The Photolysis of Methoxy-Substituted Benzoin Esters. A Photosensitive Protecting Group for Carboxylic Acids

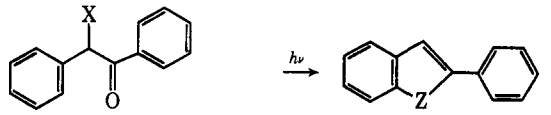
John C. Sheehan,* R. Marshall Wilson, and A. W. Oxford

Contribution from the Department of Chemistry, Massachusetts Institute of Technology, Cambridge, Massachusetts 02139.
Received March 8, 1971

Abstract: The unsymmetrical benzoin acetates, 4′-methoxybenzoin acetate (**8**), 3′-methoxybenzoin acetate (**9**), and 3′,5′-dimethoxybenzoin acetate (**15**) were photolyzed. All of these materials cyclize to the appropriately substituted 2-phenylbenzofurans **10**, **13** and **14**, and **16**, respectively. However, the *m*-methoxy substituent greatly enhances the yield of this cyclization, whereas the *p*-methoxy substituent has a moderate depressing effect upon the yield of cyclization. Moreover, the cyclization of **15** is not appreciably inhibited by piperylene, while the cyclization of **8** is completely suppressed by this quencher. The mechanistic aspects of this reaction are discussed and unusual oxetane intermediates (oxabicyclo[2.1.0]pentanes) are proposed as transient species. A preliminary investigation of the application of this furanization reaction in the unmasking of carboxylic acid esters of appropriately substituted benzoins is reported.

Some years ago the observation was reported from this laboratory that benzoin esters and other desyl compounds yield 2-phenylbenzofuran (**1**) upon irradiation with ultraviolet light (Scheme I).[1] Of particular

Scheme I. Photochemical Cyclizations of the Desyl System



$X = \overset{+}{N}H(CH_3)_2\overset{-}{Cl}$, OCOR, Cl, OTs
$X = SCH_2Ph$, $SCPh_3$, SS–desyl

1, Z = O
7, Z = S

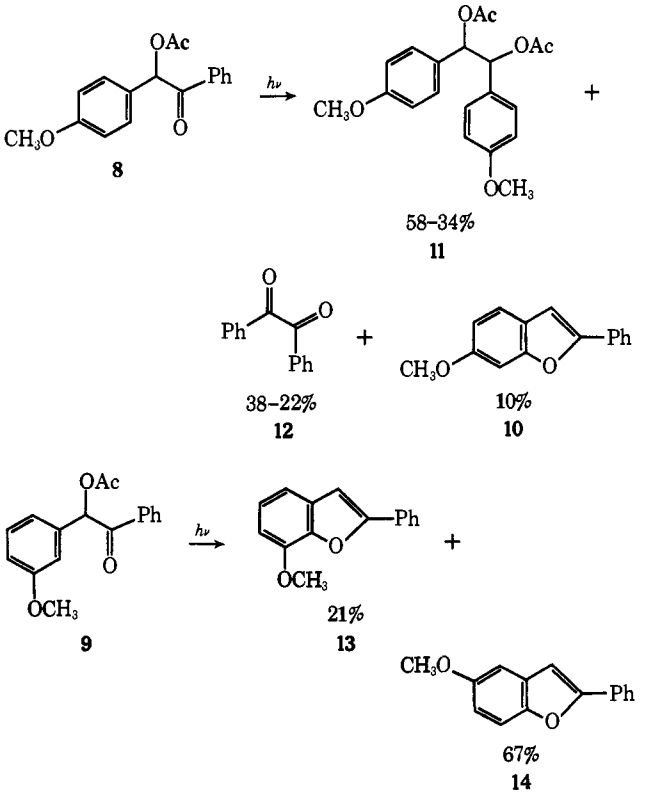
interest was the ease with which this cyclization could be influenced by modifications of the parent desyl system. Thus, the cyclization was found to be critically dependent upon the nature of the leaving group X. If X was an amine salt, the cyclization proceeded in high yield (~70%). Fair yields of **1** (20%) were obtained when X was an ester, while only traces of **1** were detected when X was Cl or OTs. Furthermore, the cyclization was also very sensitive to the substitution of the phenyl groups. The symmetrically substituted 4,4′-dimethoxybenzoin acetate (**2**) cyclized to 2-(4′-methoxyphenyl)-6-methoxybenzofuran (**3**) in only about 1% yield, whereas 3,3′-dimethoxybenzoin acetate (**4**) cyclized to a mixture of 2-(3′-methoxyphenyl)-5-methoxy and -7-methoxybenzofuran, **5** and **6**, respectively, in about 48% combined yield. Subsequent to this work Collier and Hill have further illustrated the variability of desyl photochemistry with their report of the photolysis of compounds in which X is a sulfur-containing moiety.[2] In these instances 2-phenylbenzo[*b*]thiophene (**7**) was the only reported cyclization product (Scheme I).

All of these reactions might reasonably be expected to proceed through excited carbonyl species. Consequently, the desyl system, with its extreme variability, offers a unique opportunity to study the behavior of excited carbonyl species in close proximity to reactive functional groups. In the present paper this subject is broached with an examination of the interaction between the excited desyl carbonyl and the nonconjugated phenyl group. It is this interaction that results in benzofuran formation through the formal loss of HX, and that provides a novel method of photochemically unmasking a blocked carboxylic acid in those cases where X equals OCOR.

Results

The disparity in the yields of benzofuran formation from symmetrically substituted benzoin esters **2** and **4** is difficult to interpret mechanistically, since it is not possible to distinguish between the effects of the methoxy substituent on the benzoyl moiety and the methoxy substituent on the benzyl acetate moiety. This can

Scheme II. The Influence of the Position of Methoxy Substitution upon Benzofuran Formation

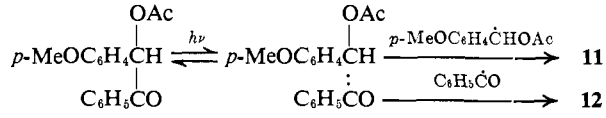


(1) J. C. Sheehan and R. M. Wilson, *J. Amer. Chem. Soc.*, **86**, 5277 (1964).
(2) J. R. Collier and J. Hill, *Chem. Commun.*, 640 (1969).

be a particularly important point since methoxy substitution of a benzoyl group can lead to significant changes in the relative energies of the n–π^* and π–π^* carbonyl excited states. The amount of π–π^* character of the triplet acetophenone carbonyl decreases in the following fashion: *m*-methoxyacetophenone > *p*-methoxyacetophenone > acetophenone.[3] In order to eliminate this uncertainty as to the nature of the benzoin carbonyl excited state, the unsymmetrical benzoin acetates **8** and **9** were prepared[4] and irradiated (Scheme II).

The photolysis of 4′-methoxybenzoin acetate (**8**) affords 2-phenyl-6-methoxybenzofuran (**10**) in only 10% yield which compares with a cyclization yield of 20% for the parent benzoin acetate.[1] The explanation for the low yield of **10** is found in the relatively efficient formation of **11** and **12**. These products reflect the predominant reaction mode of **8** which seems to be the homolytic dissociation of **8** into benzoyl and 4-methoxyphenylacetoxymethyl radicals (Scheme III). These

Scheme III. Homolytic Cleavage and Recombination Scheme



radical fragments might possibly combine in an unsymmetrical fashion to re-form **8**, or they could combine in a symmetrical fashion to form either **11** or **12**. Although benzils and dihydrobenzoin diacetates had previously been isolated from the photolysis of other benzoin esters,[1] **8** is the only ester from which it was possible to isolate both of the complementary radical dimerization products, **11** and **12**. Furthermore, the *p*-methoxy substituent of the unsymmetrical ester **8** serves as a label which lends support to the cleavage–dimerization scheme depicted in Scheme III. The yields of **11** and **12** are dependent upon the irradiation times with shorter irradiation times favoring higher yields. Therefore, these products are probably undergoing further photochemical reaction(s) which might account for the failure to observe complementary dimerization products from other benzoin esters. Finally, **8** is essentially unaffected when irradiated in a 1 *M* benzene solution of piperylene. This quenching of the photoproducts **10**, **11**, and **12** would seem to indicate that they arise from the triplet n–π^* state of the carbonyl in **8**.

In sharp contrast to the above results, the photolysis of 3′-methoxybenzoin acetate (**9**) afforded as the only isolable products the isomeric benzofurans **13** and **14** in a combined yield of 88%. This result makes it clear that the benzofuran formation is critically dependent upon the position of the methoxy substituent on the nonconjugated phenyl group, and that methoxy substitution of the benzoyl group can only retard the progress of the reaction.

In an effort to reinforce this effect and to simplify the product mixture for purposes of quantitative study, 3′,5′-dimethoxybenzoin acetate (**15**) was synthesized and irradiated. The reaction proceeded in an ex-

(3) R. D. Rauh and P. A. Leermakers, *J. Amer. Chem. Soc.*, **90**, 2246 (1968), and references therein.

(4) The esters **8** and **9** were synthesized by a modification of the methods of (a) Y. Asahina and M. Terasaka, *J. Pharm. Soc. Jap.*, 494, 219 (1923); *Chem. Abstr.*, 17, 3028 (1923); (b) A. McKenzie and E. M. Luis, *Ber. Deut. Chem., Ges. B*, **65**, 794 (1932).

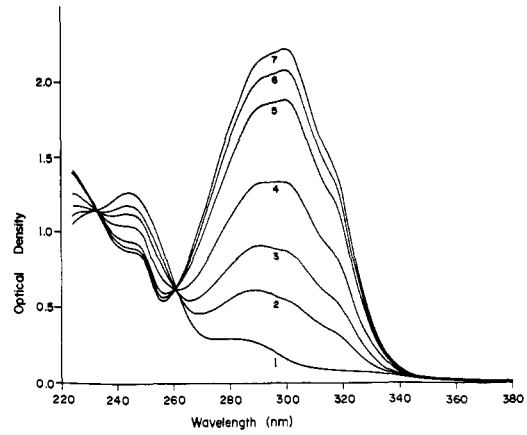
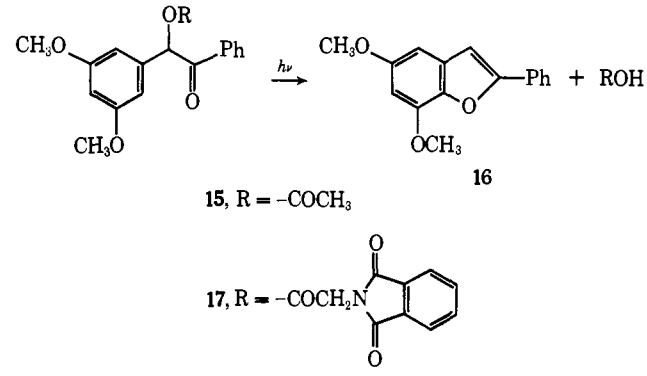


Figure 1. Course of the photolysis of 3′,5′-dimethoxybenzoin acetate (**15**) to 2-phenyl-5,7-dimethoxybenzofuran (**16**); 8.22×10^{-5} *M* in acetonitrile; irradiated in a Rayonet reactor with 360-nm lamps; irradiation time in seconds: 1, 0; 2, 20; 3, 40; 4, 80; 5, 180; 6, 260; 7, 420 sec.

traordinarily smooth fashion as illustrated by the spectra shown in Figure 1 which display two isosbestic points at 261 and 233 nm throughout the course of the reaction. The expected product 2-phenyl-5,7-dimethoxybenzofuran (**16**) (Scheme IV) is formed to the extent of 99.5%

Scheme IV



yield as determined spectroscopically and 94% yield as determined after isolation and purification. The quantum yield of this reaction was determined using a "merry-go-round" apparatus and 366-nm light isolated from a medium-pressure mercury arc through a series of filters (see the Experimental Section). The analysis of six quantum yield determinations provided a figure of $\Phi = 0.644 \pm 0.029$. Of considerable significance is the observation that the cyclization of **15** to **16** is not quenched by either naphthalene or neat piperylene. Thus, it would seem that **16** arises from either an n–π^* singlet state or an extremely short-lived n–π^* triplet state within about 10^{-10} sec following excitation.[5]

In view of the extremely facile elimination of acetic acid in the photolysis of **15** it seemed desirable to examine the potential of **15** as a blocking group for the

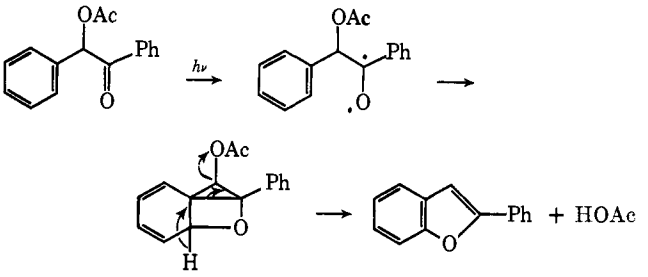
(5) The phosphorescence emissions of benzoin acetate and the variously substituted methoxybenzoin acetates **8**, **9**, and **15** are all very similar in their band structure and 0–0 energies (73–74 kcal/mol). They do, however, exhibit two component decay characteristics which differ slightly from each other; unpublished data, R. M. Wilson and W. H. Ballard. Nevertheless, these differences are small, and all of these compounds must emit from what is basically a carbonyl n–π^* triplet state. Unfortunately, no fluorescence data are available for these compounds. Such data might be accessible using mode locked laser sources, and would be much more useful in describing the nature of these reactive short-lived singlet or triplet excited states.

carboxylic acid function. Therefore, the phthaloyl glycinate ester **17** was prepared and photolyzed to yield 87% of recovered phthaloylglycine. No particular effort was made to optimize this yield. Even though the unsymmetrical benzoin ester **15** is readily available,[6] it was thought that a slightly more accessible symmetrical benzoin ester might serve equally well in this blocking capacity. However, the phthaloyl glycinates of 3,3′,4,4′-dimethylenedioxybenzoin (**18**) and 2,2′,3,3′-tetramethoxybenzoin (**19**) afforded only a 75 and 76% yield of recovered phthaloylglycine, respectively. In addition to demonstrating the masking potential of 3′,5′-dimethoxybenzoin esters, these experiments demonstrate the heterolytic nature of the ester cleavage step in the cyclization to the benzofuran. If this cleavage were proceeding through a homolytic mechanism, the resulting acyloxy radical would most probably undergo extensive decarboxylation before stabilization could be achieved *via* hydrogen abstraction.[7]

Discussion

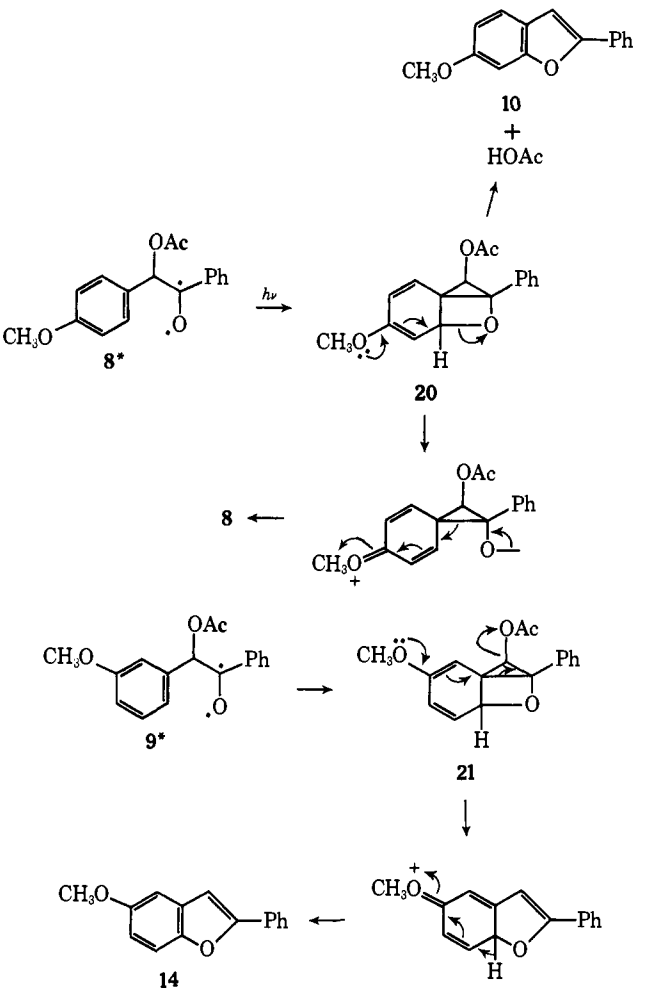
Absorption and emission data for these benzoin esters indicate that in all cases the lowest excited singlet and triplet states are associated with the benzoyl carbonyl and may be considered n–π^* in the solvent systems used in this work. The observation that the cyclization is enhanced by the presence of an appropriately situated electron-donating group is consistent with the electrophilic nature of the n–π^* carbonyl state. On the basis of these considerations, the propensity of the n–π^* excited carbonyl to form oxetanes, and the heterolytic requirement imposed on the ester cleavage step, the following mechanism for benzofuran formation is favored.

Scheme V. The Mechanism of Benzofuran Formation



The dependence of the cyclization upon the position of methoxy substitution can be rationalized with this mechanism in the following manner (Scheme VI). The *p*-methoxy substitution of **8** might not necessarily facilitate attack of the electrophilic n–π^* carbonyl oxygen since this attack can only take place at a position meta to the methoxy group. Should oxetane formation occur to yield **20**, ground-state considerations might lead one to predict that the methoxy substituent would facilitate reversal of the reaction leading back to the starting ketone **8**. Such a process might be considered a form of radiationless decay, and thus, *p*-methoxy substitution of the unconjugated phenyl group might only serve to retard the photochemical decomposition of **8** *via* the furan cyclization mode. In contrast the *m*-methoxy substituent of **9** would facilitate electrophilic attack of the n–π^* carbonyl oxygen since attack would be directed at either the ortho or para positions. Once oxetane formation occurred, ground-state considerations indicate that the methoxy group should facilitate the loss of the carboxylate anion from **21**, and direct the system along a course that leads to the benzofurans **13** and **14**.

Scheme VI. The Influence of Methoxy Substitution upon Benzofuran Formation



Qualitative quenching studies have revealed the extremely interesting observation that in the *p*-methoxy case, **8**, both the furan cyclization and the radical fragmentation processes are completely quenchable. Therefore, both of these reactions are proceeding through a long-lived triplet state ($\tau > 10^{-10}$ sec) and are in competition with each other. On the other hand in the di-*m*-methoxy case, **15**, this same cyclization is not quenched to any appreciable extent, and therefore, must be proceeding from a short-lived excited state ($\tau < 10^{-10}$ sec). This state could possibly be the n–π^* singlet state, although this need not necessarily be since the rate of intersystem crossing for aryl ketones is extremely rapid. Direct measurements of the rate of intersystem crossing for benzophenone indicate that its singlet state has a lifetime of about 1.5×10^{-11} sec.[8] Consequently, it is also possible that in the case of **15** cyclization is proceeding very rapidly from the n–π^* triplet state. In fact it is becoming increasingly evident that the reactivities of both the n–π^* singlet and triplet

(6) The 3′,5′-dimethoxybenzoin is easily prepared in 10-g quantities in a single day from commercially available starting materials.

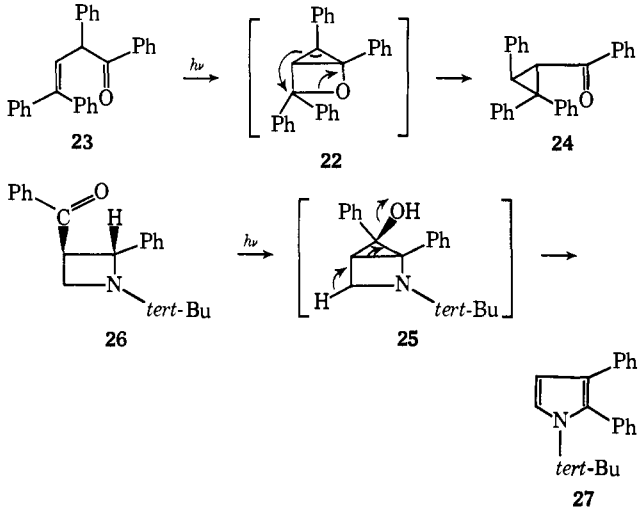
(7) A similar argument has been used for the photochemical cleavage of 2,4-dinitrobenzenesulfenyl esters: D. H. R. Barton, Y. L. Chow, A. Cox, and G. W. Kirby, *J. Chem. Soc.*, 3571 (1965).

(8) P. M. Rentzepis, *Science*, **169**, 239 (1970).

states are comparable and that the preponderance of reaction products arising from the n–π^* triplet state may reflect nothing more than the longer lifetime of this state relative to that of the n–π^* singlet state. Indeed, this seems to be the case for oxetane formation.[9] These considerations allow one to say only that the cyclization of **15** is faster than the diffusion-controlled limit of quenching (10^{-10} sec), and proceeds through an excited state that may be either an n–π^* singlet or triplet state, or both of these states. Nevertheless, the extremely rapid cyclization of the excited state(s) of **15** tends to support the suggestion that a *m*-methoxyphenyl group serves as a much more suitable substrate for attack by an excited carbonyl than does a *p*-methoxyphenyl group.[10]

Finally, it should be noted that ephemeral oxabicyclo[2.1.0]pentane intermediates related to **20** and **21** are not without precedent. Tenney, Boykin, and Lutz have proposed a similar highly strained bicyclic oxetane (**22**) as an intermediate in the rearrangement of the β,γ-unsaturated ketone **23** to the cyclopropyl ketone **24** (Scheme VII).[11] Analogy also exists for the

Scheme VII. The Intermediacy of Heterocyclic Bicyclo[2.1.0]pentanes



aromatization step of the bicyclic oxetanes discussed here. Padwa and Gruber have proposed azabicyclo[2.1.0]pentane intermediates (**25**) as transient species involved in the conversion of benzoylazetidines (**26**) to pyrroles (**27**) (Scheme VII).[12] These authors would like to consider the step **25** → **27** an orbital symmetry controlled electrocyclic opening proceeding *via* a cyclopropyl cation, and have suggested that hydrogen bonding between the hydroxyl group and azetidine nitrogen as well as steric hindrance might provide the requisite endo stereochemistry for the hydroxyl leaving group.[13] While this is an appealing suggestion, no similar constraints on the stereochemistry of the acetoxy group in **20** or **21** are readily apparent. Perhaps the combined driving forces of aromatization and relief of steric strain are large enough to effect the required bond alterations in a stepwise fashion in the case of *exo*-acetoxy isomer. Whatever the case may be, it is clear that bicyclic heterocycles related to **22** and **25** must be considered very labile intermediates since they have yet to be detected.[11,12,14]

Finally, this novel cyclization would seem to provide a very desirable means of unmasking a blocked carboxylic acid, and the preliminary experiments in this vein have been conducted. Since several photochemical reactions have been proposed as a means of removing protecting groups from carboxylic acids,[15] and since one of the most promising areas for the application of such a technique is peptide synthesis, it might be of interest to evaluate the furanization of esters of 3′,5′-dimethoxybenzoin in this context. The qualities expected in an ideal blocking group might be the following. (1) A virtually quantitative yield for the unmasking step is mandatory. The cleavage of esters **15** and **17** proceeds in virtually quantitative yield as estimated by spectroscopic methods although the yields suffer slightly in the isolation process; an 87% yield of phthaloylglycine is realized upon isolation. (2) The blocking group photoproduct (benzofuran **16**) should be readily separated from the freed acid. The benzofuran **16** is a very nonpolar, inert substance, and readily separated from acidic or polar components. (3) The question of the lifetime of the excited state that leads to the unmasking reaction is of considerable significance. If the blocked acid has a long excited state lifetime (triplet) before cleavage occurs then a greater opportunity exists for undesirable quenching processes to reduce the efficiency of the unmasking reaction. Such quenching processes would be particularly important with peptides containing tryptophan or any of the sulfur-containing amino acids.[16] Not only would this quenching impede the removal of the blocking group, but it might labilize the quenching species. Thus, racemization and photooxidation[17] might result from such undesired energy dissipation processes. With these considerations in mind it would seem a distinct advantage to have a protecting group with a short-lived excited state (singlet or short-lived triplet). Esters of 3′,5′-dimethoxybenzoin would seem to satisfy this requirement. (4) However, a rapid unmasking reaction does not necessarily assure that complications will not be encountered when dealing with large peptide molecules.

(9) N. J. Turro and P. A. Wriede, *J. Amer. Chem. Soc.*, **92**, 320 (1970), and references therein.

(10) It has previously been proposed that the ease of this cyclization might correlate with the strength of the interaction between the carbonyl and the nonconjugated aryl moiety.[1] This interaction is displayed in the unusually intense n–π^* absorption of the acetates discussed here, benzoin acetate, **8**, **9**, and **15**. However, the absorption spectra of these compounds, in which the n–π^* transitions are not obscured by other stronger transitions within the spectrum, indicate that the strongest interaction is displayed by **8** (*p*-methoxyphenyl group) and indeed, the n–π^* intensities of **9** and **15** (*m*-methoxyphenyl groups) are only slightly greater than those of the unsubstituted benzoin acetate. Therefore, this type of interaction is not involved in the furan formation in any straightforward manner.

(11) L. P. Tenney, D. W. Boykin, Jr., and R. E. Lutz, *J. Amer. Chem. Soc.*, **88**, 1835 (1966).

(12) A. Padwa and R. Gruber, *ibid.*, **92**, 100, 107 (1970). Various other examples of this reaction are given in these papers.

(13) R. B. Woodward and R. Hoffmann, "The Conservation of Orbital Symmetry," Verlag Chemie, Weinheim/Bergstr., Germany, 1970, pp 46–48 and 55–57.

(14) A preliminary examination of the cyclization of **15** by flash photolysis indicated that furan formation is complete within the flash period ($<10^{-6}$ sec). Further investigation of this point would be most interesting.

(15) P. G. Sammes, *Quart. Rev., Chem. Soc.*, **24**, 37 (1970); A. Patchornik, B. Amit, and R. B. Woodward, *J. Amer. Chem. Soc.*, **92**, 6333 (1970).

(16) A. D. McLaren and D. Shugar, "Photochemistry of Proteins and Nucleic Acids," Pergamon Press (distributed by the MacMillan Co.), New York, N. Y., 1964, Chapters 3 and 4.

(17) G. Galiazzo, G. Jori, and E. Scoffone, *Biochem. Biophys. Res. Commun.*, 31, 158 (1968); J. A. Barltrop and P. Schofield, *J. Chem. Soc.*, 4758 (1965).

Thus, the reaction should proceed with a quantum yield as close to 1.0 as possible. A lower quantum yield might mean that some of the excited molecules are passing through short-lived states to longer lived states which in turn might cause damage in remote sites within the peptide molecule as mentioned above (point 3). The quantum yield for the cleavage of **15** (0.644 ± 0.029) is quite high albeit far from unity. The fate of the unaccounted for excited species is uncertain, although apparently of little chemical significance in the model systems examined here. (5) The wavelength of the exciting light is of primary importance, and should fall within the range of about 320–400 nm. This would be necessary to ensure that tyrosine, phenylalanine, cystine, cysteine (absorption below 300 nm), and tryptophan (absorption below 320 nm) do not absorb light intended for the blocking group. The longer wavelength limitation would be beneficial so as not to require the exclusion of visible light in the handling of the blocked species.[18] The 3′,5′-dimethoxybenzoin esters are cleaved by the 366-nm mercury line.[19] (6) Finally, it would seem most reasonable to have a blocking group that did not contain any asymmetric centers, as this may cause problems in the manipulation of blocked amino acids which would exist as enantiomeric pairs, or require prior resolution of the blocking group. In this respect the 3′,5′-dimethoxybenzoin esters are deficient. However, the final evaluation of the utility of this blocking group must await further experimentation with a variety of amino acid and peptide systems.

Experimental Section[20]

Preparation of Unsymmetrical Benzoins. The unsymmetrical benzoins were prepared according to the following modified procedures.[4]

(A) 3′,5′-Dimethoxybenzoin. To a solution of sodium bisulfite (13 g, 0.125 mol) in 75 ml of water was added 3,5-dimethoxybenzaldehyde (9.8 g, 0.050 mol). A clear solution was obtained with vigorous shaking. The solution was cooled in an ice bath and a cold solution of potassium cyanide (8.15 g, 0.125 mol) in 30 ml of water was added. The solution was shaken for 15 min by which time a yellow oil (cyanohydrin) had separated. This material was extracted with benzene (four 40-ml portions) and the combined benzene extracts were dried. Phenylmagnesium bromide was prepared in 500 ml of anhydrous ether from bromobenzene (39.2 g, 0.25 mol) and magnesium turnings (6.15 g, 0.25 mol). The aforementioned cyanohydrin solution was added dropwise with stirring under a nitrogen atmosphere to the phenylmagnesium bromide solution. Upon completion of the addition the reaction mixture was refluxed for 30 min. The cooled reaction mixture was poured onto an ice–ammonium chloride mixture. Upon melting of the ice three layers developed: a yellow benzene–ether layer, a colorless aqueous layer, and a solid phase suspended between the previous two layers. The solid is probably the imine resulting from Grignard addition to the cyanohydrin, and is essentially insoluble in either the organic or aqueous layers. This solid was collected by filtration of the three-phase mixture through a Büchner funnel, and hydrolyzed directly in the funnel by stirring with 3% hydrochloric acid and washing the oily paste that resulted into a fresh receiving flask with ether. This procedure was repeated several times until all of the solid had been allowed to react and washed through the funnel. The combined ether washings were washed with sodium bicarbonate solution and dried. Removal of the ether and recrystallization of the residue from benzene–methanol yielded 3′,5′-dimethoxybenzoin: 6.84 g (43%); mp 110–111.5°; $\nu_{max}^{CCl_4}$ 3455, 1675, and 1600 cm^{-1}; λ_{max}^{EtOH} 246 nm (ε 24,800), shoulder 284 (5820), and shoulder 316 (1385).

Anal. Calcd for $C_{16}H_{16}O_4$: C, 70.60; H, 5.88. Found: C, 70.64; H, 5.92.

(B) 3′-Methoxybenzoin. The preparation of this material was very similar to the aforementioned procedure. The only variations were the following. The bisulfite adduct was prepared from sodium bisulfite (23 g, 0.22 mol) in 150 ml of water and 3-methoxybenzaldehyde (15 g, 0.110 mol). The cyanohydrin formation required potassium cyanide (14.5 g, 0.224 mol) in 50 ml of water, and extraction after 0.5 hr with 200 ml of benzene. The phenylmagnesium bromide was prepared in 300 ml of anhydrous ether from bromobenzene (69 g, 0.440 mol) and magnesium turnings (10.5 g, 0.438 mol). Addition of cyanohydrin solution to the Grignard required 0.5 hr followed by 0.5 hr of reflux. Quenching, collection of the solid imine, and hydrolysis yielded 11.7 g (44%) of 3′-methoxybenzoin: mp 78–80°; $\nu_{max}^{CHCl_3}$ 3430, 1680, and 1600 cm^{-1}.

Anal. Calcd for $C_{15}H_{14}O_3$: C, 74.39; H, 5.79. Found: C, 74.28; H, 5.76.

Preparation of Unsymmetrical Benzoin Acetates. The unsymmetrical benzoin acetates were prepared in a similar fashion as follows.

(A) 3′,5′-Dimethoxybenzoin Acetate (15). To a solution of 2.7946 g (0.0103 mol) of 3′,5′-dimethoxybenzoin and 1.2 ml (1.18 g, 0.015 mol) of pyridine in 60 ml of dry methylene chloride (passed through Woelm activity I alumina) was added dropwise with stirring at 0° a solution of 1.44 ml (2.2 g, 0.015 mol) of acetyl chloride in 20 ml of dry methylene chloride. Addition required about 0.5 hr and the solution was allowed to warm to room temperature over about 2 hr. The reaction mixture was extracted with water, dilute hydrochloric acid, dilute sodium hydroxide, and water. The organic layer was dried, the solvent was removed, and the residue was recrystallized from methylene chloride–methanol to afford 3′,5′-dimethoxybenzoin acetate: 2.972 g (92%); mp 105–107°; $\nu_{max}^{CCl_4}$ 1745, 1700, 1600 cm^{-1}; λ_{max}^{MeOH} 246 nm (ε 14,250), 282 (3050); n–π* shoulder 320 (550); $\lambda_{max}^{n\text{-heptane}}$ n–π* 326 (300).

Anal. Calcd for $C_{18}H_{18}O_5$: C, 68.81; H, 5.73. Found: C, 68.77; H, 5.82.

(B) 3′-Methoxybenzoin Acetate (9). Using the same procedure used in the preparation of **15**, 3′-methoxybenzoin (10 g, 0.0414 mol) and pyridine (5.1 g, 0.0645 mol) in 25 ml of dry methylene chloride were allowed to react with acetyl chloride (4.95 g, 0.063 mol) in 25 ml of dry methylene chloride to afford 10.5 g (90%) of **9**: mp 90–92°; $\nu_{max}^{CHCl_3}$ 1735, 1695, 1600 cm^{-1}; λ_{max}^{EtOH} 246 nm (ε 13,800), 281 (3450); n–π* shoulder 330 (590); $\lambda_{max}^{n\text{-heptane}}$ n–π* 326 (286).

Anal. Calcd for $C_{17}H_{16}O_4$: C, 71.85; H, 5.63. Found: C, 72.00; H, 5.68.

(C) 4′-Methoxybenzoin Acetate (8). Using the same procedure used in the preparation of **15**, 4′-methoxybenzoin[21] (8.69 g, 0.036 mol) and pyridine (3.93 g, 0.049 mol) in 20 ml of dry methylene chloride were allowed to react with acetyl chloride (4.97 g, 0.063 mol) in 20 ml of dry methylene chloride to afford an oil that resisted all attempts to induce crystallization. The material displayed one spot on tlc and one peak by vpc at 255° isothermal on a 6-ft SE-30 column. An analytical sample was obtained by short-path distillation at 0.03 mm: bp 212–215°; $\nu_{max}^{CHCl_3}$ 1730, 1690, and 1610 cm^{-1}; λ_{max}^{EtOH} 246 nm (ε 14,100), shoulder 275 (4900), n–π* 320

(18) Even the benzoin ester **15**, which does not exhibit significant absorption above about 375 nm, will undergo photochemical cleavage to an appreciable extent if exposed in solution to ambient laboratory light for a few days.

(19) Two other appropriate monochromatic light sources which, although considerably more expensive, are ideally suited for rapid photocleavage would be the 337.1-nm output of a nitrogen laser, and the 351.1- and 363.8-nm lines of an argon ion laser.

(20) The authors are indebted to Dr. S. M. Nagy and his associates for microanalyses (Chemistry Department, Massachusetts Institute of Technology, Cambridge, Mass. 02139). All melting points are uncorrected and were taken on a Reichert hot-stage microscope. The infrared spectra were determined with a Perkin-Elmer Model 237 grating spectrophotometer. The nmr spectra were determined at 60 MHz using TMS as an internal standard and with a Varian Model A-60 spectrometer. The ultraviolet spectra were determined with Cary Model 11 and 14 spectrophotometers. All solvents were removed under reduced pressure and solutions dried over magnesium sulfate unless stated otherwise.

(21) This material, mp 90–91°, was prepared by the aforementioned modification of the procedure of McKenzie and Luis;[4b] however, it differed from their material, mp 100–101°,[4b] but seemed to be the same as the benzoin isolated by Asahina and Terasaka, mp 89°.[4a] The more stable isomeric 4-methoxybenzoin is reported to have mp 106.5–107° [P. D. Gardner, *J. Amer. Chem. Soc.*, 78, 3421 (1956)]. That the material used here was the 4′-methoxybenzoin was established by nmr and ultraviolet spectroscopy which displayed only the features of the 4-methoxybenzyl alcohol moiety and none of those expected for the 4-methoxybenzoyl moiety.

(830); $\lambda_{max}^{n\text{-hexane}}$ n–π^* 328 (430); nmr ($CDCl_3$) δ 2.23 (s, 3 H), 3.69 (s, 3 H), doublet centered at 6.85 (J = 8 Hz, 2 H), 6.85 (s, 1 H), 7.25–7.50 (m, 5 H), and 7.82–8.05 (m, 2 H).

Anal. Calcd for $C_{17}H_{16}O_4$: C, 71.85; H, 5.63. Found: C, 71.78; H, 5.46.

Preparation of Benzoin Phthaloyl Glycinates. The benzoin phthaloyl glycinates were prepared in a similar fashion as follows.

(A) 3′,5′-Dimethoxybenzoin Phthaloyl Glycinate (17). To a solution of 3′,5′-dimethoxybenzoin (1.5 g, 5.52 mmol) and pyridine (0.638 g, 8.08 mmol) in 25 ml of methylene chloride at 0° was added over a period of 15 min with shaking a solution of phthaloyl glycyl chloride (1.8 g, 8.07 mmol) in 25 ml of methylene chloride. The solution was allowed to warm to room temperature and stand overnight, diluted with methylene chloride, washed with water (25 ml), dilute hydrochloric acid (two 25-ml portions), water (three 15-ml portions), and dried. Removal of the solvent and recrystallization of the residue from benzene–methanol afforded 2.207 g (87%) of 3′,5′-dimethoxybenzoin phthaloyl glycinate (**17**): mp 181–182°; $\nu_{max}^{CH_2Cl_2}$ 1775, shoulder 1750, 1730, shoulder 1695, and 1600 cm^{-1}; $\lambda_{max}^{CH_2Cl_2}$ 248 (ϵ 15,370), 289 (5500), shoulder 304 (3630), shoulder 320 nm (1140).

Anal. Calcd for $C_{26}H_{21}NO_7$: C, 67.99; H, 4.58; N, 3.05. Found: C, 67.83; H, 4.44; N, 3.02.

(B) 3,3′,4,4′-Dimethylenedioxybenzoin Phthaloyl Glycinate (18). To a solution of 3,3′,4,4′-dimethylenedioxybenzoin[22] (2 g, 10.1 mmol) in 20 ml of methylene chloride was added a solution of phthaloyl glycyl chloride (2.25 g, 10.1 mmol) in 20 ml of methylene chloride. After stirring for 20 hr at room temperature the reaction mixture was diluted with methylene chloride (100 ml), washed with water (20 ml), 1 N hydrochloric acid (15 ml), 1 N sodium bicarbonate (two 15-ml portions), and water (two 15-ml portions), and dried. Removal of the solvent and recrystallization from methylene chloride–methanol afforded 2.89 g (89%) of 3,3′,4,4′-dimethylenedioxybenzoin phthaloyl glycinate (**18**): mp 189.5–190.5°; $\nu_{max}^{CH_2Cl_2}$ 1775, 1750, 1725, 1690, and 1605 cm^{-1}; $\lambda_{max}^{CH_2Cl_2}$ 246 nm (ϵ 6780), 282 (9770), 294 (9360), 306 (8840), and shoulder 314 (8720).

Anal. Calcd for $C_{26}H_{17}NO_9$: C, 64.08; H, 3.49; N, 2.87. Found: C, 63.93; H, 3.51; N, 2.86.

(C) 2,2′,3,3′-Tetramethoxybenzoin Phthaloyl Glycinate (19). To a solution of 2,2′,3,3′-tetramethoxybenzoin[23] (6.0 g, 18.1 mmol) and pyridine (2.2 g, 27.9 mmol) in 30 ml of methylene chloride was added with stirring at room temperature a solution of phthaloyl glycyl chloride (6.1 g, 27.4 mmol) in 30 ml of methylene chloride. The solution was protected from light, stirred for 23 hr, diluted with methylene chloride (250 ml), washed with water (20 ml), 1 N hydrochloric acid (two 20-ml portions), 1 N sodium bicarbonate (two 20-ml portions), and water (three 20-ml portions), and dried. Removal of the solvent and recrystallization from benzene–methanol afforded 9.0 g (96%) of 2,2′,3,3′-tetramethoxybenzoin phthaloyl glycinate (**19**): mp 139.5–141.5°; $\nu_{max}^{CH_2Cl_2}$ 1775, 1750, and 1725 cm^{-1}; $\lambda_{max}^{CH_2Cl_2}$ 247 (ϵ 7640), 253 (7720), 290 (5570), and shoulder 303 nm (4770).

Anal. Calcd for $C_{28}H_{25}NO_9$: C, 64.76; H, 4.82; N, 2.70. Found: C, 64.67; H, 4.93; N, 2.67.

Photolysis of 4′-Methoxybenzoin Acetate (8). A solution of 4.164 g (14.2 mmol) of 4′-methoxybenzoin acetate (**8**) in 300 ml of benzene was irradiated under a nitrogen atmosphere for 9 hr using a 200-W, type S, Hanovia medium-pressure mercury immersion lamp with a Pyrex filter sleeve. Removal of the solvent and chromatography on 85 g of silica gel afforded the following.

(A) 2-Phenyl-6-methoxybenzofuran (10). The first band eluted (85:15 to 70:30 CCl_4–$CHCl_3$) was **10** (0.342 g, 10%) which after recrystallization from hot methanol had mp 83–84° (lit.[24] 83°).

(B) Benzil (12). The next material eluted (60:40, CCl_4–$CHCl_3$) was a yellow crystalline substance (0.343 g, 22%) which after recrystallization from hot methanol had with benzil mp and mmp 95–96°.

(C) 4,4′-Dimethoxydihydrobenzoin Diacetate (11). The last discrete material eluted (60:40, CCl_4–$CHCl_3$) was an oily yellow substance, **11** (0.892 g, 34%), which after several recrystallizations from hot methanol had mp 152–153°: $\nu_{max}^{CHCl_3}$ 1735 and 1615 cm^{-1}; nmr ($CDCl_3$) δ 1.97 (s, 6 H), 3.73 (s, 6 H), 6.01 (s, 2 H), 6.78 (d, J = 8 Hz, 4 H), 7.15 ppm (d, J = 8 Hz, 4 H).

Anal. Calcd for $C_{20}H_{22}O_6$: C, 67.06; H, 6.15. Found: C, 67.15; H, 6.40.

This reaction is quenched completely when conducted in a 1 M benzene solution of piperylene.

Photolysis of 3′-Methoxybenzoin Acetate (9). A solution of 2.00 g (7.05 mmol) of 3′-methoxybenzoin acetate (**9**) in 300 ml of benzene was irradiated under a nitrogen atmosphere for 11 hr using a 200-W, type S, Hanovia medium-pressure mercury immersion lamp with a Pyrex filter sleeve. Removal of the solvent and chromatography on 50 g of silica gel afforded only a benzofuran fraction (1.372 g, 88%, mp 105–123°). This material consisted of a mixture of **2-phenyl-5-methoxybenzofuran (14)** and **2-phenyl-7-methoxybenzofuran (13)** in a ratio of 76:24 as determined by vpc on a SE-30 column at 210° isothermal. Recrystallization of the crude fraction from methylene chloride–methanol afforded pure **14** (0.867 g), mp 129.5–130.5 (lit.[25] 127°). Careful fractional recrystallization of the mother liquors of the previous recrystallizations from methylene chloride–methanol and then from n-hexane yielded pure **13**; mp 71.5–73° (lit.[24] 73°).

Photolysis of 3′,5′-Dimethoxybenzoin Acetate (15). A solution of 0.2057 g (0.655 mmol) of 3′,5′-dimethoxybenzoin acetate (**15**) in 80 ml of benzene was irradiated under an atmosphere of nitrogen in a Pyrex flask in a Rayonet photochemical reactor using lamps with maximum output at 360 nm. After 1 hr of irradiation, the solvent was removed and the residue was passed through about 200 mg of silica gel eluting with petroleum ether (bp 40–69°)–benzene (4:1) to yield 0.1556 g (93.5%) of **2-phenyl-5,7-dimethoxybenzofuran (16)**, which, after one recrystallization from petroleum ether, had mp 89.1–89.6° (Mettler FP2): λ_{max}^{EtOH} 246 (ϵ 10,020), shoulder 292 (26,130), 301 (27,480), and shoulder 317 nm (18,500).

Anal. Calcd for $C_{16}H_{14}O_3$: C, 75.60; H, 5.51. Found: C, 75.54; H, 5.56.

This reaction is not quenched to any appreciable extent in a 1 M benzene solution of piperylene.

(A) Quantum Yield Determinations. The quantum yield determinations of the reaction of **15** were conducted using a "merry-go-round" apparatus. The light source was a 550-W medium-pressure mercury lamp (Hanovia 673-36) mounted in a water-jacketed quartz immersion well. The 366-nm line of the lamp was isolated by filtering the light through two filter solutions contained in Pyrex tubes mounted concentrically with respect to the immersion well. The inner solution[26,27] (1.1-cm path) consisted of $CoCl_2 \cdot 6H_2O$ (150.0 g), $NiCl_2 \cdot 6H_2O$ (75.0 g), and naphthalene (0.4806 g) diluted to 750 ml with 65% ethanol–35% water 1 N in HCl. The outer solution[26] (1.4-cm path) consisted of K_2HPO_4 (4.353 g/l.), N-(5-dimethylamino-3-methylpenta-2,4-dienylidene)dimethylammonium perchlorate[28] (0.0136 g/l.), and 2,7-dimethyl-3,6-diazocyclohepta-1,6-diene perchlorate (K & K) (0.100 g/l.) dissolved in water. This combination of filter solutions provides 10–15% transmission at 366 nm. Benzophenone–benzhydrol actinometry was used.[29] Samples of **15** (0.1974 M in acetonitrile) and actinometer solutions were degassed with four freeze–thaw cycles and irradiated in 12-mm Pyrex tubes. The reaction progress was followed by ultraviolet spectroscopy and only allowed to proceed to the extent of 8% completion. On the basis of six determinations the quantum yield for the photolysis of **15** was estimated to be 0.644 ± 0.029.

Photolysis of Benzoin Phthaloyl Glycinates. These reactions were all conducted using a 450-W medium-pressure mercury lamp (Hanovia, type L) with Pyrex filter sleeves, and in 300-ml benzene solutions under an atmosphere of nitrogen.

(A) Photolysis of 3′,5′-Dimethoxybenzoin Phthaloyl Glycinate (17). The ester **17** (0.487 g, 1.05 mmol) was irradiated in benzene solution for about 45 min. Removal of the solvent afforded a crystalline residue which after several washings with benzene gave phthaloylglycine as the undissolved crystalline material (0.187 g, 87%), mp 195–198°, after crystallization from methanol–benzene, identical infrared spectrum with that of an authentic sample, and an undepressed mixture melting point. The benzene washings were

(22) F. M. Perkin, *J. Chem. Soc.*, **59**, 150 (1891).
(23) J. L. Hartwell and S. R. L. Kornberg, *J. Amer. Chem. Soc.*, **67**, 1606 (1945).
(24) S. Kawai, T. Nakamura, and M. Yoshida, *Ber. Deut. Chem., Ges. B*, 73, 581 (1940).
(25) A. N. Grinev, I. A. Zaitsev, N. K. Venevtseva, and A. P. Terent'ev, *Zh. Obshch. Khim.*, **28**, 1853 (1958); *Chem. Abstr.*, **53**, 1299b (1959).
(26) This solution is a modified version of a solution described by W. W. Wladimiroff, *Photochem. Photobiol.*, **5**, 243 (1966).
(27) Unpublished procedures of D. Morgan, M. Orchin, and M. G. McCoy.
(28) G. Köbrich, *Justus Liebigs Ann. Chem.*, **648**, 114 (1961).
(29) W. M. Moore and M. Ketchum, *J. Amer. Chem. Soc.*, **84**, 1368 (1962).

concentrated and the residue chromatographed on activity I Woelm alumina, eluting with benzene to yield 2-phenyl-5,7-dimethoxybenzofuran (**16**) (0.238 g, 88%), mp 87–90°.

(B) Photolysis of 3,3′,4,4′-Dimethylenedioxybenzoin Phthaloyl Glycinate (18). The ester **18** (0.878 g, 1.80 mmol) was irradiated in benzene solution for about 1.75 hr. Removal of the solvent afforded a brown crystalline solid which was washed several times with small quantities of ether. The ether washings were concentrated and diluted with methanol to induce crystallization of phthaloyl glycine (0.279 g, 75%), mp 192–196°, identical infrared spectrum with that of an authentic sample, and undepressed mixture melting point. The furan fraction was not investigated.

(C) Photolysis of 2,2′,3,3′-Tetramethoxybenzoin Phthaloyl Glycinate (19). The ester **19** (3.6817 g, 7.09 mmol) was irradiated in benzene solution for about 3.5 hr. The reaction mixture was concentrated until crystallization was induced. The crystalline phthaloylglycine (1.1046 g, 76%) was collected and after recrystallization from methanol–benzene had mp 195–198° and an identical infrared spectrum with that of an authentic sample. The mother liquor from the concentrated reaction mixture was diluted with ether (200 ml) and methylene chloride (100 ml), washed with 1 *N* sodium bicarbonate (two 20-ml portions) followed by water (two 25-ml portions), and dried. Removal of the solvent and chromatography of the residue on activity I Woelm alumina, eluting with benzene, afforded **2-(2′,3′-dimethoxyphenyl)-4,5-dimethoxybenzofuran** (1.384 g, 62%) which after recrystallization from *n*-hexane had: mp 72–74°; λ_{max}^{EtOH} shoulder 289 (ε 31,260), 303 (33,960), and shoulder 318 nm (23,700).

Anal. Calcd for $C_{18}H_{18}O_5$: C, 68.81; H, 5.73. Found: C, 68.86; H, 6.00.

Acknowledgment. This investigation was aided by a Public Health Service Fellowship (Grant No. 5-FI-GM 15,948-02) to R. M. W. for which we wish to express our appreciation. An expression of appreciation is also extended to W. H. Ballard who assisted in the preparation of some of the starting materials.

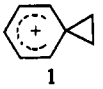
Studies of Homoconjugation in Pyridylalkyl Organometallic Compounds[1,2]

Gideon Fraenkel* and James W. Cooper

Contribution from the Department of Chemistry, The Ohio State University, Columbus, Ohio 43210. *Received April 15, 1971*

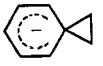
Abstract: In a study of homoconjugative contributions to bonding in carbanions, a series of pyridylalkyl metallic compounds has been prepared and their nmr spectra determined. The spectra indicate that these compounds exist mainly in the open chain form. The compounds display unusual ambidentate reactivity to acylating reagents forming stable *N*-acyl derivatives of dihydropyridines which themselves are useful precursors to other organometallic compounds. Attempts to prepare the lithium compound and Grignard reagent from 3-(4-pyridyl)-3-methylbutyl chloride resulted in fragmentation with loss of ethylene to 2-(4-pyridyl)-2-metallopropanes. The latter display in their nmr spectra considerable delocalization of charge into the ring; chemically they acylate with ethyl chloroformate on *nitrogen* with formation of a stable pyridine methide–*N*-carbethoxy-4-isopropylidene-1,4-dihydropyridine. Whereas 2-(2-pyridyl)-2-methylpropylmagnesium chloride undergoes reaction at carbon with ethyl chloroformate, 2-(4-pyridyl)-2-methylpropylmetallic compounds (M = Hg, Mg, Li) acylate at *nitrogen* with ring closure to stable 1-acyl-4-(1,1-dimethylspirocyclopropyl)-1,4-dihydropyridines. These compounds are cleaved by organometallic compounds of sodium, magnesium, and lithium back to open chain pyridylpropyl metallic compounds which behave similarly to the reagents prepared *via* the halides. From competition experiments it is shown that ethyl chloroformate acylates pyridines faster than it reacts with alkylmagnesium halides. Thus when ethyl chloroformate is added to a mixture of pyridine and a Grignard reagent, 2-substituted *N*-carbethoxy-1,2-dihydropyridines are formed. By analogy it is proposed that the cyclization of 4-pyridylalkyl organometallic reagents by acylating agents proceeds *via* the *N*-acylpyridiniumalkyl metal species. While homoconjugative interactions are not detected from the nmr data, the failure of these pyridylalkyl metal reagents to react with excess butyllithium indicates a small degree of homoconjugative stabilization.

Phenyl participation in carbonium ion reactions is one example of many homoconjugative interactions which are thought to stabilize carbonium ions or transition states with carbonium ion character. Bridged phenylethyl cations originally proposed to accompany the solvolysis of 1-phenyl-1-methyl-2-butanol tosylate[3] have now been prepared in stable salts, and unequivocally identified by nmr spectroscopy.[4,5]



1

In principle the effects responsible for the stability of **1** should also apply to its negative counterpart, the as yet unknown phenanion, **2**. Species similar to **2**



2

have been suggested by Zimmerman[6] and Grovenstein[7]

(1) Presented in part at the 157th National Meeting of the American Chemical Society, Minneapolis, Minn., April 1969.

(2) Abstracted from the Ph.D. Thesis of J. W. Cooper, The Ohio State University, 1969.

(3) D. J. Cram, *J. Amer. Chem. Soc.*, **71**, 3863, 3875, 3883 (1949); **74**, 2159 (1952); **86**, 3767 (1964).

(4) L. Eberson and S. Winstein, *ibid.*, **87**, 3506 (1965).

(5) G. Olah, E. Namanworth, M. Comisarow, and B. Ramsey, *ibid.*, **89**, 711 (1967).

(6) H. E. Zimmerman and F. J. Smentowski, *ibid.*, **79**, 5455 (1957); H. E. Zimmerman and E. Zweig, *ibid.*, **83**, 1196 (1961).

(7) E. Grovenstein, Jr., *ibid.*, **79**, 4895 (1957); E. Grovenstein, Jr., and G. Wentworth, *ibid.*, **85**, 3305 (1963); E. Grovenstein, Jr., and G.