Biomimetic Control of Chemical Selectivity

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The style of laboratory organic chemistry differs from that used in living systems to perform biochemical reactions. In general, organic chemists allow small reactive reagents to attack a free substrate randomly from solution. Any selectivity achieved is the result of the selective reactivity of particular sections of the substrate or of steric crowding blocking certain approach directions.

By contrast, biochemical reactions involve enzymes, which bind and orient the reactants. Biochemical selectivity usually reflects such orientation, rather than the intrinsic reactivity of the substrate molecule. For instance, it is common to observe the selective oxidation of an unreactive segment of a substrate molecule in an enzymatic reaction while much more reactive segments (with respect to ordinary chemical reactivity) are left untouched.

The results of this biochemical style of reaction are frequently superior to the results of simple chemical processes. For one thing, enzymatic reactions are usually very rapid even under mild conditions of acidity, temperature, etc. It is not unusual for an enzyme-catalyzed reaction to be 10^{10} times as fast as the same reaction without catalyst, comparing pseudo-first-order rate constants for reaction of the enzyme–substrate complex with those for substrate alone. Perhaps more important to synthetic chemists, enzymatic processes frequently achieve levels of selectivity which are not yet attainable by simple chemical means. Most enzyme-catalyzed reactions are stereoselective, selective in the choice of substrates, selective in the type of chemical reaction performed, and selective in the region of the molecule attacked when there are several possibilities (regioselective). Selective attack on some substrates, not others, is important for biochemistry carried out in a veritable soup of chemical compounds but is less important for synthetic chemistry where mixtures of substrates need not be present. Acceptable selectivity in the type of reaction performed is common in chemical reactions as well as in biochemical reactions. However, regioselectivity and stereoselectivity, particularly the formation of pure product enantiomers from nonchiral precursors, are aspects of enzymatic chemistry which are to be admired and imitated by synthetic chemists. Learning how to imitate enzymatic rates for important chemical reactions is also desirable.

Some years ago[1] we initiated a program aimed at mimicking the selectivity of enzymatic reactions. Biochemical selectivity is the result of the geometry of enzyme–substrate complexes, in which only certain substrates can fit the enzyme and only certain points in the substrate are then in a position to be attacked. Thus we decided to mimic this geometric control by using reagent–substrate complexes in which a relatively rigid reagent would direct attack into a particular region of the substrate. We called such systems "biomimetic";[2] the term "biomimetic" has since come into wide use, generally referring to any aspect in which a chemical process imitates a biochemical reaction.

One aspect of biochemistry which was particularly intriguing was the ability of certain enzymes to carry out selective functionalizations of hydrocarbon segments of a molecule remote from any functional groups. An example is the enzymatic conversion of stearic to oleic acid. By contrast, selective chemical reactions

$$\underset{\text{stearic acid}}{CH_3(CH_2)_{16}CO_2H} \xrightarrow[\text{oxidation}]{\text{enzymatic}} \underset{\text{oleic acid}}{CH_3(CH_2)_7CH{=}CH(CH_2)_7CO_2H}$$

normally must be in the vicinity of, and directed by, the already present functional groups of the substrate. Thus we set as a particular target the development of "remote oxidation" or "remote functionalization" reactions. We wanted to achieve selective reactions at arbitrarily large distances from any functional groups of the substrate, the distance being determined by the geometry of a complexed reagent, catalyst, or template.

Steroid Photochemistry

Our earliest work[3–6] involved benzophenone photochemistry. As one substrate we examined 3α-cholestanol (**1**) and tried to carry out selective oxidations of this substrate remote from its hydroxyl group. For simplicity, the "complex" between substrate and reagent was achieved with a covalent ester link, so 3α-cholestanyl (*p*-benzoylphenyl)acetate (**2**) was synthesized and irradiated.[6,7] A single olefinic product is formed (**3**), with a double bond which is quite remote from the original substrate functional group. Isotopic labeling studies[7] show that the reaction sequence is as shown in Scheme I. That is, the oxygen atom of the benzophenone excited triplet state removes the hydrogen at C-14, the radical then inverts at C-14, and the hydrogen at C-15 is transferred to the carbon radical of the attached reagent.

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(1) For an early review, see R. Breslow, "Biomimetic Chemistry", *Chem. Soc. Rev.*, 1, 553 (1972).
(2) The word "biomimetic" was introduced in ref 1 and previous lectures. Deno was at the same time referring to this field as "enzyme-mimetic chemistry".
(3) R. Breslow and M. A. Winnik, *J. Am. Chem. Soc.*, **91**, 3083 (1969).
(4) R. Breslow and S. W. Baldwin, *J. Am. Chem. Soc.*, **92**, 732 (1970).
(5) R. Breslow and P. Kalicky, *J. Am. Chem. Soc.*, **93**, 3540 (1971).
(6) R. Breslow, S. Baldwin, T. Flechtner, P. Kalicky, S. Liu, and W. Washburn, *J. Am. Chem. Soc.*, **95**, 3251 (1973).
(7) R. L. Wife, D. Prezant, and R. Breslow, *Tetrahedron Lett.*, 517 (1976).

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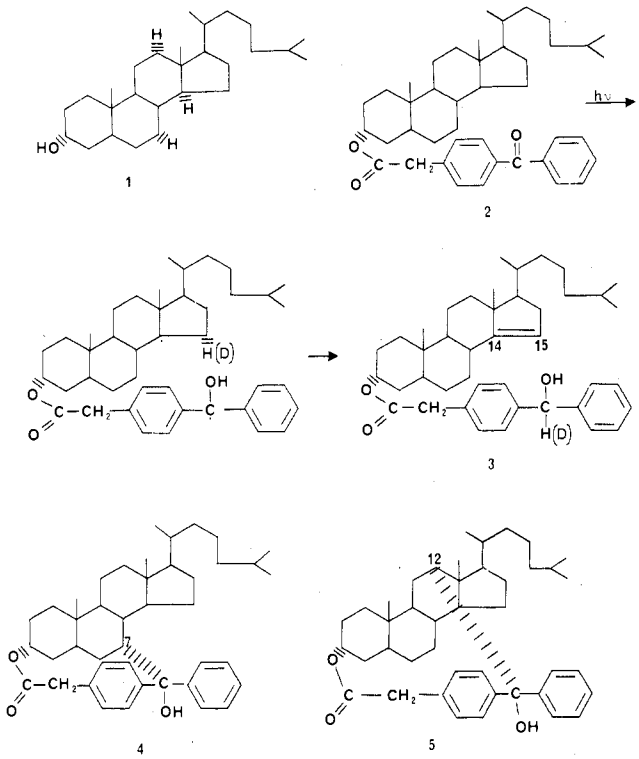
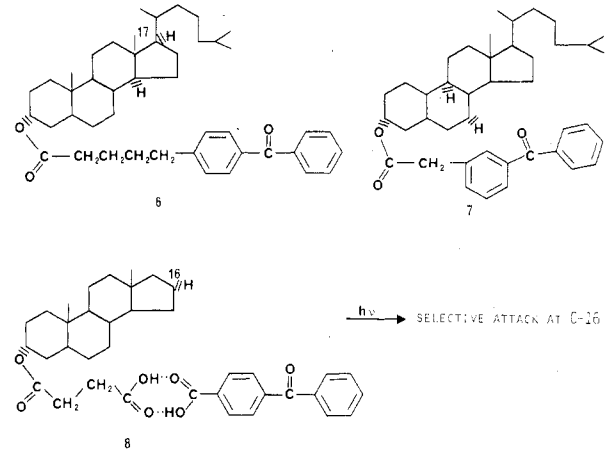
Scheme I
Attack of Photoexcited Benzophenone on Hydrogens at Carbons 7, 14, and 12 of Cholestanol



Molecular models are consistent with this process, which is not only regiospecific in its introduction of the 14,15 double bond but also stereospecific in the hydrogen it removes at C-15. The selectivity is induced by the geometry of the system, specifically the match-up of the C-3 oxygen to C-14 hydrogen distance in the substrate with the carboxyl-to-ketone distance in the attached reagent.

This particular reaction was examined with some care.[7] Some of the benzophenone (16%) is reduced by solvent and does not attack the steroid; of the products, 65% are compound **3** and another 10% also have the 14,15 double bond but differ in the final fate of the benzophenone piece. The remaining 25% consists of **4** (20%) and **5** (5%), two lactones formed by removal of the hydrogens at C-7 and C-12 and coupling of the resulting diradicals. In molecular models it is clear that benzophenone reagent in **2** can swing in an arc under the substrate so that its excited carbonyl oxygen can reach hydrogens on carbons 7, 14, and 12. Attack on carbons 7 and 12 leads to coupling rather than olefin formation, and *both* new asymmetric centers in **4** and **5** are apparently formed stereospecifically. While this reaction is thus quite selective, the freedom of movement in **2** does allow attack on three different carbons to some extent.

Such steroid–benzophenone reactions were examined more generally.[6] With the longer reagent of compound **6**, we saw attack on the even more remote hydrogen at C-17, although the flexibility of the link still permitted some attack at C-14. With a shorter link in **7**, attack occurred closer to the original substrate oxygen and no attack at C-14 was detected. In another study,[8] it was found that the reagent need not be directly attached



to the substrate, since the hydrogen-bonded complex **8** underwent rather selective attack on photolysis. Thus geometric control of selectivity was certainly clear for these systems. However, improvements were definitely needed.

In all of these cases, the residual freedom of motion in the reagent–substrate "complex" led to some randomness of attack. With less rigid substrates this was even more of a problem, as will be discussed later. The other difficulty is that benzophenone photochemistry, with a quantum yield[6] of ca. 0.2, is not attractive for large-scale synthetic work. Thus we decided to try to achieve geometric control of a more useful functionalization reaction.

Directed Chlorination of Steroids

Free-radical chlorination is a highly practical process, commonly run on an enormous industrial scale. Furthermore, chlorine atoms can attack completely unactivated C–H bonds. The trick in achieving selectivity was to learn how to hold the chlorine atom next to a particular hydrogen of the substrate. One attractive way to do this is suggested by the fact that phenyliodine dichloride (**9**) can also be used in chlorinations by a

$$\underset{\mathbf{9}}{\mathrm{PhICl_2}} + \mathrm{R\cdot} \rightarrow \mathrm{RCl} + \mathrm{PhICl}$$

$$\mathrm{PhICl} + \mathrm{RH} \rightarrow \mathrm{PhI} + \mathrm{HCl} + \mathrm{R\cdot}$$

free-radical chain mechanism.[9] Since the species PhICl· which removes the hydrogen atom has significant structure, one could imagine binding it to the substrate so as to achieve geometric control.

There is another feature of this scheme which was attractive. Even with a rigid steroid substrate, the attachment of the benzophenone reagent at only one point allowed it to swing over an arc, attacking several different hydrogens. However, it was known[9] that PhICl is quite selective for attack on tertiary C–H bonds rather than on CH_2's or CH_3's. In general, there is only a single tertiary C–H along any arc generated by pivoting around the C-3 α oxygen. Furthermore, several important practical goals in steroid chemistry could be achieved if such tertiary hydrogens were selectively attacked. Thus in a temporary compromise, some chemical selectivity was allowed to intrude in a program based on geometric control.[10]

(8) R. Breslow and P. C. Scholl, *J. Am. Chem. Soc.*, **93**, 2331 (1971).

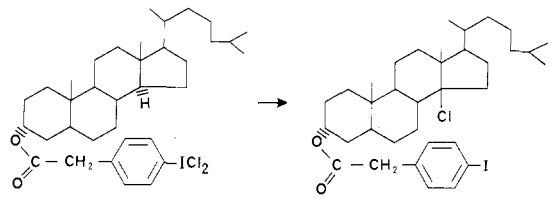
(9) G. A. Russell and C. DeBoer, *J. Am. Chem. Soc.*, **85**, 3136 (1963); D. D. Tanner and P. B. van Bostelen, *J. Org. Chem.*, **32**, 1517 (1967).

3α-Cholestanol (**1**) was converted[14] to the ester **10** with *m*-iodobenzoic acid, and with Cl_2 in the dark this gave the attached iododichloride **11**. A free-radical chain reaction was then initiated, either with light (quantum yield ca. 20) or with other free-radical initiating methods. As shown (Scheme II), the product of this reaction (**14**) was exclusively chlorinated at C-9 of the steroid. Base hydrolysis removed the *m*-iodobenzoic acid and produced the 9,11-unsaturated steroid **15** in excellent yield as the only detectable product.

This was the result expected from an examination of molecular models or from a calculation of distances.[13] The hydrogen at C-9 is 4.4 Å from the C-3 oxygen, while in the reaction intermediate **12** we calculate that the distance from that same oxygen to the chlorine atom is 4.3 Å. Thus the attached chlorine atom of **12** can be directly under the C-9 hydrogen, so as to attack it. It could also reach the hydrogen at C-7, from models, but this hydrogen is less reactive and is not detectably attacked. After hydrogen abstraction, the intermediate radical **13** must then collide with a second molecule of substrate **11** to complete the chlorination and regenerate intermediate **12**.

A unimolecular reaction of **12** produces the selectivity, so at high concentration there might have been competing bimolecular attacks by **12** on another molecule of **11**, with loss of selectivity. By contrast, the radical **13** must undergo a bimolecular reaction to pick up the chlorine atom. Thus the conditions needed for the two processes could have been incompatible, but they were not. At attractive preparative concentrations (0.01–0.1 M) the selectivity is complete, while the chlorine transfers are fast enough to produce a radical chain reaction with ca. 20 cycles before termination.

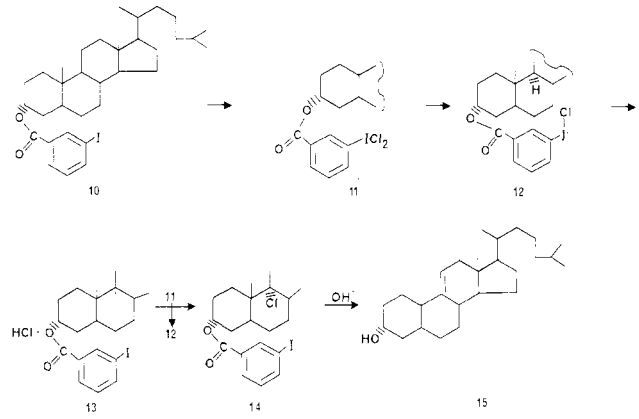
If the reaction is indeed geometrically controlled, we should be able to change the selectivity with a different iodoaryl reagent. This proved to be true. For example, with **16** we obtained[12,13] a 14-chlorosteroid (**17**) because



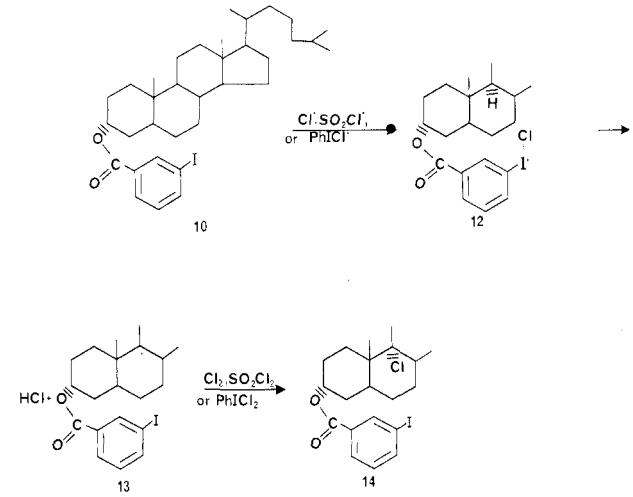
16 17

this longer reagent now attacks further from the attachment point. The calculated distance from the C-3 oxygen to the attached chlorine atom in the reaction of **16** is 6.8 Å, while the C-3 oxygen to C-14 hydrogen distance is 6.5 Å. As expected from this or from models, no attack is seen on the C-9 hydrogen (4.4-Å distance) or on the C-17 tertiary hydrogen (8.5 Å from the oxygen). Note that in **17** the new chlorine is delivered with

Scheme II
Selective Chlorination at C-9 of Cholestanol



Scheme III
Radical-Relay Chlorination Directed by a Template



stereochemistry opposite that of the hydrogen replaced. It does not come from the attached reagent but from a second molecule of **16** (cf. Scheme II) whose approach is not under special geometric control.

Radical-Relay Chlorination under Template Control

For a number of practical goals this process was not completely satisfactory. The conversion of **10** to **11** with Cl_2 caused a problem in other molecules with sensitive functional groups and seemed an unnecessary extra step. It occurred to us that it might instead be possible to generate the key intermediate **12** directly from **10**, bypassing **11** entirely. We envisioned a process in which a chlorine atom (Cl·) or a chlorine-atom donor such as PhICl· approaches **10** and transfers the chlorine to **10** so as to generate **12**. The chlorine would then be relayed to the correct hydrogen atom of substrate, and the iodobenzoate group of **10** would have acted as a template, not a reagent, in directing the attack of an external reagent. Thus we called such a process a radical-relay mechanism.[13,15]

This indeed proved to be a preferable process. We were able to carry out the sequence of Scheme III using chlorinating agents such as $PhICl_2$, SO_2Cl_2, or even Cl_2 under free-radical conditions. In all cases, the attacking radical preferentially put a chlorine atom on the iodine

(10) The selective attack of PhICl· on tertiary C–H's results from the deactivation of a chlorine atom by binding to the iodine atom. Chlorines can also be made selective by complexing[11] to aromatic solvents such as benzene. We[12,13] and others have shown that such complexed chlorine atoms can sometimes have useful chemical selectivity in steroid functionalizations even in the absence of geometric control.

(11) G. A. Russell, *J. Am. Chem. Soc.*, 80, 4987 (1958).

(12) R. Breslow, R. Corcoran, J. A. Dale, S. Liu, and P. Kalicky, *J. Am. Chem. Soc.*, 96, 1973 (1974).

(13) R. Breslow, R. J. Corcoran, B. B. Snider, R. J. Doll, P. L. Khanna, and R. Kaleya, *J. Am. Chem. Soc.*, 99, 905 (1977).

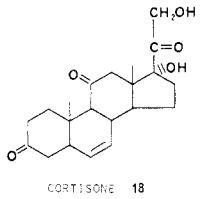
(14) A. K. Bose, B. Lal, W. A. Hoffman, and M. S. Manhas, *Tetrahedron Lett.*, 1619 (1973), describe an inversion–esterification procedure which can be applied to 3β-cholestanol.

(15) R. Breslow, R. J. Corcoran, and B. B. Snider, *J. Am. Chem. Soc.*, 96, 6791 (1974).

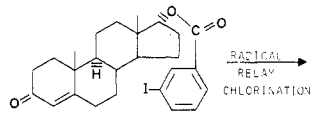
of **10** to generate **12**, rather than directly attack a substrate hydrogen. Thus even such indiscriminate species as Cl· or ·SO_2Cl were tamed and geometrically directed by the template.

Although such a template-directed radical-relay reaction was not known previously, there was reason to suspect that it could take place. Russell had shown[11] that chlorine atoms form complexes with aromatic solvents and that with iodobenzene as solvent the chlorine atom complex was probably with the iodine and not the aromatic ring. In our case, the critical point was that such a complex forms faster than substrate hydrogens are attacked, so an otherwise indiscriminate and useless random halogenation is tamed and directed by the radical-relay mechanism. In most of our subsequent work, we have used this mechanism rather than convert the aryl iodide template to a dichloride first. The radical relay is simpler, and it also lets us use a moderate excess of halogenating agent so as to drive the reactions to completion.

The 9,11 olefins produced by selective halogenation and then dehydrochlorination are of great interest in the synthesis of corticosteroids. We have described[13,16] a synthesis of cortisone (**18**) which uses our process, and



CORTISONE 18



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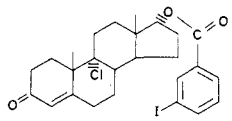
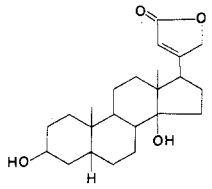
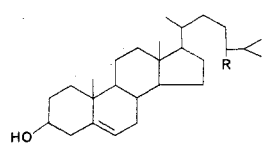


another version is even more attractive with respect to available intermediates. We find[13] that precisely the same *m*-iodobenzoate template which halogenates at C-9 when attached to C-3 also halogenates at C-9 when attached to C-17, as in **19**. The coincidence of geometry is not surprising since in both cases the template has to reach across a six-membered ring and one extra bond. More remarkable is the ability of the radical-relay process to dominate this molecule, so that the functional groups in ring A of the steroid are ignored and an excellent yield of selective attack at unactivated C-9 is obtained.

Selective halogenation at C-14 also occurs[13] under radical-relay conditions with the simple aryl iodide precursor of **16**, forming **17**. Such 14-halosteroids are of interest in the synthesis of cardenolides such as **20**.



DIGITOXIGENIN (20)



21 R=H
22 R=Et

The other practical goal for selective steroid functionalization is the removal of the hydrocarbon side chain in cholesterol (**21**) or highly available sitosterol (**22**) so as to produce useful intermediates in the synthesis of steroid hormones, corticosteroids, etc. This is currently carried out by selective biochemical oxidation, just the sort of process that biomimetic chemistry was designed to mimic. Thus we have designed a radical-relay process to achieve this goal also.[13,17]

As a template we require a rather long molecule if we are to anchor the template at C-3, where functionality is available. The distance from the C-3 oxygen to the hydrogen at C-17, where the side chain is attached, is 8.5 Å. We were able to carry out the radical-relay halogenation at C-17 with the template of **23**, in which

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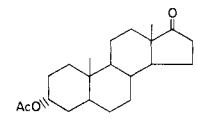

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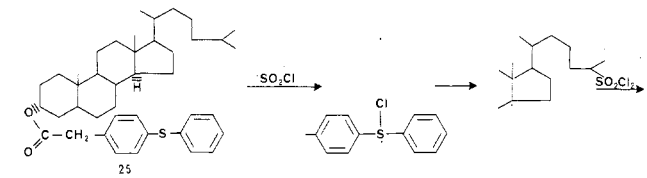
the oxygen-to-chlorine distance in the intermediate radical is 8.7 Å. This process was quite selective, showing no evidence of halogenation at other positions, and proceeded in good yield in either the cholesterol or sitosterol series. A short sequence of further chemical steps, not of the biomimetic variety, completed the side-chain removal to produce androsterone acetate (**24**).

In his studies on the complexing of chlorine atoms by organic solvents, Russell[11] had obtained evidence that both iodobenzene and diphenyl sulfide behaved in an unusual fashion. Thus he suggested that in these cases the Cl· is bound directly to the heteroatom, although with other substituted benzenes it is complexed to the aromatic ring. We have already discussed the application of this idea to directed halogenation using an iodoaryl template; we found[18] that it also works with diphenyl sulfide. Thus compound **25** was halogenated



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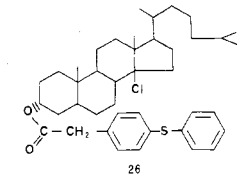

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with SO_2Cl_2 under free-radical conditions, and it spe-

(16) R. Breslow, B. B. Snider, and R. J. Corcoran, *J. Am. Chem. Soc.*, **96**, 6792 (1974).

(17) B. B. Snider, R. J. Corcoran, and R. Breslow, *J. Am. Chem. Soc.*, **97**, 6580 (1975).

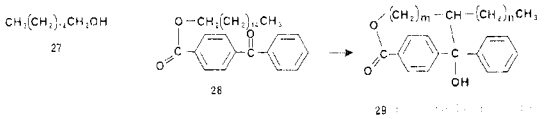
(18) R. Breslow, R. L. Wife, and D. Prezant, *Tetrahedron Lett.*, 1925 (1976).

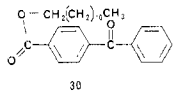
cifically formed the 14-chloro derivative **26**. This particular specificity is expected for the $Ar_2SCl\cdot$ intermediate, by analogy with the corresponding iodo case (**16**) of similar geometry.

Another feature of these template-directed halogenations should be mentioned. In the absence of the template, the reactions are unselective, but they also go less readily. That is, under the actual concentration conditions used for the halogenation of **25**, for instance, a simple cholestanol acetate ester without a template is recovered essentially unchanged (although at high concentrations it can give unselective halogenation). This means that the template *catalyzes* the substrate halogenation preferentially in competition with other processes such as attack on solvent. We have also observed such catalysis with the iodoaryl template; it must reflect an increased rate because of the higher local concentration of the bound chlorine atom. These reactions show both catalysis and specificity and are indeed biomimetic.

Directed Functionalizations of Flexible Substrates in Solution, in Micelles, and in Membranes

Useful as the selective reactions proved to be in steroid chemistry, they represented a simplified challenge. Steroids have rigid well-defined geometry. Thus the fixing of a single parameter, distance from a substance oxygen, defined selectivity fairly well. By contrast, most molecules are floppy. Selective reaction on hexadecanol (**27**), for instance, has the extra challenge

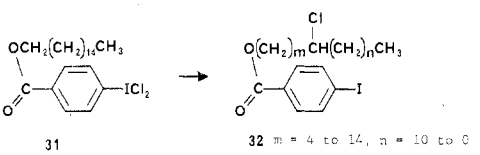




that the hexadecyl chain is extensively coiled. As a result, in CCl_4 solution the benzophenone ester **28** on photolysis gives a series of products (**29**) from attack on various hydrogens of the hexadecyl chain.[3,19]

We devised an analytical method[19] to characterize the distribution of attack sites in **29** and found that there was significant insertion into carbons 10–15. The geometry of the excited state of **28** is such that the benzophenone cannot attack closer to the attachment end than C-10, and the C-16 CH_3 group is unreactive compared with a CH_2 group. For these reasons, on photolysis the dodecyl ester **30** undergoes significant attack on only two carbons, C-10 and C-11. However, in general, there is no useful selectivity for long flexible substrates. For instance, the eicosanol (20 carbons) ester corresponding to **29** or **30** undergoes almost random attack[19] over half its carbons, from C-10 to C-19. The chief product of such a reaction is information about the conformations of flexible chains under various conditions.

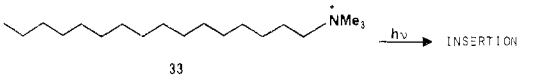
Remote chlorination was also examined,[19] using an attached iodochloride as in compound **31**. Chlorination

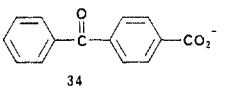


of CH_2's occurs because no tertiary CH's are present, but again a wide distribution of attack sites is seen. Because the conformational requirements of the halogenation reaction differ from those for benzophenone photochemistry, the chlorine in **32** is actually more widely distributed than were the attack sites in **29**. Significant chlorination occurs over carbons 5 to 15.

We have followed two possible approaches to introducing further selectivity into such reactions. In one study, we have examined other phases in which the chains are more ordered than they are in homogeneous solutions. The other approach is to introduce additional interactions between the reagent and the substrate so as to bind the latter into a defined shape.

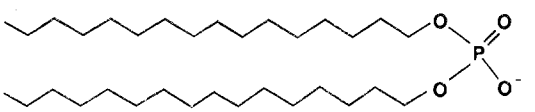
Some ordering of flexible chains could be expected in micelles. For example, cetyltrimethylammonium bromide (**33**) (CTAB) and other detergents form





structures in water which are not true solutions but contain semiordered globular clusters. In these structures, the chains tend to be oriented so that the polar head group is at the surface and at least some of the chains are extended. However, it is impossible to fill a spherical volume with only straight chains extended perpendicular to the surface, so many of the chains must be disordered. We incorporated probes such as benzophenonecarboxylate ion **34** and related compounds into such micelles, but photolysis led to a distribution of attack sites.[20] Interesting structural information about micelles was obtained, but not chemical selectivity.

Biological membranes are composed of bilayers in which most of the chains are in an extended conformation. Thus we prepared and examined[21] a simple homogeneous bilayer from didodecyl phosphate (**35**).



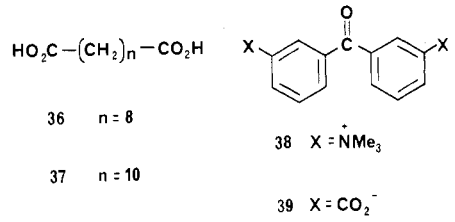
This bilayer can be made as a multilamellar system of flat sheets or (by ultrasonic irradiation) as a spherical vesicle. We examined both of these types of membranes with **34** and similar probes. Very interesting structural information was obtained about the amount of order in bilayers, but again the reaction was not particularly selective. Thus micelles and bilayers have so far not solved the problem of conformational disorder in flexible chains.

(19) R. Breslow, J. Rothbard, F. Herman, and M. L. Rodriguez, *J. Am. Chem. Soc.*, **100**, 1213 (1978).

(20) R. Breslow, S. Kitabatake, and J. Rothbard, *J. Am. Chem. Soc.*, **100**, 8156 (1978).

(21) M. F. Czarniecki and R. Breslow, *J. Am. Chem. Soc.*, **101**, 3675 (1979).

In these studies, the reagent was not attached to the substrate but simply aligned by ion pairing or similar forces. We had earlier shown[8] that selectivity could be achieved in steroid photochemistry with the simple hydrogen-bonded association in **8**. Thus we have examined[22] the possibility that a flexible chain can be held in a fixed geometry by association of *both* ends of the chain with a rigid reagent. The substrates examined are long chain diacids such as **36** and **37**, while the



36 n = 8

37 n = 10

38 X = $\overset{+}{N}Me_3$

39 X = CO_2^-

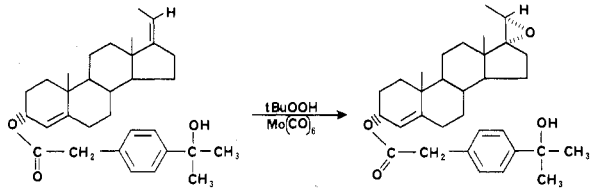
reagents are benzophenone derivatives such as **38** and **39**. Photolysis leads to insertion of the benzophenone into the substrate, with good selectivity in appropriate cases.

For example, in water solution the salt of **36** with **38**, which can have two ionic associations, gives 93% attack on the two equivalent central carbons. With **37** the fit is looser, and reaction is less selective. Furthermore, in CH_2Cl_2 solution the double complex of **36** with **39** undergoes 80% attack on the two central carbons. Again **37** shows less selective reaction. Only time will tell whether this double-interaction approach indeed solves the problem of useful selectivity with flexible substrates and whether it can be applied in cases of synthetic interest.

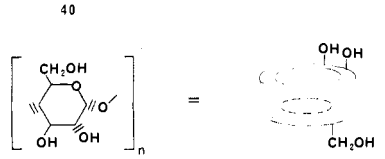
Template-Directed Epoxidations

Olefins are converted to epoxides by alkyl peroxides with catalytic metal compounds of molybdenum, tungsten, etc. When the substrate olefin is an allylic alcohol, the metal forms a complex with the hydroxyl group and directs the regiochemistry and stereochemistry of the epoxidation reaction.[23] We reasoned that we might be able to achieve regioselective and stereoselective epoxidations of other olefins if we attached a template of appropriate length, with a hydroxyl group to bind the metal catalyst. This proved to be the case.

Treatment of **40** with *tert*-butyl hydroperoxide and



40 **41**

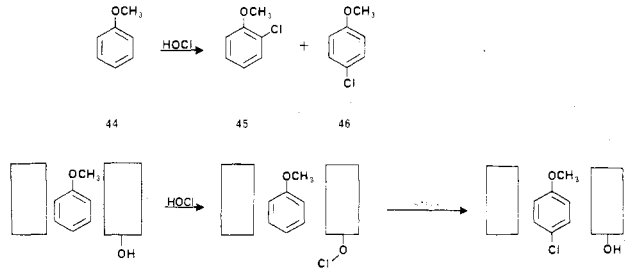


42 n = 6

43 n = 7

$Mo(CO)_6$ led to clean stereospecific epoxidation[24] to form **41**. The other double bond was ignored, and with a template of different geometry (the meta isomer of the template in **40**) there was no epoxidation of either double bond under our reactions conditions. Thus again the reaction is both catalyzed and directed by a template of the precise geometry needed. This reaction has also been applied[25] to flexible polyenes, the terpenes farnesol and geranylgeraniol. Here once again the flexibility resulted in interesting conformational information but lack of useful selectivity.

Scheme IV
Ionic Relay Chlorination in a Cyclodextrin Complex



44 **45** **46**

Selective Reactions in Cyclodextrin Complexes

The cyclodextrins[26] are doughnut-shaped molecules composed of glucose units; the commonly available species are α-cyclodextrin (**42**) (cyclohexaamylose) and β-cyclodextrin (**43**) (cycloheptaamylose). Great interest surrounds the fact that these cyclic molecules can bind good-sized organic species into the central cavity, in imitation of the binding of hydrophobic groups by enzymes. Thus a substantial chapter in biomimetic chemistry has been based on the reactions of such complexes, and many laboratories are actively working on producing enzyme models based on the cyclodextrins. We will not review this field, but will focus on the work in our laboratory which is aimed at producing regioselective reactions with the aid of cyclodextrins.

The earliest study was directed at increasing the selectivity of aromatic substitution reactions. We knew that an aromatic compound such as anisole (**44**) would bind into the cavity of cyclodextrin in water solution. Our initial simple hope was that in the complex the ortho and meta positions of anisole would be protected against external attack so that we might achieve exclusive para substitution with an appropriate reagent, since in models of such a complex the para position seems less shielded. This turned out to be successful, but for a more interesting reason.

The reaction examined[27,28] was the chlorination of anisole in aqueous solution by hypochlorous acid (HOCl). This was known to produce both *o*-chloroanisole (**45**) and *p*-chloroanisole (**46**) in the absence of cyclodextrin (see Scheme IV), so we hoped to redirect the reaction to the exclusive formation of the para isomer **46** by shielding the ortho positions in the cyclodextrin complex. This is what was observed. The 60/40 ratio of **46** to **45** in the absence of cyclodextrin became instead a 96% para/4% ortho product ratio when 0.01 M α-cyclodextrin (**42**) was present. When β-cyclo-

(22) R. Rajagopalan, unpublished work.
(23) Cf. K. B. Sharpless and R. C. Michaelson, *J. Am. Chem. Soc.*, **95**, 6136 (1973), and subsequent papers.
(24) R. Breslow and L. M. Maresca, *Tetrahedron Lett.*, 623 (1977).
(25) R. Breslow and L. M. Maresca, *Tetrahedron Lett.*, 877 (1978).
(26) For a review, see M. L. Bender and M. Komiyama, "Cyclodextrin Chemistry", Springer-Verlag, New York, 1977.
(27) R. Breslow and P. Campbell, *J. Am. Chem. Soc.*, **91**, 3085 (1969).
(28) R. Breslow and P. Campbell, *Bioorg. Chem.*, 1, 140 (1971).

dextrin was used at the same concentration an 80% para/20% ortho product mixture was formed.

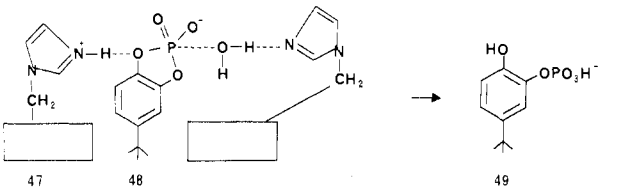
Reactions which involve molecular complexes can have complicated mechanisms which are uncovered only by detailed study. The complex is in equilibrium with the free species, and in our cases the dissociation constant was easily determined. From this determination we were able to show[28] that when α-cyclodextrin was present at 0.01 M concentration the anisole was 72% complexed and 28% uncomplexed, while with 0.01 M β-cyclodextrin it is 59% complexed and 41% free. Both free anisole and complexed anisole have the possibility of being chlorinated by HOCl, and because of this the complexing might have had no effect on the product ratio. If complexing simply slowed down the reaction, then all the product would be derived from the free anisole which is present at equilibrium with unaltered composition. Precisely the opposite was actually observed. That is, although with 0.01 M α-cyclodextrin there was still 28% free anisole, only 10% of the product was derived from its random 60/40 chlorination.

A detailed treatment[28] of the data, using various concentrations of cyclodextrin and HOCl, provided the rate constants for all the possible processes. We found that there was indeed no detectable chlorination of the ortho positions of anisole in either cyclodextrin complex, so the complexing did shield them. However, chlorination of the para position was *catalyzed*, not slowed, by complexing. The extent of the catalysis depends on the concentration of HOCl, since the reactions of the cyclodextrin complexes are first order in HOCl while the reaction of free anisole is second order in HOCl (it forms Cl_2O, the active chlorinater for uncomplexed anisole). Thus at 10^{-3} M HOCl the complex of anisole with α-cyclodextrin reacts 53 times as rapidly at the para position as does uncomplexed anisole, while complexing the β-cyclodextrin increases the reactivity of the anisole para position by 11-fold at this HOCl concentration.

As we discuss in detail elsewhere,[28] the entire picture is most consistent with a catalytic mechanism in the complexes (Scheme IV) in which the HOCl first transfers its chlorine to a hydroxyl group of the cyclodextrin. The resulting cyclodextrin hypochlorite then relays the chlorine to the para position of the bound anisole. The catalysis results from the increased local concentration of the chlorinating species in the complex, and it is somewhat more effective with α-cyclodextrin in which the tighter fit leaves less freedom of motion in the complex. In line with this, an aromatic substitution by diazonium salts, which could not be delivered from a hydroxyl group in this way, is blocked by cyclodextrin complexing of the substrate.[28] Diazonium coupling only occurs to the uncomplexed aromatic substrate which is present at equilibrium.

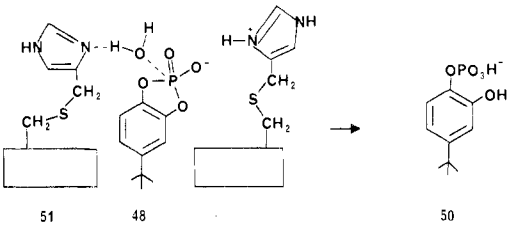
The resemblance of this chlorination mechanism to template-directed radical-relay chlorination of steroids is striking, although this is not a free-radical process. As with radical-relay chlorination, the template binds a chlorine so as to accelerate and direct an otherwise more random process. Further work with specifically methylated cyclodextrins[29] established which particular hydroxyl of the cyclodextrin is involved in this template-directed relay aromatic chlorination. A solid cyclodextrin polymer was also examined.[29] It suppressed the uncatalyzed random chlorination by binding the anisole completely, so as to produce essentially pure *p*-chloroanisole.

Work with cyclodextrin derivatives tends to focus on incorporating typical enzyme catalytic groups so as to achieve high rates. However, interesting specificities are also often observed. For example, we have prepared[30] a cyclodextrin bis(imidazole) (**47**) and examined



it as a bifunctional catalyst for the hydrolysis of the cyclic phosphate **48**. The enzyme ribonuclease also uses two imidazole catalytic groups in a similar way to hydrolyze cyclic phosphates derived from ribonucleic acids. Simple chemical hydrolysis of **48** proceeds randomly, forming an equal mixture of **49** and **50**, but the hydrolysis of **48** catalyzed by our enzyme mimic is selective. The product is largely (>90%) **49**, as expected from the mechanism in which attacking H_2O is delivered by the imidazole.

Cleavage of **48** to form **50** would have required de-



livery of H_2O from further out, beyond reach of the catalytic groups of **47**. However, we have also prepared[31] another ribonuclease mimic **51**, in which the catalytic groups are indeed further from the binding site. Gratifyingly, this now reverses the selectivity and cleaves **48** almost exclusively (98%) to **50**. The change in selectivity for the same substrate produced by a change in catalyst geometry is reminiscent of the effects we saw in steroid functionalizations.

Prospects of the Future

Synthetic chemistry has developed to the point at which greater selectivity is demanded. Synthetic methods are needed which can meet the same high standards of chemical yield and purity of the desired product that we see in biochemical reactions. Thus biomimetic methods should play an ever-increasing role.

Some useful results can still be expected from reactions directed by rigid templates temporarily attached to the substrates at a single point, as in our radical-relay halogenation. However, real progress demands the development of multiply interacting catalyst–substrate systems, so that geometric control can be generally

(29) R. Breslow, H. Kohn, and B. Siegel, *Tetrahedron Lett.*, 1645 (1976).

(30) R. Breslow, J. Doherty, G. Guillot, and C. Lipsey, *J. Am. Chem. Soc.*, **100**, 3227 (1978).

(31) R. Breslow, P. Bovy, and C. L. Hersh, *J. Am. Chem. Soc.*, **102**, 2115 (1980).

effective. If these interactions are not covalent, a single catalyst could pass from substrate to substrate, as in real enzymes or in the cyclodextrin systems. The use of such artificial enzymes would change the style of synthetic chemistry. Synthesis would have moved from the age of clever functional group manipulation to a new era in which our reactions mimic both the style and the selective results of biochemistry.

I acknowledge the experimental and intellectual contributions of my co-workers, who are named in the references. This work has been supported by grants from the National Science Foundation and the National Institutes of Health.

Electrochemistry of Well-Defined Surfaces[1]

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Reflection electron diffraction and electron spectroscopy, combined with the availability of efficient commercial ultrahigh vacuum equipment, have led to dramatic progress in gas–solid surface chemistry by permitting the preparation of atomically clean, highly ordered surfaces and by providing a means of studying the structure, electronic characteristics, and chemical reactivity of these "well-defined" surfaces. In particular, low-energy electron diffraction (LEED) provides data from which surface crystallographic structure can be determined, including the structure of the first few atomic layers of the substrate and any adsorbed material which might be present. Auger electron spectroscopy yields spectral data indicative of the identity and quantity of elements present in the surface region. All elements except H and He are determinable by means of Auger spectroscopy provided that their abundance in the surface region exceeds about 1%.

Photoelectron spectroscopy is of particular usefulness in characterizing surfaces with regard to valency and other aspects of electronic structure. Thermal-desorption mass spectroscopy is a ready source of valuable clues regarding the stability and molecular constitution of adsorbed layers. A growing number of related techniques are also available with which to explore various aspects of surface behavior; these include reflection high-energy electron diffraction, electron-stimulated desorption, with the option of determining the angular distribution of desorbed ions or neutrals, secondary-ion mass spectrometry, and electronic-vibrational analysis of surface layers by electron energy loss spectroscopy (analysis of the excitation-energy dependence of the energy distribution of inelastically reflected low-energy electrons). These techniques are the subject of a number of excellent reviews.[2-12]

Preparation of well-defined surfaces has been overlooked by electrochemists until recently, even in studies employing electrodes made from single crystals. This lapse is significant. Definition of surface structure is as crucial to understanding the specific chemical

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(1) Acknowledgment is made to the donors of the Petroleum Research Fund, administered by the American Chemical Society, and to the National Science Foundation for support of this research.

(2) G. A. Somorjai, "Principles of Surface Chemistry", Prentice Hall, Engelwood Cliffs, N.J., 1972; M. Prutton, "Surface Physics", Clarendon, Oxford, 1975.

(3) Reviews of low-energy electron diffraction: (a) E. Bauer, in "Techniques of Metals Research", Vol. 2, R. F. Bunshah, Ed., Wiley-Interscience, N.Y., 1969, p 559; (b) C. B. Duke, *Adv. Chem. Phys.*, **27**, 1 (1974); (c) P. J. Estrup in L.-H. Lee, Ed., "Characterization of Metal and Polymer Surfaces", Vol. 1, Academic Press, New York, 1977, p 187; (d) T. W. Haas, G. J. Dooley, III, J. T. Grant, A. G. Jackson, and M. P. Hooker, *Prog. Surf. Sci.*, **1**, 155 (1971); (e) Alex Ignatiev, *Am. Lab.*, **5(3)**, 12 (1972); (f) J. J. Lander, *Prog. Solid State Chem.*, **2**, 26 (1965); (g) J. W. May, *Ind. Eng. Chem.*, **57**, 19 (1965); *Adv. Catal.*, **21**, 151 (1970); (h) J. B. Pendry, "Low-Energy Electron Diffraction", Academic Press, London, 1974; (i) E. N. Sickafus and H. P. Bonzel, *Prog. Surf. Membr. Sci.*, **4**, 115 (1971); (j) G. A. Somorjai, *Surf. Sci.*, **34**, 156 (1973); (k) G. A. Somorjai and H. H. Farrell, *Adv. Chem. Phys.*, **20**, 215 (1971); (l) G. A. Somorjai and L. L. Kesmodel, *MTP Int. Rev. Sci.* **7**, 1 (1975); (m) J. A. Strozier, D. W. Jepsen, and F. Jona in "Surface Physics of Materials", J. M. Blakely, Ed., Academic Press, New York, 1975, Chapter 1; (n) M. A. Van Hove, *Surf. Sci.*, **80**, 1 (1979); (o) M. B. Webb and M. G. Legally, *Solid State Phys.*, **28**, 301 (1973).

(4) Reviews of Auger electron spectroscopy: (a) C. C. Chang, *Surf. Sci.*, **25**, 53 (1971); (b) D. T. Hawkins, "Auger Electron Spectroscopy. A Bibliography, 1925–1975", Plenum Press, New York, 1977; (c) G. A. Somorjai and F. J. Szalkowski, *Adv. High Temp. Chem.*, **4**, 137 (1971); (d) N. J. Taylor in "Techniques of Metals Research", Vol. 7, R. F. Bunshah, Ed., Wiley-Interscience, New York, 1971, p 117.

(5) Reviews of photoelectron spectroscopy: (a) A. D. Baker, M. A. Brisk, and D. C. Liotta, *Anal. Chem.*, **50** (5), 328R (1978); (b) B. G. Baker in "Modern Aspects of Electrochemistry", Vol. 10, J. O'M. Bockris and B. E. Conway, Eds., Plenum Press, New York, 1975, p 93; D. Betteridge, "Photoelectron Spectroscopy: Chemical and Analytical Aspects", Pergamon, New York, 1972; (d) T. A. Carlson, "Photoelectron and Auger Spectroscopy", Plenum Press, New York, 1975; (e) W. N. Delgas, T. R. Hughes, and C. S. Fadley, *Catal. Rev.*, **4**, 179 (1970); (f) D. M. Hercules, *Anal. Chem.*, **42** (1), 20A (1970); **44** (5), 106R (1972); **48** (5), 294R (1976); (g) D. M. Hercules and J. C. Carver, *Anal. Chem.*, **46** (5), 133R (1974); (h) H. Ibach, Ed., "Electron Spectroscopy for Surface Analysis", Springer-Verlag, New York, 1977; (i) D. A. Shirley, Ed., "Electron Spectroscopy", North-Holland, Amsterdam, 1972; (j) K. Siegbahn, C. Nordling, and A. Fahlman, "ESCA: Atomic, Molecular and Solid State Structure Studied by Means of Electron Spectroscopy", Amqvist-Wiksell, Uppsala, Sweden, 1967; (k) H. K. Herglotz and H. L. Suchan, *Adv. Colloid Interface Sci.*, **5**, 79 (1975).

(6) Ultrahigh vacuum theory and practice: (a) S. Dushman, "Scientific Foundations of Vacuum Technique", 2nd ed., J. M. Lafferty, Ed., Wiley, New York, 1962; (b) P. A. Redhead, J. P. Hobson, and E. V. Kornelson, "The Physical Basis of Ultrahigh Vacuum", Chapman and Hall, London, 1968; (c) R. W. Roberts and T. A. Vanderslice, "Ultrahigh Vacuum and Its Applications", Prentice-Hall, Englewood Cliffs, NJ, 1963; (d) N. W. Robinson, "The Physical Principles of Ultrahigh Vacuum Systems and Equipment", Chapman and Hall, London, 1968.

(7) A generous sampling of articles dealing with well-defined surfaces will be found in *Surf. Sci.*

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