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CHEMISTRY OF INTERFACIAL ORGANIC PROCESSES

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Abstract - This article summarizes our work with (1) reaction mechanisms at hydrocarbon-water interfaces, (2) the use of emulsifying agents in synthetically useful interfacial systems, (3) the conformations of bolaform electrolytes at air-water interfaces, (4) the analysis of reaction kinetics at micellar surfaces, (5) the rotamer population at a micelle interface, (6) mechanisms of fast proton transfers at a micelle interface, (7) the properties of organic and enzymatic reactions occurring inside water pools, (8) the design of a polymeric reducing agent and (9) the pyrochromatography of structurally related steroids using hot quartz and platinum surfaces in the absence of O_2.

If people climb mountains because they are there, then chemists study interfaces because they are everywhere. Interfacial processes range from enzyme-catalyzed reactions in cells to emulsion polymerizations in vats. Yet interfacial systems have been, relatively speaking, barely touched by the blossoming of physical organic chemistry. Experimental problems are the major cause of this. A heterogeneous mixture does not provide a spectrum or rate constant as readily as does a homogeneous solution. Those, however, who endure the complexities of interfacial systems are rewarded by something not often found with compounds sequestered in solution: molecular order. Whereas the orientation of reactants in solution is usually random, molecules at a phase boundary have well-defined orientations which can impact critically upon their behavior. In this article, I summarize concisely our experiences with liquid-liquid interfaces, interfaces of normal micelles in water, interfaces of inverted micelles in hydrocarbons, and solid-liquid interfaces. For an older but less egocentric account of reactivity at phase boundaries, I refer the reader to a Chemical Society review (Ref. 1).

Liquid-Liquid Interfaces

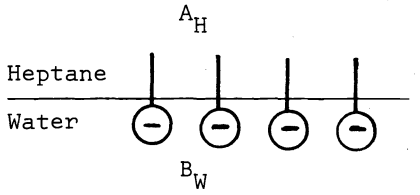
Only a few mechanistic studies have ever been carried out on reactions at a hydrocarbon-water interface. We have probed this type of reaction by stirring rapidly a solution of p-nitrophenyl laurate in heptane with a larger volume of imidazole in water (Ref. 2). Since the ester is insoluble in water and the imidazole is insoluble in the heptane, we hoped that an imidazole-catalyzed hydrolysis would occur at the heptane-water boundary of the dispersed heptane droplets. This expectation was realized as borne out by the following observations: (1) Partitioning of ester from heptane to water was not detectable by sensitive spectrophotometric methods. Hydrolysis rates are too fast to be explained by minute amounts of ester dissolving into bulk water prior to hydrolysis in that medium. (2) The hydrolysis rate does not change when the chain-length (and presumably water-insolubility) of the ester is increased. (3) Previous work had demonstrated a great sensitivity of colloidal or sub-colloidal esters in water to precipitation by sodium chloride (Ref. 3). If ester hydrolysis occurs only in the bulk water phase of the heptane-water mixture, then addition of salt should drastically reduce the reaction velocity by "salting out" the ester. In actual fact, the rates are slightly increased by large amounts of salt. (4) Solvent isotope effects, rate ratios for different aqueous catalysts, sensitivity to additives, and activation parameters are all different for the interfacial and corresponding bulk-water reactions.

We have also ruled out a reaction occurring in the dispersed hydrocarbon phase where imidazole and ester could conceivably exist in an unfavorable equilibrium with acylimidazole and p-nitrophenol:

$$\text{imidazole} + \text{ester} \overset{\text{heptane}}{\rightleftarrows} \text{acylimidazole and p-nitrophenol}$$

The water would function here simply to remove one or both of the products, thereby driving the equilibrium to the right. This mechanism appears unlikely because, among other reasons, the interfacial kinetics are first-order in imidazole. If the heptane becomes saturated with imidazole during the rapid stirring, then addition of more imidazole to the water should not increase the rate (i. e. the reaction should be zero-order in imidazole). If saturation is not achieved under kinetic conditions, then a homogeneous reaction in heptane could indeed be first-order in aqueous imidazole. But this possibility was eliminated by showing that heptane pre-saturated with imidazole gives the same rates as untreated heptane.

Hydrolysis rates were determined as a function of stirring speed, concentration of reactants, temperature, viscosity of the hydrocarbon phase, volume of the heptane and water solutions, structure of the catalyst, and presence of additives. Interesting differences were found between the hetereogeneous hydrolysis and homogeneous hydrolyses of a short-chain ester. For example, a plot of the heterogeneous reaction rate vs. concentration of ester in the heptane shows a pronounced saturation effect like that in an enzyme system. In contrast to the bulk water reaction, the interfacial hydrolysis displays extremely small temperature coefficients; this suggests that migration of reactants into the interfacial region is at least partially rate-determining. Small amounts of laurate anion (2×10^{-5} to 2×10^{-4} M) added to the aqueous phase significantly retard the interfacial hydrolysis (while having no effect on the homogeneous analog). Laurate adsorbs at the interface (see drawing below) where it impedes the transport of one or both of the reactants to the hydrocarbon-water boundary. Competition for reaction sites suggests a potentially useful method for controlling interfacial reactions not usually available with simple bimolecular reactions in solution. Although the interfacial hydrolysis behaves differently in many respects from the corresponding bulk-water reaction, the two modes do apparently operate by the same mechanism (nucleophilic catalysis as opposed to general base catalysis).



$$A_H \rightleftarrows A_I$$
$$B_W \rightleftarrows B_I$$
$$A_I + B_I \rightarrow \text{products}$$

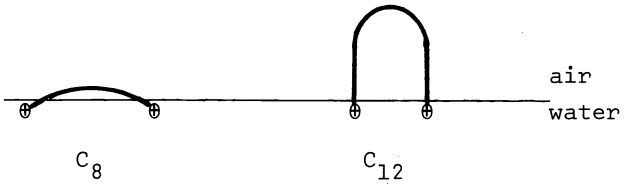
Synthetic chemists are frequently faced with the problem of reacting a water-insoluble organic compound with a water-soluble reagent such as hydroxide, hypohalite, formate, or hydrazine. We have investigated the possibility of improving the yields or decreasing the reaction times in this type of situation by adding an emulsifying agent (Ref. 4). The idea was to disperse the organic phase in the water phase, thereby increasing the contact area and facilitating the reaction. Table 1 shows data for the hydrolysis of α,α,α-trichlorotoluene to benzoic acid in the presence and absence of the emulsifying agents, hexadecyltrimethylammonium bromide and Brij 35. A 0.01 M solution of the former compound reduces the reaction time under standard conditions from 60 hours to 1.5 hours. This improvement does not arise from a phase-transfer catalysis because $n\text{-}Bu_4N^+Br^-$ (a particularly good phase-transfer catalyst) is less potent than the long-chain surfactant. Brij 35 also reduces the reaction time and, being a neutral surfactant, must without question operate by a mechanism other than phase-transfer. We have in addition demonstrated the efficacy of emulsion catalysis in preparative-scale permanganate oxidations of a water-insoluble aldehyde (Ref. 4).

TABLE 1. Hydrolysis yields of α,α,α-trichlorotoluene to benzoic acid in 20% NaOH at 80°

Additive	Reaction time, hr	% yield
0.01 M $C_{16}H_{33}N(CH_3)_3^+Br^-$	1.5[a]	98
None	1.5	0
None	60[a]	97
0.006 M Brij 35[b]	11[a]	97
0.02 M n-$Bu_4N^+Br^-$	15[a]	98
20% dioxane[c]	1.5	0

[a] This is roughly minimum time required for completion of the reaction.
[b] $C_{12}H_{25}(OCH_2CH_2)_{23}OH$.
[c] Two phases.

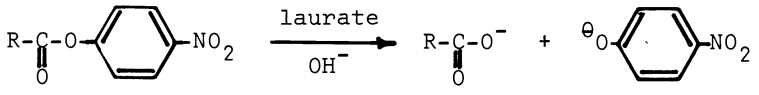
In the introduction I mentioned the fact that molecules have well-defined orientations at phase boundaries. This is nicely illustrated by a study of ours on bolaform electrolytes at an air-water interface (Ref. 5). A bolaform electrolyte is an organic molecule having two positive or negative sites separated by relatively great distances. We found from surface tension data that $Me_3\overset{+}{N}-(CH_2)_8-\overset{+}{N}Me_3$ occupies 3 times more area per molecule at an air-water interface than does $Me_3\overset{+}{N}-(CH_2)_{12}-\overset{+}{N}Me_3$. The best explanation for this result is that the 12-chain compound can "loop" at the interface whereas the 8-chain bolaform lies flat on the surface:



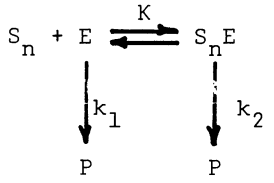
One wonders if this first proven case of "wicket" formation could lead to a synthetically useful method for closing large rings.

Interfaces of Normal Micelles in Water

"Micelle" is the name given to roughly spherical aggregates formed in water by 30-150 surfactant molecules (molecules having ionic or polar heads and long hydrocarbon tails). Although the exact structure of micelles is a matter of considerable controversy (Ref. 6), they can be viewed as having their ionic heads near the bulk water and the tails extending inwardly into the micelle interior. Perhaps the most important property of micelles is their ability to solubilize non-polar compounds into water. Micellar adsorption generally changes the chemical reactivity of the guest, and this fact has been used to probe the micelle-water interface. Some time ago we delineated the equations and assumptions for analyzing quantitatively the kinetics of micellar reactions (Ref. 7). This so-called "enzyme model" for micellar reactions originated from at attempt to understand the inhibition of ester hydrolysis by micellar sodium laurate at pH = 9.59:



We proposed a scheme in which an ester-micelle complex (S_nE) is in equilibrium with ester (E) and micelle (S_n):

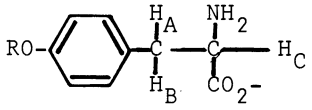


Both the hydrolysis rate of adsorbed ester (k_2) and the binding constant (K) can be evaluated from the following equation by plotting $1/(k_1 - k_{obs})$ vs. $1/(S_n)$:

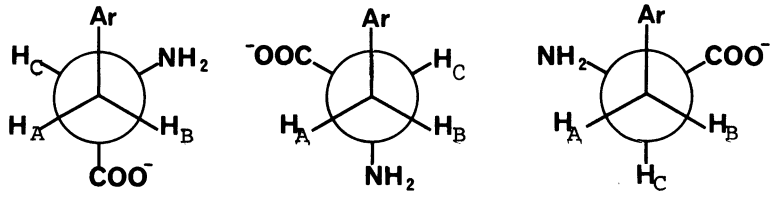
$$\frac{1}{(k_1-k_{obs})} = \frac{1}{(k_1-k_2)} + \frac{1}{(k_1-k_2)K(S_n)}$$

It was found that k_2 values for the esters lie within experimental error of zero; in other words, ester bound to the laurate micelles does not contribute to hydrolysis product. In contrast, micelles composed of cationic surfactants (e. g. trimethylhexadecylammonium bromide) catalyze ester hydrolysis. According to present notions about micelles, the ester probably adsorbs near the micelle-water interface. If a micelle is comprised of anionic surfactants, then the resulting charge repels hydroxide ion, and the base hydrolysis is impeded. If the surfactants are cationic, then both ester and hydroxide collect at the micelle surface; the rate of the bimolecular reaction thus increases because the concentration of the reactive entities are greater at the interface than in the bulk water.

Not only does micellization change rate constants, it affects conformation. This was demonstrated recently in an ^1H NMR study of O-alkyl-D,L-tyrosines (0.10 M in D_2O, pD = 13.1, 33°)(Ref. 8):



When R = C_6H_{13} or C_8H_{17} (but not H or CH_3), the amino acids form micelles. By analyzing the ABC multiplet, we could calculate the relative populations of the following three staggered rotamers in the monomeric and aggregated states:



a b c

In Table 2 one sees that aggregation markedly enhances the population of conformer a at the expense of conformer b. Since conformer a is the only one of the three with a carboxylate trans-coplanar to the hydrocarbon tail, it can most easily expose its ionic group to external water while at the same time pointing its chain toward the center of the micelle. Clearly, analyses of micellar reactions must take into account the possibility that molecules fold and twist differently within an assemblage than in the monomeric form. Micellar conformational changes have not yet been exploited for synthetic purposes.

TABLE 2. Fractional rotamer populations for O-alkylated tyrosines in basic aqueous solutions at 33°

Compound	Aggregation State	a	b	c
L-Tyrosine	Monomeric	0.48	0.23	0.29
O-Methyl-L-tyrosine	Monomeric	0.52	0.24	0.24
O-Hexyl-D,L-tyrosine	Micellar	0.67	0.12	0.21
O-Octyl-D,L-tyrosine	Micellar	0.65	0.05	0.30

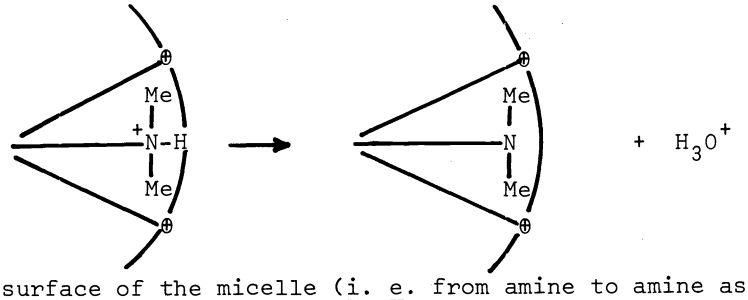
We were interested in studying the kinetics of a reaction which occurs unquestionably at a micelle-water interface. Although experiments with reactive additives adsorbed into or onto micelles provide useful information, there is always a lingering uncertainty as to the various locations of the additives within the aggregates. The problem was solved by examining NH-proton exchange of dimethyldodecylammonium ion in the micellar state (Ref. 9); since the proton transfer reaction involves the surfactant heads, there is no doubt that we were probing the micelle interface. The proton exchange (followed by dynamic NMR methods) was found to obey the mechanism below:

$$R_3N\underline{H}^+\cdot\cdot OH_2 + H_2O \underset{k_{-a}}{\overset{k_a}{\rightleftharpoons}} R_3N\cdot\cdot\underline{H}OH + H_3O^+$$

$$R_3N\cdot\cdot\underline{H}OH \xrightarrow{k_H} R_3N + \underline{H}OH$$

$$R_3N + H_3O^+ \xrightarrow{\text{fast}} R_3NH^+$$

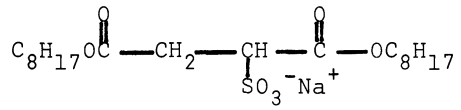
The N-proton is delivered initially to a water of solvation which in turn passes a proton to another water molecule. This is followed by a desolvation step to give R_3N. R_3N accepts a new proton in a diffusion-controlled step, and the overall result is a proton interchange. We found that the rate of proton exchange increases dramatically when the concentration of the long-chain tertiary amine salt exceeds its "critical micelle concentration". (Below the CMC, the salt is monomeric; above it, salt is mainly aggregated.) The pH necessary to bring observed exchange rates into the NMR "window" is 3 units lower for micellar $C_{12}NHR_2^+$ than for monomeric $C_6NHR_2^+$. This enhanced micellar exchange stems primarily from a fast Grotthus proton transfer (k_a) rather than an abnormally fast amine desolvation (k_H). Micellization was also found to reduce the apparent pK_a of the protonated amine by 1.4 units, testifying to the compacted condition of the ammonium ions at the micelle surface. We were able to show that transfer of a proton along



the surface of the micelle (i. e. from amine to amine as can occur in bulk water) is a much less favored pathway than proton transfer from amine to interfacial water.

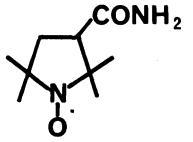
Interfaces of Inverted Micelles in Hydrocarbons

Di-2-ethylhexyl sodium sulfosuccinate (called commercially "AOT") dissolves freely in hydrocarbon solvents despite its ionic character. When present in non-polar solvents, AOT aggregates into "inverted" micelles capable of solubilizing large amounts of water. Thus, a 0.1 M solution of AOT in octane can incorporate nearly 10% water! We have coined the term "water pool" to describe these inverted micelles.



"AOT"

The cause of the remarkable water-solubilizing powers of AOT is not fully understood, but it is interesting in this regard that the n-octyl analog of AOT does not so effectively induce pool formation. We have carried out light-scattering studies which show that, as might be expected, the pool size depends on the molar ratio of water to AOT (designated "R") (Ref. 10). Thus, there are roughly 400 water molecules per pool when R = 8.9; the number of water molecules climbs steeply as the R value reaches its maximum of about 50 (after which the phases separate). Both inorganic and organic molecules dissolve in the pools, and this has allowed us to probe the micropolarity of the pools by UV-VIS, fluorescence, and ESR methods. For example, all three techniques show that when R is large (35-50), the water inside the pools resembles bulk water closely. Table 3 presents hyperfine splitting constants (a_N) and line-width parameters (W) for a water-soluble spin label inside the pools (Ref. 11).



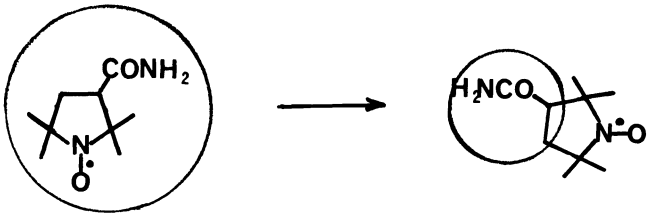
The splitting constant is solvent-sensitive and thus provides polarity information; the W parameter responds to the motional freedom of the spin label. By comparing the data from pure solvents with those from water pools of varying size (Table 3), one sees that decreasing the pool size does two things: (1) The polarity of the pool gravitates from water-like (R = 51.6) to benzene-like (R = 2.6). (2) The W parameter increases monotonically as R decreases, indicating that the spin label is experiencing ever increasing restrictions on its motional freedom. The combination of these two observations leads to conclusion that the spin label is being "squeezed" from the aqueous interior of the large pools onto the interface of the small ones. Loss of motional freedom frequently accompanies interfacial adsorption.

TABLE 3. Dependence of the hyperfine splitting constant, a_N, and line width parameter, W, of a label on the size of the water pools

Solvent or $[H_2O]/[I]$[a]	a_N, G (±0.7%)	W, G (±15%)
Water	16.27	0.03
1.0 M aq SBS[b]	16.26	0.02
4.7 M aq NaCl	16.30	0.04
Methanol[c]	15.30	0.04
1-Butanol[c]	15.31	0.17
1-Octanol[c]	15.23	0.42
Benzene	14.40	0.01
51.6	16.00	0.16
36.1	15.84	0.21
25.8	15.68	0.28
25.8[d]	15.63	0.24
15.5	15.51	0.39
12.9	15.42	0.43
10.3	15.26	0.46
10.3[e]	15.29	0.48
5.2	14.74	0.76
2.6	14.48	0.83

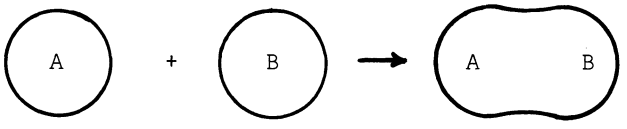
(For footnotes see next page)

[a][I] = 0.11 M in the heptane-water mixture. [b] SBS = sodium benzenesulfonate. [c]The viscosities in millipoises of methanol, 1-butanol, and 1-octanol at 20° are 5.93, 29.48 and 89.47, respectively. [d]This sample was degassed by the freeze-thaw method at 5 x 10^{-6} mm. None of the other samples was degassed. [e] The concentration of label was 2.1 x 10^{-5} M. In all other samples the concentration was 7.2 x 10^{-5} M.



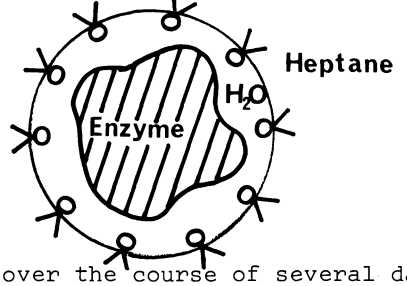
Imidazole inside water pools is capable of catalyzing the hydrolysis of esters added initially in the octane (Ref. 10). p-Nitrophenyl acetate, propionate, caproate, and laurate display relative hydrolytic rates of 56:16:1.7:1. Rates are proportional to the imidazole concentration in the pools at constant R. It appears, therefore, that although transfer of ester from organic phase to the aqueous phase does not limit the rate, partitioning of the substrate into the pools from the octane is certainly an important pre-equilibrium.

Two octane-AOT-water solutions were prepared, one with pools containing imidazole and the other with pools containing a water-soluble ester. When these solutions were mixed, hydrolysis was found to occur. Clearly, reactant in one set of pools is able to "communicate" with reactant in the second set. The most likely explanation is that the pools merge and separate rapidly as shown below:



The kinetics of water pool formation is a relatively unexplored area and one that we are currently investigating by ultrasonic techniques (Ref. 12).

Finally, mention should be made of preliminary unpublished work on an enzyme dissolved in water pools (Ref. 13). The discovery that enzymes retain activity in water pools (Ref. 14) prompted us to examine chymotrypsin solubilized by AOT in a solvent composed largely of heptane. The solubilized enzyme

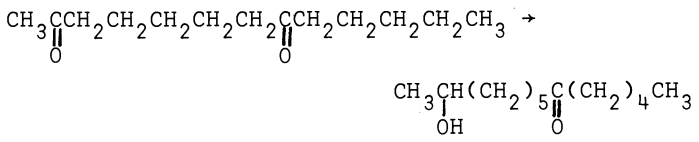


denatures over the course of several days at room temperature, but this loss of activity is sufficiently slow that one can easily determine the kinetics. It appears that the sigmoidal pH-rate profile for the enzyme-catalyzed hydrolysis of a specific substrate (N-acetyl-L-tryptophan methyl ester) shifts to higher pH by 1.5 units in the water pool. Although the enzyme is much more active at pH = 7.0 in bulk water than in the pool, the two activities are similar at pH = 9.0. Strangely, the kinetics seem independent of the pool size from R = 10 to R = 40. Mechanistic work on enzymes under these bizarre conditions is being actively pursued.

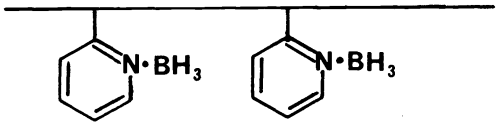
Solid Interfaces

Someday, perhaps, when a chemist wishes to carry out an oxidation he will grasp a bottle of insoluble oxidizing beads, pour them into a benzene solution of his compound, stir the mixture until the reaction is over, remove

the beads by filtration, evaporate his solvent, and collect his product. If he wishes to carry out a reduction, he will use reducing beads; bromination, bromination beads, and so on. This procedure not only has the merit of easy work-up, it has the potential of great reaction selectivity. Consider, for example, the reduction shown below:

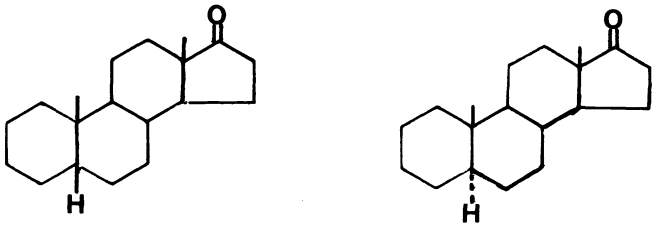


There is no simple way of carrying out such a reaction in high yield using current solution technology. On a solid surface, however, this reaction is a distinct possibility. After all, enzymes achieve their great stereo- and regioselectivity through surface binding. We have recently begun synthesizing "reaction beads" such as the borane complex of poly-2-vinylpyridine: (Ref. 15)



When this polymer is reacted heterogeneously at 25° with ketones dissolved in benzene, the ketones are recovered unaltered. Addition of $BF_3 \cdot OEt_2$ does not improve the situation. However, when the polymer is first boiled under reflux in benzene for 1 hour and then mixed with ketone and $BF_3 \cdot OEt_2$ at 25°, alcohol is isolated in 85% yield. Apparently, refluxing the polymer in benzene swells the beads and exposes the reducing sites to the carbonyls. Attempts are being made to modify the polymer surface (by placing hydrophobic chains on some of the pyridine nitrogens) with the aim of imparting binding selectivity to the polymeric reducing agent.

In conclusion, I wish to mention work which although "interfacial" only in the broadest sense of the word has nonetheless occupied our attention for some time. We were interested in examining how complex substances behave when exposed to hot surfaces in the absence of O_2. Our initial efforts were directed toward the identification of pathological proteins and bacteria (Refs. 16, 17). More recently, we subjected 15 structurally related steroids to quartz and platinum surfaces at 1000° and separated the resulting breakdown products with a gas chromatograph (Ref. 18). It was found that the steroids have characteristic pyrochromatographic "fingerprints" and that thermal degradation patterns are far more sensitive to minor structural and stereochemical differences than one might have thought possible from the seemingly brutal treatment. For example, 5β-androstan-17-one and 5α-androstan-17-one each have a large peak missing in the other. Pyrochromatography can differentiate individual steroids, discern sets of steroids containing



particular types of functional groups and, as mentioned above, can even distinguish one epimer from another. Although much more work remains, our results suffice to illustrate the potential of PGLC in structure elucidation and mechanistic studies. Identifying the steroid fragments by mass spectrometry will add another dimension to the method. Perhaps someday thermal degradation in combination with mass spectrometry will complement mass spectrometry by itself as a common tool in structure analysis.

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