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Remote Functionalization Reactions as Conformational Probes for Flexible Alkyl Chains

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Abstract: Photolysis of benzophenone carboxylic acid esters of long chain alkanols leads to intramolecular hydrogen atom abstraction and carbon-carbon coupling, resulting in overall insertion of the benzophenone carbonyl into the alkyl chain. An appropriate degradative sequence permits the quantitative determination of the positions functionalized; the distribution of functionalization sites is related to the conformations adopted by the chain in solution. The distribution is affected by the polarity of the solvent, indicating that solvents must be explicitly taken into account in any theory used to account for chain coiling. Another probe of such conformations is the intramolecular halogenation of alkyl chains in a free-radical chain reaction of *p*-dichloroiodobenzoate esters of long-chain alkanols, and of corresponding *m*-dichloroiodo derivatives. A degradative sequence was devised to locate the site of chlorination, in which one of the steps is a novel and unusual copper-assisted displacement by benzoate ion on a thioether under free-radical conditions. The distribution of functionalization sites with these reactions also depends on the nature of the solvent. There is a general relationship between these chlorination reactions and those with the benzophenone probe which can be understood in terms of simple conformational factors.

Much interest has surrounded attempts to understand the conformational preferences of long alkyl chains.[1] Such chains might be thought to prefer a fully extended conformation with no gauche interactions, and indeed in bilayers this seems to be the conformation adopted.[2] However, except in such special phases alkyl chains are extensively coiled. Each gauche interaction introduces an increased enthalpy of ca. 0.5 kcal/mol,[3] but entropy operates to promote coiling. Thus the Boltzmann factor for the fully extended conformation can be set as unity, but the factor for all possible hexadecyl chains containing exactly one gauche interaction is then $30e^{-0.5/RT}$, with a value of 13.04. The inclusion of further gauche interactions introduces additional exponential terms and successively decreasing preexponential terms, but the exponential enthalpy factor does not dominate until the chain is almost completely coiled.

Solvation effects can also influence the relative energies of different conformations, since in the more compact coiled conformations alkyl chains present a smaller surface to the solvent. This means that chain coiling is favored in polar solvents.[4]

Some years ago we reported with Winnick[5] a study of the intramolecular insertion reaction of benzophenone carboxylic esters of octadecanol and similar alkanols. This preliminary study was followed by extensive work using such benzophenone reactions on rigid steroid substrates,[6] in which conformational flexibility is not present. Such studies led to the development of a number of ways to perform remote functionalization reactions on steroids, and the reactions have been applied to perform some very practical specific steroid transformations.[7]

It was obvious even from our preliminary work[5] that selective reaction did not occur in the functionalization of flexible alkanol substrates, since a distribution of attack sites was observed reflecting the flexible conformation of the substrate. However, such distributions are of considerable interest in their own right as a reflection of the conformational preferences of alkyl chains. Winnick has independently pursued this line in some detail,[8] concentrating on theoretical models to interpret the distributions observed and also on triplet lifetime studies as a function of chain length to furnish an independent parameter related to conformation. Several studies on mass spectral intramolecular reactions are also related to the alkyl chain preferred conformations.[9] Since such studies are performed in the gas phase, they do not reflect the solvation effect on conformational preferences. In that sense gas-phase work is more relevant to any theoretical model in which solvation effects are ignored.

In our original report[5] the benzophenone photolysis product was converted to a keto derivative in the alkyl chain by the sequence shown in Scheme I. This was then submitted to Baeyer-Villiger cleavage and the resulting ester was saponified to produce an alkanol which was analyzed by gas-liquid

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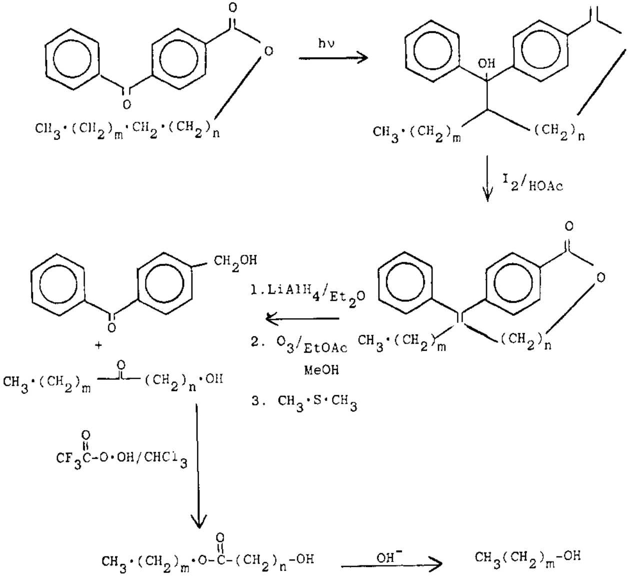
Scheme I



chromatography. Subsequently we found[10] that a much more preferable method was the conversion of the alkanone to a thioketal, followed by mass spectroscopy as shown in Scheme II. Control reactions, described in the Experimental Section, establish that this analytical method correctly reproduces the composition of mixtures of positional isomeric ketones, and is thus reliable. Thus, the data to be presented here are derived from Scheme II, and they differ in significant quantitative detail from those derived earlier in Scheme I.

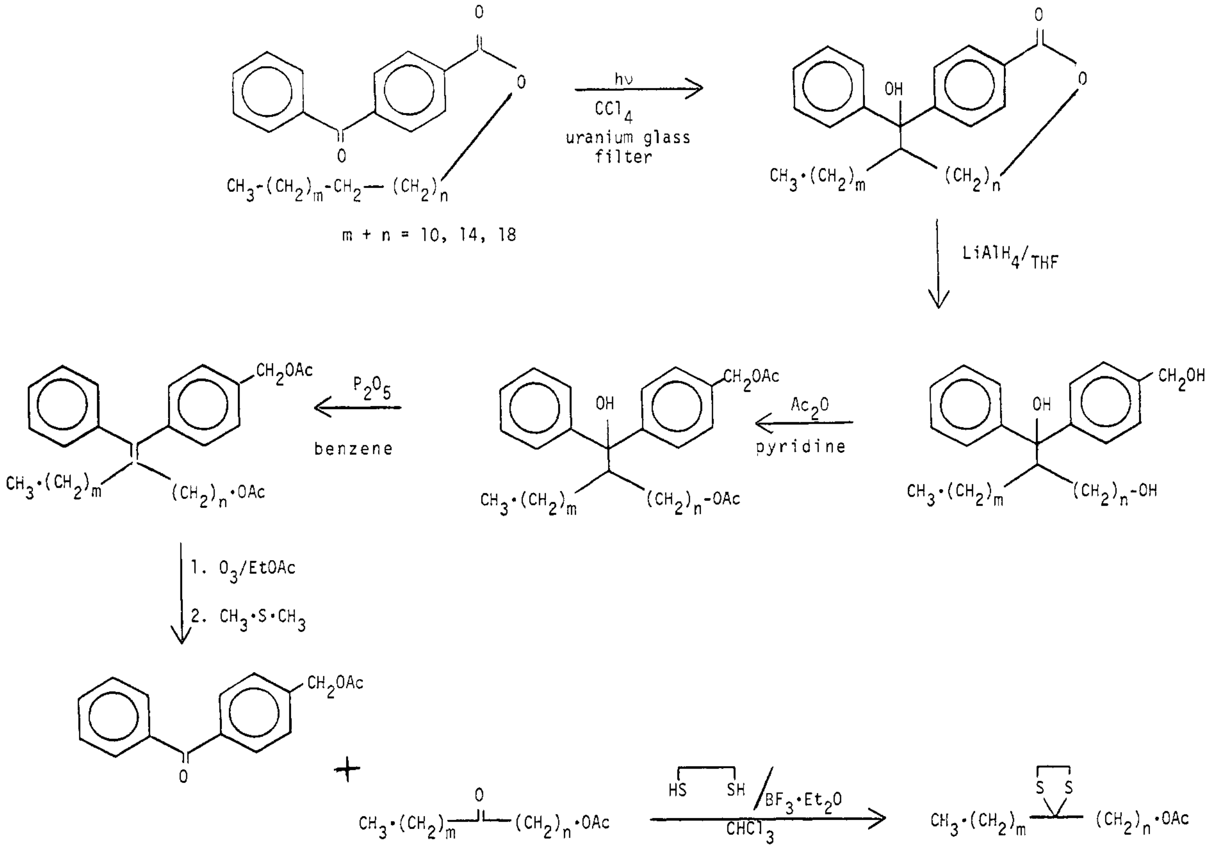
We have reported an intramolecular halogenation reaction in which iodophenyl groups are attached to steroid substrates and used to direct halogenation of specific carbons of the steroid. In the earliest version of this reaction[11] an iodobenzoate ester, for instance, was converted to the aryliodine dichloride derivative with Cl_2 and this was then irradiated to initiate a free-radical chain halogenation sequence. In a later version[12] of our halogenation processes the iodine was instead used to capture a chlorine atom from an external radical, and the aryliodine dichloride intermediate was not prepared. Both processes involve the intermediacy of a chloroaryl iodide radical as the significant hydrogen abstracting species.

Such radicals have a strong preference for removing tertiary hydrogen if it is available,[13] but we have found that with a simple alkyl ester carrying only secondary and primary hydrogens we can still observe intramolecular selective halogenation directed by such iodoaryl templates. The halogenation occurs preferentially on secondary carbons, producing a chloroalkyl ester of the iodoaryl acid.

In order to determine the position of the chlorine atom a sequence had to be devised by which a chloromethine group was converted to a carbonyl group. It was desirable that this process occur in good yield without significant HCl elimination to produce olefins, since such eliminations could be positionally selective and bias the analysis. After a variety of approaches were investigated, the sequence shown in Scheme III was devised. Displacement of the chlorine by thiophenoxide was a clean process, but all attempts to convert this thioether to a ketone by use of the Pummerer reaction led to a significant side reaction as well. Accordingly we attempted to perform a benzoyloxylation of the thioether using *tert*-butyl perbenzoate and cuprous ion. The product from this reaction was not the expected benzoyloxy thioether, but instead simply the benzoate in which the thiophenyl group had been replaced.

The mechanism of the replacement is not obvious. To clarify its stereochemistry we performed the experiments shown in Scheme IV. From these results, a clean inversion of configuration is involved. This seems to exclude processes involving free alkyl radicals, and suggests a simple S_N2 displacement by benzoate ion. However, the conversion of 2-octyl phenyl thioether to the benzoate with cuprous bromide and *tert*-butyl perbenzoate occurs rapidly, while treatment of the thioether

Scheme II



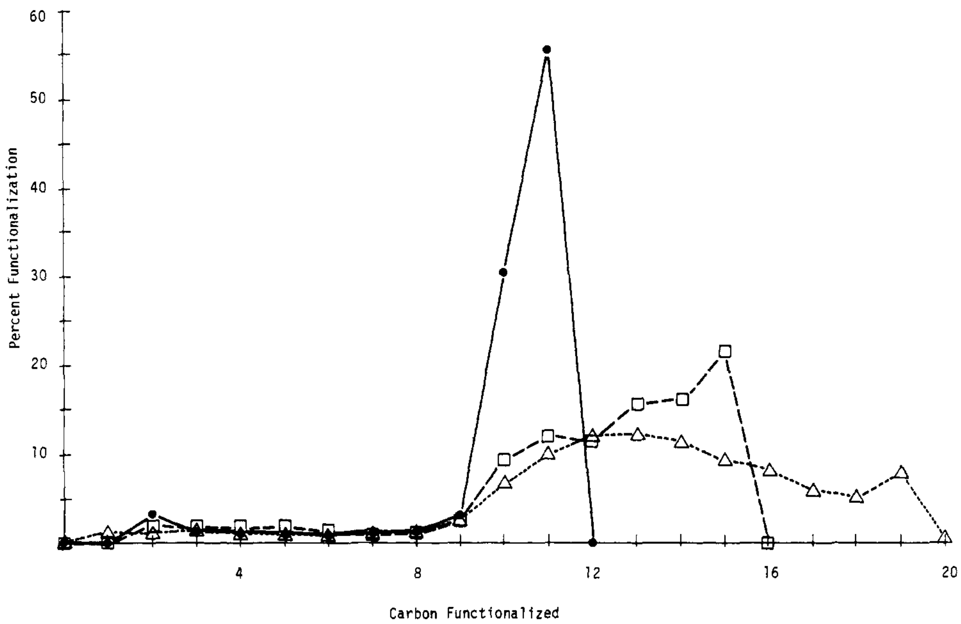
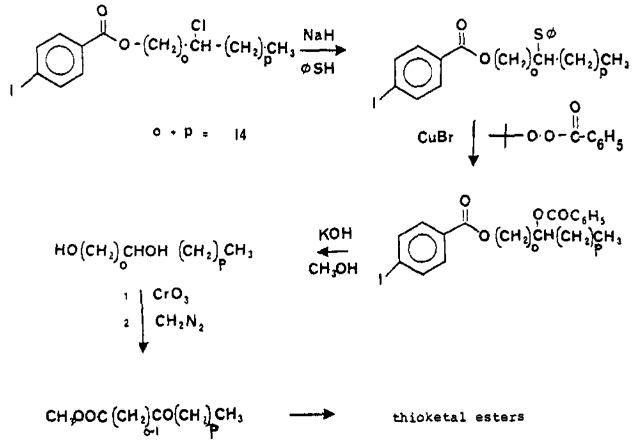
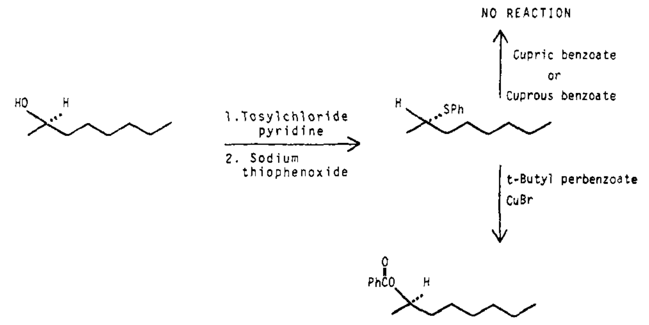


Figure 1. Product distribution from photolysis, in CCl_4 at 0.001 M, of the benzophenone-4-carboxylic acid esters of *n*-dodecanol (●), *n*-hexadecanol (□), and *n*-eicosanol (△).

Scheme III



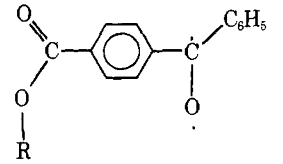
Scheme IV

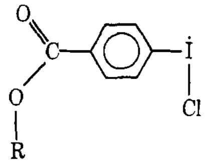


with either cupric benzoate or cuprous benzoate under the same conditions leads to recovered thioether. Our favored interpretation at the current time is that the reaction is indeed an S_N2 displacement by benzoate ion, but that departure of the leaving group is assisted by species such as soluble copper ions or oxidized sulfur formed during the redox reaction.

In any case this double inversion sequence led to the overall replacement of chlorine by benzoate, and saponification and oxidation then converted this to the corresponding ketone. This could again be converted to the thioketal and examined in the mass spectrometer. A similar sequence was performed using the dichloride derived from *m*-iodobenzoic acid esters of the alkanols.

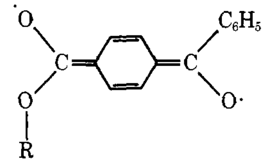
The results of these studies are shown in Figures 1-3. Several striking points emerge. First of all, hydrogen abstraction by the *p*-chloroiodobenzoate ester is initiated at carbon 5 of the alkanol chain, much closer than is hydrogen abstraction by the corresponding *p*-benzophenone carboxylic ester. The difference is surprising since in a formal sense the oxygen of the benzophenone triplet which removes the alkane hydrogen is in almost





the same position as is the chlorine atom on the intermediate iodochloride radical derived from the *p*-iodobenzoate.

Molecular models indicate that in the chloroiodo radical the alkyl chain can be brought across the face of the benzene ring, and under these circumstances if the chlorine atom on the iodine is bonded perpendicular to the benzene plane it can indeed attack a hydrogen at C-5. Of course the attack further out in the chain reflects other conformations, such as those in which coiling shortens the effective length of the chain. By contrast, in benzophenonecarboxylic ester the n-π^* triplet state should fix the ketone carbonyl group in the plane of the benzene ring, and it should also fix the ester group in the plane, since the π^* orbital has significant bonding contributions between the benzene and both carbonyl groups.[14] Molecular models show that with this fixation of atoms the alkyl chain can pass around the edge of the benzene ring and bring C-9 or C-10 into contact with the benzophenone carbonyl oxygen. Other conformations, including those in which the chain is more extensively coiled, will lead to functionalization further out in the chain, but no conformation is available by which functionalization can occur closer to the ester group than C-9. In the *m*-iodobenzoate ester the iodine-ester distance is shorter than in the para isomer, and



planar

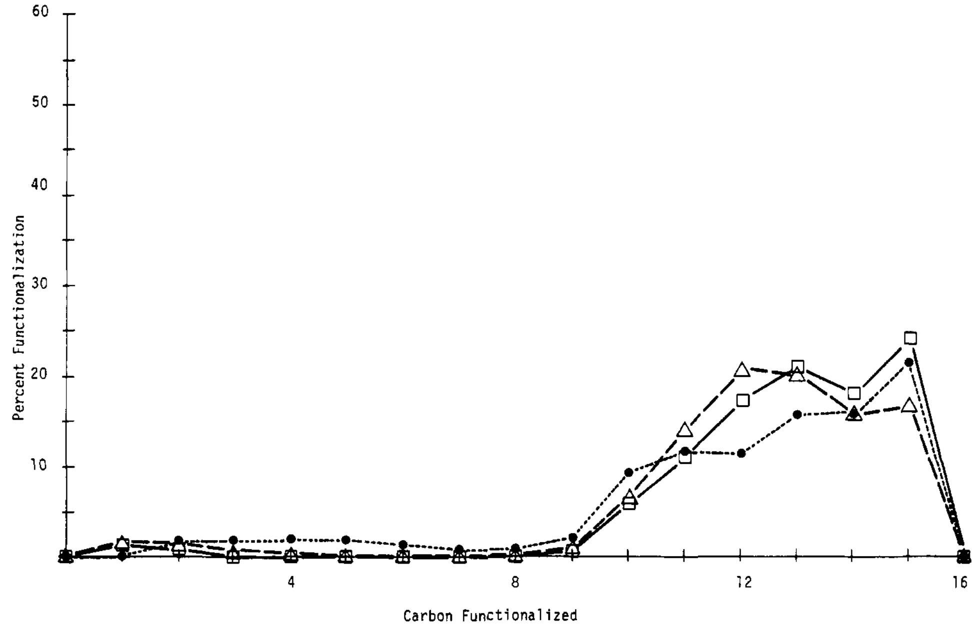


Figure 2. Product distribution from photolysis of 0.001 M solutions of the *n*-hexadecyl ester of benzophenone-4-carboxylic acid in CCl_4 (●) and in acetic acid (□) and of the *n*-hexadecyl ester of *p*-(4-cyclohexylbenzoyl)benzoic acid in acetic acid (△).

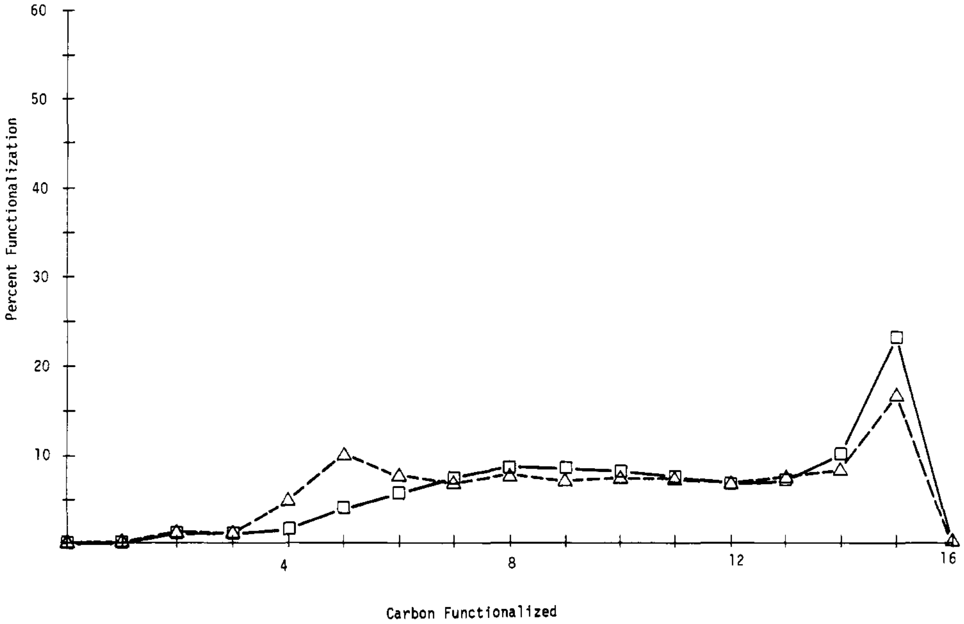


Figure 3. Product distribution from the intramolecular chlorination of *n*-hexadecyl *p*-dichloroiodobenzoate (□) and *m*-dichloroiodobenzoate (△) at 0.001 M in CCl_4.

as expected functionalization of the chain occurs one atom closer to the ester group as a result.

The second general observation is that there is strong preference for attack at the penultimate carbon in all of these reactions, and with relatively short chains this can lead to a rather selective functionalization (Figure 1). Examination of molecular models suggests that the functionalization of the penultimate carbon is related to steric effects. A number of conformations which result in attack at the penultimate carbon would not be permitted if the chain were longer, since the extended chain would then bump into other atoms of the molecule. It should be noted that the preference for penultimate functionalization is seen both with a benzophenone probe, in which there is an additional phenyl ring past the functionalizing system, and with the aryliodine dichloride probe, in which there is no such group beyond the functionalizing halogen atom.

An interesting is effect is seen in Figure 2. The increased chain coiling observed in acetic acid is diminished somewhat when an additional cyclohexane ring is attached to the benzophenone probe. This suggests that the chain is now partially packed onto the additional cyclohexane hydrocarbon residue.

We have examined models of a few simple conformations of hexadecyl benzophenonecarboxylate in order to interpret the distribution of functionalization sites shown in Figure 1. With the chain in the fully extended conformation, no carbon is accessible to the benzophenone carbonyl, and this is also true when one, two, or three gauche interactions are introduced into the chain, regardless of its position. Only when four gauche interactions are present in the chain do molecular models suggest that attack can occur on carbons 10, 11, 12, 13, 14, and 15. It is obvious that in order to mimic the observed distribution of functionalization sites an extensively coiled chain must be invoked, and the random walk calculation of Winnick or a similar method would have to be used. However, in view of the solvent effects seen in Figure 2, it is apparent that any method which does not take account of such solvation effects cannot fully reproduce these data.

One measure of such solvent effects is the ratio of attack at C-15 (requiring a coiled chain) to attack at C-10 (expected for an essentially extended chain). This ratio for the benzophenonecarboxylic ester of *n*-hexadecanol goes from 2.27 in CCl_4 to 4.07 in acetic acid solvent, from the data in Figure 2. The probe with an extra cyclohexyl group to bind the extended chain (Figure 2) has a C-15/C-10 ratio of only 1.19 in acetic acid.

Solvent effects can in principle be included in a statistical calculation of conformations by adjustment of the excluded volume terms.[4] The data in Figures 1–3 thus represent a significant challenge to theorists interested in conformations of flexible chains.

Experimental Section

Preparation of the Esters. Purest grade commercial 1-dodecanol, 1-hexadecanol, and 1-eicosanol were recrystallized from ethanol. Mass spectral analysis indicated no detectable contamination by higher homologues. Esterification with acid chlorides in pyridine in the standard fashion afforded the following esters. ***n*-Eicosanyl *p*-benzoylbenzoate,**[15] mp 64.8–65.1 °C, *m/e* 506. Anal. Calcd for $C_{34}H_{50}O_3$: C, 80.61; H, 9.89. Found: C, 80.30; H, 10.16. ***n*-Hexadecyl *p*-benzoylbenzoate,**[15] mp 52–53 °C, *m/e* 450. Anal. Calcd for $C_{30}H_{42}C_3$: C, 79.96; H, 9.39. Found: C, 80.01; H, 9.40. ***n*-Dodecyl *p*-benzoylbenzoate,**[15] mp 34.2–35.6 °C, *m/e* 394. Anal. Calcd for $C_{26}H_{34}O_3$: C, 79.15; H, 8.69. Found: C, 79.36; H, 8.62. ***n*-Dodecyl *p*-iodobenzoate,**[16] mp 33.5–35 °C. ***n*-Hexadecyl *p*-iodobenzoate,**[16] mp 52–53 °C. ***n*-Hexadecyl *m*-iodobenzoate,**[16] mp 44.5–45 °C.

***p*-(4-Cyclohexylbenzoyl)benzoic acid,** mp 221 °C, *m/e* 308, was prepared by Friedel–Crafts acylation of cyclohexylbenzene with *p*-carbomethoxybenzoyl chloride, then saponification. This was converted to the corresponding acid chloride, then to ***n*-hexadecyl *p*-(4-cyclohexylbenzoyl)benzoate,** mp 59.8–61.8 °C, *m/e* 532.

Photolysis of the Benzophenone Esters and Product Identification. The following procedure is typical. A 1.00 mM solution of 2.54 g of ***n*-eicosanyl *p*-benzoylbenzoate** in 5 L of purified CCl_4 was degassed (N_2) and photolyzed with a 450-W medium-pressure UV lamp through a uranium glass filter in a quartz immersion well for 24 h, whereupon the starting material had disappeared (TLC, UV, IR). The solvent was evaporated, and the residue taken up in tetrahydrofuran and reduced with 0.7 g of $LiAlH_4$ for 12 h at room temperature. Workup with 5% HCl afforded 2.30 g of the oily product triols which were treated for 12 h at room temperature with 1.5 mL of acetic anhydride in 50 mL of pyridine. The resulting 2.49 g of diacetate product was treated for 8 h at room temperature with 5.0 g of P_2O_5 in 50 mL of benzene. Standard workup afforded 2.22 g of the olefin diacetate mixture, which was ozonized for 20 min at 0 °C in 50 mL of ethyl acetate, followed by addition of 1 mL of dimethyl sulfide. The crude product, 2.96 g, showed IR bands at 1735 (acetate), 1710 (aliphatic ketone), and 1665 cm^{-1} (benzophenone).

This product was taken up in 50 mL of $CHCl_3$, and treated with 1 mL of ethanedithiol and 1 mL of $BF_3 \cdot Et_2O$. Workup and careful chromatography on silica gel afforded 0.18 g of the thioketals of the mixed keto-hexadecyl acetates. This was then submitted to electron impact (15–19 eV) mass spectral analysis on a Finnigan Model 3300 spectrometer. Spectra were recorded every second until the sample was completely volatilized, and the percent functionalization at a given carbon was determined by summing the total integrated ion intensity for the two thioketal cation fragments resulting from cleavage on one or the other side of that carbon, and dividing by the total for all the thioketal fragments.

Intramolecular Halogenation and Product Identification. The iodo esters in pentane were treated with Cl_2 for 30 min at 0 °C. The resulting aryliodine dichlorides precipitated, and were collected by filtration. In a typical reaction, 0.815 g (1.5 mmol) of *n*-hexadecyl *m*-dichloroiodobenzoate dissolved in 1500 mL of CCl_4 was deoxygenated (N_2) and irradiated for 1 h with a 275-W sunlamp. After solvent removal the product was treated with 4 mmol of sodium thiophenoxide in 10 mL of DMF for 63 h at 60 °C, affording the thiophenyl ether mixture. This was refluxed with 2.9 g (15 mmol) of *tert*-butyl perbenzoate and 56 mg of Cu_2Br_2 in 40 mL of benzene (argon) for 41 h, affording the benzoate. Saponification afforded the dihydroxyhexadecane mixture, converted to the ketohexadecanoic acid mixture with CrO_3 and H_2SO_4, in aqueous acetone. Thioketalization with ethanedithiol and *p*-toluenesulfonic acid in benzene, followed by diazomethane reaction, afforded 0.056 g of the mixed thioketals of ketohexadecanoate methyl esters, isolated by careful chromatography on silica gel. These were analyzed by mass spectral fragmentation, as described above.

Controls. 6-Oxopentadecanoic acid methyl ester was synthesized by reaction of di-*n*-nonylcadmium with the acid chloride derived from monomethyl adipate, and converted with ethanedithiol to the thioketal, *m/e* 346 (parent), 219, 231 (ketal cation fragments). Similarly the **14-oxopentadecanoic acid methyl ester** was prepared from dimethylcadmium and the monoester monochloride of 1,12-dodecanedicarboxylic acid. Its ketal with ethanedithiol had *m/e* 346 (parent) and 331 and 119 (ketal cation fragments). In an analytical control experiment mixtures of these two isomers were submitted to mass spectral analysis. A 25.0% C-14, 75.0% C-6 mixture gave 27.1 and 72.9%, while an 18.2% C-14, 81.8% C-6 mixture gave 17.8 and 82.2%.

2-Methyloctanoic acid was prepared by carboxylating 2-bromooctane, and reacted as its ethyl ester with an excess of phenylmagnesium bromide. The resulting product, (2-octyl)diphenylcarbinol, is the nominal product of benzophenone photoinsertion into C-2 of octane. It was submitted to our standard degradation to afford pure 2-octanone in 68% overall yield.

n-Hexadecyl *p*-dichloriodobenzoate and hexadecane, both at 10^{-3} M, were photolyzed and the ratio of chlorohexadecane to hexadecane was determined by GLC on 10% SE-30 at 150 °C. In CH_2Cl_2 solvent 1.7% of hexadecane was chlorinated along with 77% of the ester; in CCl_4 the ratio of intermolecular to intramolecular chlorination was 5.6/94, while in CH_3CN the ratio was 6.7/85. In benzene the ratio was high, 24.5/89, suggesting that the iodoaryl chloride radical transfers chlorine to a benzene solvent.

Reaction of *tert*-Butyl Perbenzoate with Optically Active 2-Octyl Phenyl Sulfide. *l*-2-Octanol was converted to the tolylate, and this with NaH and thiophenol in DMF afforded 2-octyl phenyl sulfide, $[\alpha_D^{CHCl_3}]$ +2.79°. With *tert*-butyl perbenzoate (4.75 g) and cuprous bromide (0.0635 g) in 75 mL of benzene the thioether (1.4193 g) was heated at reflux for 24 h. Workup afforded 2-octyl benzoate (0.778 g, 48% yield) with $[\alpha_D^{CHCl_3}]$ −30.3°. Authentic benzoate prepared from *l*-2-octanol and benzoyl chloride has $[\alpha_D^{CHCl_3}]$ −32.5°. The overall retention of configuration indicates that benzoate formation from the thioether goes with inversion.

Thin layer chromatography showed that the above reaction was essentially complete after 8 h. By contrast, 1.803 g of 2-octyl phenyl sulfide in 75 mL of benzene was heated at reflux with 5.00 g of cupric benzoate for 15 h. No 2-octyl benzoate could be detected, and 91% of the thioether was recovered. A similar result was observed with 0.503 g of thioether and 0.896 g of cuprous benzoate in 50 mL of benzene.

Acknowledgment. Support of this work by the National Institutes of Health is gratefully acknowledged.

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Structural Effects in Solvolytic Reactions. 24. Solvolysis of 1-Cycloalkyl-1-aryl-1-ethyl *p*-Nitrobenzoates. Effect of α-Cycloalkyl Groups in Stabilizing an Electron-Deficient Center as Revealed by the Tool of Increasing Electron Demand

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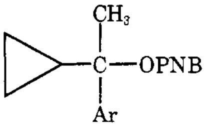
Abstract: Representative 1-cycloalkyl-1-aryl-1-ethyl *p*-nitrobenzoates of the type $(\underline{CH_2)_{n-1}C}H—C—(Ar)(CH_3)OPNB$ containing appropriate substituents in the aryl ring were synthesized and their rates of solvolysis determined in 80% aqueous acetone. The earlier work on the solvolysis of 1-cyclopropyl-1-aryl-1-ethyl *p*-nitrobenzoates ($n = 3$) and 1-cyclobutyl-1-aryl-1-ethyl *p*-nitrobenzoates ($n = 4$), utilizing the tool of increasing electron demand, clearly indicated major stabilization of the cationic center by $\pi\sigma$-electronic conjugation from the cyclopropyl group and modest σ stabilization from the cyclobutyl group. The ρ^+ values realized in the various systems examined are cyclopropyl ($n = 3$), -2.78; cyclobutyl ($n = 4$), -3.94; cyclopentyl ($n = 5$), -4.48; cyclohexyl ($n = 6$), -4.71; Δ^1-cyclohexenyl, -2.35; and Δ^2-cyclohexenyl, -4.83. The large negative ρ^+ observed by applying the tool of increasing electron demand to the solvolysis of cyclopentyl and cyclohexyl derivatives indicates that any enhanced stabilization of the cationic center by these groups, as compared to simple aliphatic groups, is borderline for cyclopentyl and not significant for cyclohexyl. Major π-electronic contributions from the allylic double bond are observed in the solvolysis of the 1-(Δ^1-cyclohexenyl)-1-aryl-1-ethyl *p*-nitrobenzoates. The homoallylic double bond in the 1-(Δ^2-cyclohexenyl)-1-aryl-1-ethyl system does not reveal any significant participation. Indeed, 1-(Δ^2-cyclohexenyl)-1-aryl-1-ethyl derivatives (p-CH_3O, p-H, p-CF_3) solvolyze slower than the saturated derivatives, presumably a result of the inductive effect of the double bond. However, with the 3,5-$(CF_3)_2$ derivative, there occurs an increase in the relative rate and a break in the log k-σ^+ plot, indicative of some kind of participation. The possibility of π participation in the 1-(Δ^3-cyclohexenyl)-1-aryl-1-ethyl system was also explored.

The tool of increasing electron demand offers major promise in evaluating objectively neighboring group effects.[2] Participation, both π[3,4] and σ,[5] could be detected with this tool in representative systems where such participation is significant. The Hammett-Brown relationship enables one to vary the electron demand at a developing cationic center over a wide range, while maintaining the steric effects around that center essentially constant.[6] We recently applied this tool to the study of the effect of ring size on the stabilization of developing carbocations on one of the ring members.[7] Ring systems ranging in size from cyclopropyl to cyclooctyl were explored. The ρ^+ values observed in these systems could be accounted for quite reasonably in terms of the I-strain concept.[8]

It seemed desirable to extend the study to the effect of α-cycloalkyl groups in stabilizing the cationic center, as measured by ρ^+. Earlier studies on 1-cyclopropyl-1-aryl-1-ethyl (**1**)[9] and 1-cyclobutyl-1-aryl-1-ethyl (**2**) systems[10] indicated that such α-cycloalkyl groups are capable of affording considerable stabilization to the carbonium ion center. Therefore, we wanted to extend this tool to the study of the related cyclopentyl (**3**) and cyclohexyl (**4**) systems, where the stabilization of the carbonium ion center, if any, must be attributed to σ-electronic contributions from the ring system. We also wanted to examine the effect of a double bond in such a ring system, α and β to the carbonium ion center. Accordingly, we synthesized 1-(Δ^1-cyclohexenyl)-1-aryl-1-ethyl *p*-nitrobenzoates (**5**), containing an allylic double bond, and 1-(Δ^2-cyclohexenyl)-1-aryl-1-ethyl *p*-nitrobenzoates (**6**), containing a homoallylic double bond, and studied their rates of solvolysis. The possibility of participation in 1-(Δ^3-cyclohexenyl)-1-aryl-1-ethyl *p*-nitrobenzoates (**7**) was also briefly explored.



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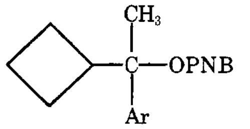

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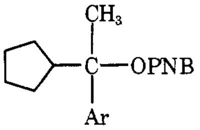

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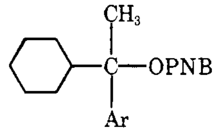

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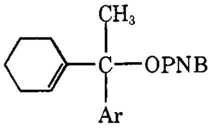

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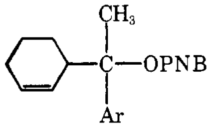

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Results

Synthesis. The tertiary alcohols corresponding to systems **3**, **4**, and **5** were obtained by the addition of the appropriate aryl

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