ln > CE-12 > CE-8 > CE-18 > CE-0; (2) BL-ol > BL-12 > BL-8 > BL-18 > BL-0; (3) CE-0 > BL-0; CE-8 > BL-8; CE-12 > BL-12; CE-ol > BL-ol; and (4) BL-18 > CE-18. Very recently, the above-mentioned observations have been reconfirmed by a spectroscopic study using decyl pyrenyl ketone as the fluorescence probe (6b).

Most striking is the fact that in contrast to the conventional wisdom on chain-length effect, the 18-carbon derivatives actually possess a smaller coaggregating tendency than even its much shorter 8-carbon counterpart, i.e., CE-12 > CE-8 > CE-18 and BL-12 > BL-8 > BL-18, whereas inserting one or two rigid double-bonds right in the middle of the 18-carbon chain will make the corresponding derivatives (CE-ol, CE-ln, BL-ol) behave "normally". All these experimental observations together may serve as a piece of convincing evidence for the veracity of the previously described "neighboring-moiety-assisted chain-foldability effect" (vide supra). Another intriguing observation, again in vivid contrast to conventional wisdom (as exemplified by order-3) which predicts that the coaggregating tendency of the bile acid derivatives BL-n should always be smaller than that of the corresponding cholesterol derivatives CE-n, is that of order-4. It suggests an interaction between the 18-carbon chain and the 8-carbon side-chain which the CE-n compounds have but the BL-n derivatives do not possess.

In conclusion, all our data indicate that for CE-18 there are conformers exceptionally low in energy which have their 18-carbon chain folded in the middle while simultaneously couching comfortably by the cholesterol-plate and interacting with the 8-carbon side-chain. Evidently, neither CE-ol nor CE-ln can play this trick because of the restricted rotation of the double-bond(s). The significance of our proposition may be exemplified by the fact that by now we can qualitatively relate the composition of the arterial plaque (CE-18, 2 %; CE-ol, 82.8 %; CE-ln, 84.9 %) to the coaggregating tendencies of its components (19). Our results also seem to support the hypothetical view that cholesterol (CE-0) itself is guilty only by association.

ESAg, the Electrostatically Stabilized Aggregate

Years ago, we were tempted to find an answer to the following question: "What is the structural niche or echelon next to and above that of the simple Ag or CoAg which exist in the concentration domain of 10^{-7}-10^{-8} M?" We proposed that this structural niche could be occupied by the ESAg species, made up of oppositely charged long-chain molecules with perhaps 8-16 CH_2 groups (20). We reckoned that without the help of electrostatic attraction which might amount to 1.2 kcal/ mol per ion pair in an aqueous

solution (cf. Schneider, 21), similarly charged long-chain molecules with less than 16 methylenes would not possess enough HLI to overpower the hydrophilicity of their charged end-groups to form measurable amounts of charged aggregates or coaggregates. This could be the reason why it had been difficult to find many definitive evidences for the premicelles of +/+ or -/- types of cationic or anionic micelles. On the other hand, the ESAg concept implies that the ESAg species will naturally grow into the +/- type of mixed micelles made up of comparable amounts of cationic and anionic surfactant molecules. In other words, in the concentration domain of 10^{-7} to 10^{-4} M, EsAg's are the precursors or premicelles of the +/- type of mixed micelles.

Both kinetic and spectroscopic methods can be used to prove or disprove the ESAg proposition. It predicts that the hydrolytic rate constants (k) of kinetic probes P will be reduced *only* by *oppositely* charged surfactants S after the concentration of the latter ([S]) has increased beyond its CoCAgC value with P. It also predicts that excimers will form or energy transfer will occur between two similarly charged fluorescence probe (FP) molecules only in the presence of *oppositely* charged surfactants S when the [S] term is larger than the CoCAgC value of S with FP (22). Kinetic probes $P16^-$, $P16^+$ and $P16^\circ$, fluorescence probes carrying α-naphthyl ($C_{10}H_7$-) or 9-anthracenyl ($C_{14}H_9$-) groups, FP^-, FP^+, FP° and AFP^-, together with cationic, anionic and neutral surfactants Sn^+, Sn^- and Sn°, where n = number of CH_2's = 12 or 16, as well as fluorinated tetrapus molecule $4S^-$, were used in our investigation (22). The solvent systems used were φ= 0.20 and φ= 0.50 DMSO-H_2O, and φ= 0.20 DX-H_2O for kinetic studies at 35 ℃; and H_2O or φ = 0.10 and 0.40 DX-H_2O for fluorescence measurements at 25 ℃.

$CH_3(CH_2)_{14}COOC_6H_4\text{-}CO_2^-$, Na^+
$P16^-$

$CH_3(CH_2)_{14}COO\text{-}C_6H_4\text{-}CH_2NMe_3^+$, Br^-
$P16^+$

$CH_3(CH_2)_{14}COO\text{-}C_6H_4\text{-}NO_2$
$P16^\circ$

$\alpha\text{-}C_{10}H_7\text{-}CH_2CH_2O(CH_2)_{10}\text{-}Br$
FP°

$\alpha\text{-}C_{10}H_7\text{-}CH_2CH_2O(CH_2)_{10}CO_2^-$, Na^+
FP^-

$\alpha\text{-}C_{10}H_7\text{-}CH_2CH_2O(CH_2)_{10}NMe_3^+$, Br^-
FP^+

$9\text{-}C_{14}H_9\text{-}CH_2OCO(CH_2)_8CO_2^-$, Na^+
AFP^-

$C[CH_2OCH_2CH_2CH_2CF_2CF_2OCF_2CF_2SO_3^-, Na^+]_4$
$4S^-$

$CH_3(CH_2)_{n-2}CO_2^-$, $^+NMe_4$
Sn^-

$CH_3(CH_2)_{n-1}NMe_3^+$, Br^-
Sn^+

On the basis of hundreds of rate constants and spectra, kinetic and spectroscopic behaviors of about forty combinations or pairings of P with S, or FP with S, were systematically examined in different solvents e. g., in φ = 0.5 DMSO-H_2O, $P16^-$ or $P16^+$ with $S16^-$, $S16^+$, $S12^-$ or $S12^+$; $P16^\circ$ with S12- or $S12^+$; in φ = 0.2 DMSO-H_2O, $P16^-$ or $P16^+$ with $S12^-$, $S12^+$; in φ = 0.20 DX-H_2O, $P16^-$ or $P16^+$ with $S12^-$, $S12^+$, $S16^+$ or $S12^\circ$; in H_2O, FP^-, Fp^+ or AFP^- with $S12^-$, $S16^+$ or $4S^-$; FP^- with FP^+; (FP^- + AFP^-) with $S16^+$; in DX-H_2O of φ= 0.10 to 0.90, FP^- with $S16^+$; in φ = 0.40 DX-H_2O, FP° with $S16^+$ or $S12^-$.

From all our data derived from the above-mentioned pairings of single-

chain probe and surfactant molecules, one pleasingly simple conclusion has emerged, namely, the P molecules will have their rate constants reduced and the FP molecules will form excimers only in the presence of *oppositely* charged surfactant molecules, as our ESAg concept has predicted. Furthermore, we have found that energy transfer from FP^- to AFP^- will occur only in the presence of $S16^+$, and that the tetrapus $4S^-$ molecule with anionic termini will form a very stable host-guest complex with FP^+ but only a loose complex with FP^- (22, 23). In short, all our first-stage studies have vindicated the ESAg concept. This concept may prove itself useful not only in furthering our understanding of the phenomena of coaggregation, but also in inspiring new lines of research, e.g., on the " chain-length-matching effect " and a different type of salt effect (15). Incidentally, the ESAg study has also unexpectedly led to the discovery of a cationic surfactant, $P16^+$, which possesses both a cmc and a CAgC (22). In other words, under some circumstances, simple but charged aggregates may trully be the premicelles to micelles of ionic surfactants after all (cf. 1).

Effective Neutral Deaggregators (deAgr's)

If there are many neutral aggregators (Agr's), why are not there neutral deaggregators or deAgr's ? If someday someone could find an extremely effective yet nontoxic deAgr, then it might turn out to be useful in preventing or even curing arteriosclerosis, if it could be continuously introduced into the blood stream near the heart by a relatively simple device, e.g., by storing it in a semipermeable capsule wrapped around a vein.

We visualize that an effective deAgr might break up or reduce the size of Ag's by the following mechanism (6b). (1) By virtue of its hydrophobicity, it gets into an Ag and associates itself with one (or two) Agr molecule(s), and (2) by virtue of its hydrophilicity, it will get out of the Ag again, but this time together with an associated Agr molecule. Consequently, the original Ag is partly or fully broken up. The "best" deAgr, therefore, should possess a golden balance between its hydrophobicity and hydrophilicity.

By combining a hydrophilic moiety (e.g., a sugar residue) with various alkyl chains, we have had some success in the initial search for effective neutral deAgr's. Their deaggregating abilities are much greater than that of a typical cationic surfactant (e.g., DTAB) (6b).

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