α-Carbonyl Carbocations.[1] 4. NMR Detection and Reactivities of Diaryl α-Carbonyl Cations

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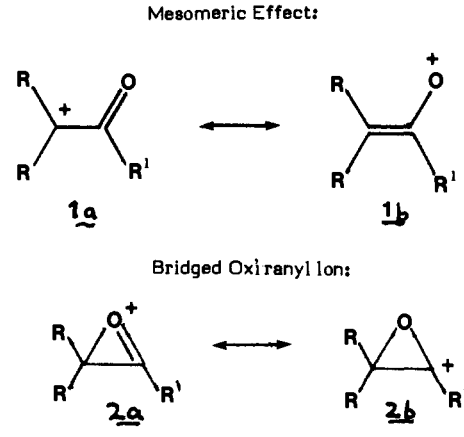
Abstract: Diaryl α-carbonyl carbocations **6** were generated from their alcohol precursors in strong acid conditions at low temperatures. The assignments of the low-field signals were obtained from specifically ^{13}C-labeled precursors. At ambient temperatures these ions undergo 6π-electrocyclization to give benzofurans or fluorenes, the particular transformation depending on the nature of the carbonyl substituent. The decomposition of these ions occurs by first-order kinetics, and the activation parameters suggest a dependence on the mesomeric and inductive effects of the carbonyl substituent. A mechanism is postulated in order to rationalize the divergence in behavior between these ions.

Recently, much research effort has been devoted to the study of destabilized carbocations with electron-withdrawing substituents at or in close proximity to a cationic center.[2,3] A formyl substituent has been calculated to destabilize a methenium ion by 9.9 kcal/mol relative to hydrogen.[4] This compares with the larger destabilizing effect of a trifluoromethyl group, which destabilizes the methenium ion by 37.3 kcal/mol and is in line with the relative electron-withdrawing nature of these two substituents as reflected by their σ^+-values.[5,6] Recently, Reynolds et al.[7] have shown that all the substituents that are π-acceptors in RC_6H_5 (R = CN, CHO, and NO_2) become π-donors in the cations RCH_2^+ and $RC_6H_4CH_2^+$. Creary's studies on the solvolyses of α-keto sulfonate esters, in which he observed a small if not negligible rate-retarding effect of the carbonyl group on the reactivity of these compounds,[8] provide further experimental evidence that the carbonyl group behaves as a π-donor in α-carbonyl cations. In at least two cases an α-keto substituent actually gave enhanced rates of solvolysis relative to hydrogen.

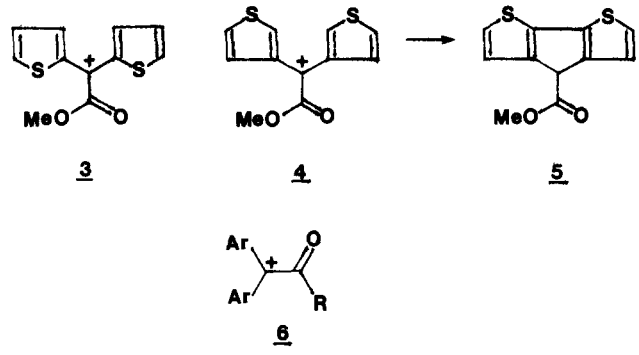
The stabilizing effect of a carbonyl group may involve two fundamentally different interactions (Scheme I), the mesomeric effect in which there is a contribution from the vinyl oxenium ion structure **1** or, alternatively, neighboring group participation by the carbonyl oxygen leading to the bridged oxiranyl ion **2**. Interestingly, Griesbaum has shown that the ionization of α-chloro epoxides provides an alternative route to α-keto cations.[9] Ab initio MO calculations indicate the bridged ion **2** for the parent formylmethyl cation (R = H) is slightly more stable than the open form **1** with a negligible barrier to interconversion.[10] However, Creary has shown that substituted chiral α-keto carbocation precursors with an α-chiral center lead to racemic products with some inversion.[11] Intervention of a bridged ion, **2**, would be expected to lead to products with net retention of configuration at the chiral center.

The involvement of α-carbonyl carbocation precursors in preparative chemistry has been demonstrated recently in a review article by Charpentier-Morize.[12] Among the many typical 1,2-alkyl and hydride migrations seen in carbocation chemistry are certain transannular hydride migrations and the remote fuc-

Scheme I



tionalization of inert methylene groups. Early proton NMR studies of stable diaryl(carboalkoxy)methyl cations were reported for the bis(thiophene) derivatives **3** and **4**.[13,14] Ion **4** undergoes



an interesting electrocyclization to the novel bis(thiophene) fluorene analogue **5**. Okamoto reported the isolation of a di-*p*-anisylbenzoylmethyl cation **6** (Ar = *p*-$CH_3OC_6H_4$, R = C_6H_5) as the SbF_6^- salt.[15] In a communication we have recently reported the ^{13}C NMR spectra of two diarylmethyl α-carbonyl cations **6**.[16] In the present study we report NMR data, product analysis, and kinetic data for the decomposition of a series of ions **6** in which Ar is phenyl.

Results

NMR Data. The carbenium ions **6** were obtained by mixing $CDCl_3$ or CD_2Cl_2 solutions of the carbinol precursor with chlo-

(1) For part 3 of this series, see: Maleki, M.; Hopkinson, A. C.; Lee-Ruff, E. *Tetrahedron Lett.* **1983**, 4911.
(2) Gassman, P. G.; Tidwell, T. T. *Acc. Chem. Res.* **1983**, *16*, 279.
(3) Tidwell, T. T. *Angew. Chem., Int. Ed. Engl.* **1984**, *23*, 23.
(4) Paddon-Row, M. N.; Santiago, C.; Houk, K. N. *J. Am. Chem. Soc.* **1980**, *102*, 6561.
(5) Vitullo, V. P.; Wilgis, F. P. *J. Am. Chem. Soc.* **1981**, *103*, 880.
(6) Oyama, K.; Tidwell, T. T. *J. Am. Chem. Soc.* **1976**, *98*, 947.
(7) Reynolds, W. F.; Dais, P.; MacIntyre, D. W.; Topsom, R. D.; Marriott, S.; von Nagy-Felsobuki, E.; Taft, R. W. *J. Am. Chem. Soc.* **1983**, *105*, 378.
(8) Creary, X. *J. Am. Chem. Soc.* **1984**, *106*, 5568.
(9) (a) Spraul, M.; Griesbaum, K. *Chem. Ber.* **1983**, *116*, 2641. (b) McDonald, R. N.; Steppel, R. N. *J. Am. Chem. Soc.* **1970**, *92*, 5664.
(10) Nobes, R. H.; Bouma, W. J.; Radom, L. *J. Am. Chem. Soc.* **1983**, *105*, 309.
(11) Creary, X.; Geiger, C. C. *J. Am. Chem. Soc.* **1982**, *104*, 4151.
(12) Begue, S. P.; Charpentier-Morize., M. *Acc. Chem. Res.* **1980**, *13*, 207.
(13) Nilles, G. P.; Schuetz, R. D. *Tetrahedron Lett.* **1969**, 4313.
(14) Ostman, B.; Sjoberg, S. *Tetrahedron Lett.* **1970**, 3137.
(15) Takeuchi, K.; Kitagawa, T.; Okamoto, K. *J. Chem. Soc., Chem. Commun.* **1983**, 7.
(16) Hopkinson, A. C.; Dao, L. H.; Duperrouzel, P.; Maleki, M.; Lee-Ruff, E. *J. Chem. Soc., Chem. Commun.* **1983**, 727.

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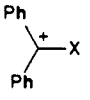
Table I. ^{13}C NMR Data[a] for Carbocations and Theoretical Charges on C^+

	δ_{C^+}	$\delta_{C=O}$[b]	charge on C^+	θ, deg
Ph_2C^+COOH	193.4	166.9 (179.9)	0.200	25.5
Ph_2C^+COOMe	191.2	168.8 (175.0)		
$Ph_2C^+CONMe_2$	182.0	166.0 (172.1)		
Ph_2C^+COMe	201.7	209.2 (208.9)	0.203	26.0
Ph_2C^+COPh	202.8	195.6 (200.6)		
$Ph_2C^+COCF_3$	193.3	184.2 (191.4)		
$RPhC^+COOMe$[c]	182.5	168.9 (175.4)		
$RPhC^+COOMe$[d]	194.1	175.4 (175.8)		
$Ph_2C^+C{\equiv}CMe$	195.7[e]			
$Ph_2C^+C{\equiv}N$	168.8[f]			
$Ph_2C^+NO_2$	189.1[g]			
$Ph_2C^+CF_3$	189.6[g]		0.165	27.0
$Ph_2C^+CH_3$	229.3[h]		0.248	28.5
Ph_2C^+H	199.4[h]		0.234	25.0

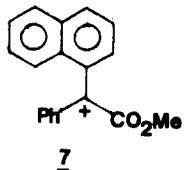
[a] Chemical shifts are relative to tetramethylsilane. [b] Numbers in parentheses are chemical shifts of carbonyl carbon in the corresponding carbinol. [c] R = α-naphthyl. [d] R = 5-acenaphthyl. [e] Olah, G. A.; Spear, R. J.; Westerman, P. W.; Denis, J. M. *J. Am. Chem. Soc.* **1974**, *96*, 5855. [f] Reference 19. [g] Reference 18. [h] Reference 17.

rosulfonic acid at −60 °C. The specifically labeled carbinol precursor to **6b** was prepared by the condensation of disodium



6a; X = CF_3
b; X = $COCH_3$
c; X = COPh
d; X = COOH
e; X = COOMe
f; X = $CONMe_2$
g; X = $COCF_3$

benzophenone dianion, labeled at the carbonyl carbon, with acetonitrile followed by hydrolysis of the resulting imine.[29a] The ^{13}C-labeled carbinol precursor to **6c** was made by the Wittig rearrangement of diphenylmethyl benzoate labeled at the carbonyl carbon.[29b] Syntheses of the ^{13}C-labeled carbinol precursors to **6d,e** were based on the condensation of benzoyl chloride with ^{13}C-labeled sodium cyanide[29c] followed by hydrolysis to benzoylformic acid,[29d] reaction with phenylmagnesium bromide, and esterification with diazomethane. At room temperature, solutions of carbinols in $CD_2Cl_2/ClSO_3H$ and in H_2SO_4 were intensely colored, but the color faded rapidly, with half-lives of a few seconds. At −80 °C the $CD_2Cl_2/ClSO_3H$ solutions of the carbenium ions were stable over a period of several hours, and the ^{13}C NMR spectra obtained gave chemical shift values listed in Table I. ^{13}C labeling at either the carbinol or the carbonyl carbon permitted an unambiguous assignment of the carbonyl and cationic carbon signals for ions **6b–e**. In the spectrum of the trifluoroacetyl-substituted ion **6g** (X = $COCF_3$), the assignments were based on the peak splitting (quartet) of the carbonyl carbon by the two-bond coupling with fluorine (J = 33 Hz). The cationic carbon signal appears as a singlet. The chemical shifts for the carbonyl and cationic carbons of carbenium ions **7** and **8** were assigned by analogy with the ion derived from methyl benzylate.



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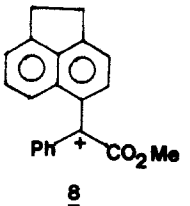

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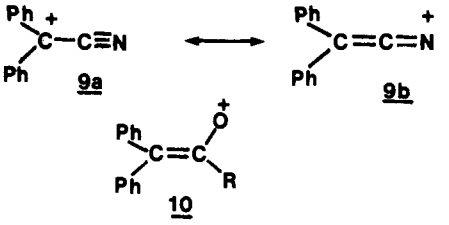
All the chemical shifts assigned to the cationic carbons of ions $ArPhC^+COX$ fall in the range 182–202 ppm. These compare with chemical shift values of 212 and 199 ppm, respectively, for the cationic carbons of the triphenylmethyl and diphenylmethylcations.[17] In other diphenylmethyl carbenium ions with electron-withdrawing groups the cationic carbon shows signals at 189.1 ppm in $Ph_2C^+NO_2$[18] and 168.8 ppm in Ph_2C^+CN.[19] For all these ions Ph_2C^+COR, except when R is NMe_2, the cationic carbons are slightly more deshielded than those in the α-nitrodiphenylmethyl cation. The greater shielding of the cationic carbon in the cyanodiphenylmethyl cation **9a** has been attributed

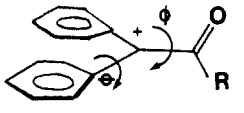


9a **9b**

10

to contributions to the structure from the nitrenium ion **9b**. This inference is further substantiated by the unusual deshielding of the nitrogen nucleus in the ^{15}N NMR spectrum of this ion, indicating electron deficiency at this center. Furthermore, the theoretically calculated bond lengths and bond orders for the cyanomethyl cation[20] are consistent with partial double-bond and somewhat less than triple-bond character for the C–N bond in this ion. By analogy with the results on the cyano-substituted ion it appears from our data on the carbonyl-substituted ions that the analogous oxo structure **10** is not an important resonance contributor except possibly when R is NMe_2. Caution must be exercised here since although correlations of ^{13}C chemical shifts with charge densities have been established for carbocations, structural changes at or in the vicinity of the charge center can have significant effects on the chemical shifts by mechanisms other than those involving charge displacement[21] so that it becomes difficult to quantitatively assess charge densities on the basis of chemical shifts alone.

Recent theoretical studies[20] of α-formyl carbenium ions, in which the carbonyl group has been shown to be a weak π-donor, have only considered the possibility of rotation of the formyl group in primary and secondary alkyl cations. We have previously[21] used the CNDO/2 method[22] to examine the simultaneous rotation (angle θ, structure **11**) of the phenyl groups out of the plane defined



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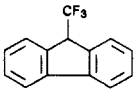
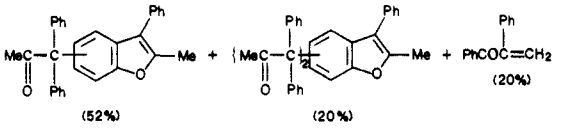
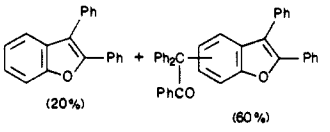
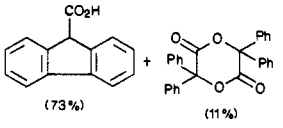
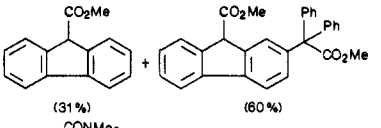
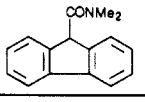
by the cationic carbon and the ipso carbons. All bond lengths and bond angles were taken as standard,[23] and single-point calculations were performed at different values of θ for **11** when R is OH and CH_3 and for ions in which COR is replaced by H, CH_3, and CF_3. The rotation of the phenyl groups (θ = 27°) is dictated mainly by the steric interactions between the ortho hydrogens and is largely independent of the substituent (Table I).

Steric interactions between the substituent COR and the phenyl rings resulted in rotation of COR to an angle ϕ of approximately 90°. In this perpendicular structure the carbonyl group and R cannot function as π-donors but are in the optimum conformation for lone-pair donation into the vacant p-orbital on the cationic carbon (structure **2**). Such a structure is most likely when R′ is a strong π-donor, e.g., NR_2. However, the size of the ions pre-

(17) Brown, H. C.; Peters, E. N. *J. Am. Chem. Soc.* **1977**, *99*, 1712.
(18) Olah, G. A.; Prakash, G. K. S.; Arvanaghi, M.; Krishnamurthy, V. V.; Narang, S. C. *J. Am. Chem. Soc.* **1984**, *106*, 2378.
(19) Olah, G. A.; Prakash, G. K. S.; Arvanaghi, M. *J. Am. Chem. Soc.* **1980**, *102*, 6640.
(20) Paddon-Row, M. N.; Santiago, C.; Houk, K. N. *J. Am. Chem. Soc.* **1980**, *102*, 6561. Dixon, D. A.; Charlier, P. A.; Gassman, P. G. *J. Am. Chem. Soc.* **1980**, *102*, 3957. Lien, M. H.; Hopkinson, A. C.; McKinney, M. A. *Theochem.* **1984**, *105*, 37.
(21) Hopkinson, A. C.; Kaye, B. R., unpublished results.
(22) Dobosh, P. A. CNINDO, Program 141, Quantum Chemistry Program Exchange, Indiana University.
(23) Pople, J. A.; Beveridge, D. L. *Approximate Molecular Orbital Theory*; McGraw-Hill: New York, 1970; p 111.

Table II. Rearrangement Products from α-X-Diphenylmethyl Cations

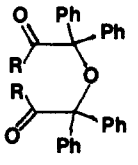
reactant	products
6a	
6b	
6c	
6d	
6e	
6f	

cluded a full structural optimization, and we did not attempt to assess the amount of bridging by optimizing ∠CCO and ∠CCX.

The calculated charges for ions Ph_2C^+X range from +0.165 (X = CF_3) to +0.248 (X = CH_3). These are consistent with the observed chemical shifts, but over the five substituents studied there is only a rough correlation between the observed chemical shift and the charge on the cationic carbon.

The carbonyl carbons of the carboxy, carbomethoxy, benzoyl, trifluoroacetyl, and amide groups are slightly more shielded in the carbenium ions than in the carbinols, while in the acetyl-substituted ion it is less shielded. The physical significance of this difference in behavior escapes us.

Reaction Products. Attempts at extracting products from the reactions of ions **6** in $CD_2Cl_2/ClSO_3H$ usually yielded only water-soluble products, indicating that chlorosulfonation had occurred. However, the reactions in 96% H_2SO_4 at 0 °C over a period of about an hour usually gave ether-soluble products. Under the same conditions but over a much shorter time span ethers **12** were recovered in almost quantitative yield, and these



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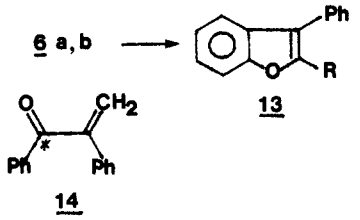
ethers were immediately converted into carbenium ions **6** when redissolved in strong acid. The products and the recovered yields obtained after the carbinols had been dissolved in strong acid for 1 h are given in Table II.

For ions **6** there are two pathways to reaction. For the ketones (R = Me or Ph) the major product is the benzofuran **13** which



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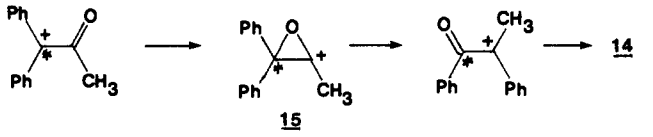
Scheme II



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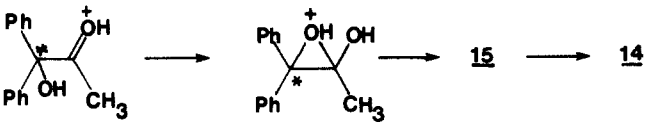
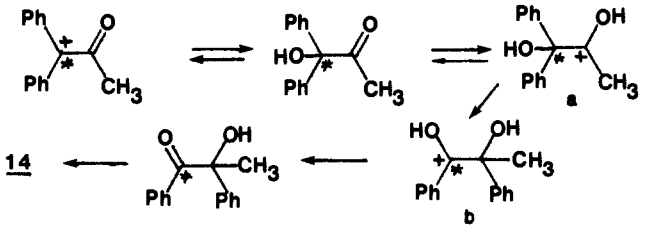
Scheme III



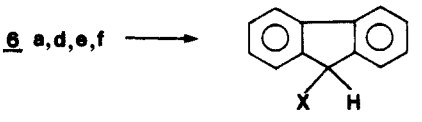
Scheme IV



then undergoes electrophilic attack by another carbenium ion. In the case of the phenyl ketone some benzofuran was isolated (20%), but with the methyl ketone mainly the "dimer" and "trimer" were isolated. The formation of the monomeric methylene ketone **14** specifically labeled at the carbonyl carbon from **6b** labeled at the cationic carbon can be rationalized by a mechanism (Scheme II) involving an oxiranyl cation **15** resulting from carbonyl oxygen bridging.[1] Alternatively, the oxiranyl cation can be formed by oxygen bridging via hydroxyl oxygen as shown in Scheme III.

An alternate plausible mechanism involving a pinacol type rearrangement (Scheme IV) with 1,2-phenyl migration has been suggested by a referee. Although this scheme avoids high-energy strained intermediates and accounts for the labeling pattern, we did not observe any intermediate cations (e.g., a or b) by NMR spectroscopy under stable ion conditions.

For ions in which R is OH, OMe, and NMe_2 and for $Ph_2C^+CF_3$, the major product formed was the fluorene **16** which is obtained by a 4π-electrocyclization in an analogous reaction to that previously observed for pentadienyl cations.[24] Methyl benzilate yielded mainly dimer resulting from electrophilic attack by the carbenium ion **6** (X = COOMe) on the initially formed fluorene.



The position of substitution on the fluorene ring was established unambiguously to be the 2-position by ^1H NMR spectroscopy. This also agrees with the structure postulated for the substituted fluorene previously obtained from the reaction of benzilic acid in sulfuric acid.[25] In our benzilic acid extraction work we did not obtain any of the dimer resulting from electrophilic attack of the fluorene, but clearly the relative yields of the fluorene and its dimer and trimer depend upon the strength of the acid used and particularly upon the concentration of the carbinol in the acid.

Results of Kinetic Study. All reactions were followed by monitoring the rate of disappearance of the carbenium ion using λ_{max} for the ion in the visible spectrum. For each ion duplicate or triplicate runs were performed at each temperature, and the average rate constant is reported in Table III. At the high dilution used in the kinetic runs all ions showed good first-order kinetics.

The $\Delta G^{\ddagger}$ values for all reactions (Table III) are remarkably similar, but we never found any evidence of both cyclization reactions occurring with the same diphenylmethyl cation. Formation of the intermediates leading to both benzofurans and

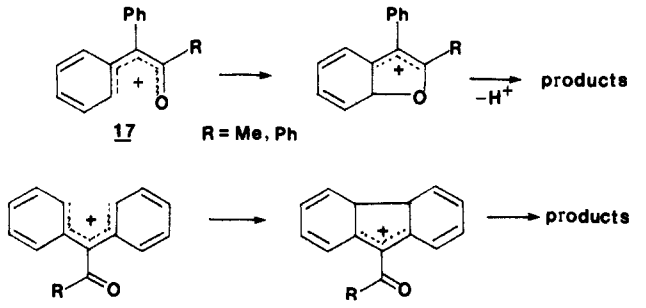
(24) Bladek, R.; Sorensen, T. S. *Can. J. Chem.* **1972**, *50*, 2806.
(25) Dobeneck, H.; Keifer, R. *Justus Liebigs Ann. Chem.* **1965**, *684*, 115.

Table III. Kinetic Data for Rearrangement Reactions of α-Substituted Diphenylmethyl Cations

	rate constants ($\times 10^{-3}$, s^{-1})[a] at T, °C									λ_{max}, nm	$\Delta G^{\ddagger}$, kcal/mol	$\Delta S^{\ddagger}$,[b] eu
	23.3	5	0	−4	−7	−13	−23	−35	−45			
Ph_2C^+COOH										479.4	17.4	−25.4
Ph_2C^+COOMe			6.38		3.79	2.35	1.07			489.4	18.6	−32.0
$Ph_2C^+CONMe_2$				22.3		7.93	1.95	0.521		502.0	17.8	−6.0
Ph_2C^+COMe			30.0		13.2	6.58	1.93			489.4	17.8	−8.6
Ph_2C^+COPh	17.4	3.43	2.20		1.06					492.5	19.3	−20.5
$Ph_2C^+CF_3$						23.8	12.2	4.16	1.56	477.6	17.5	−28.8

[a] Standard deviations on rate constants are ±2%. [b] $\Delta S^{\ddagger}$ was calculated at 273 K.

Scheme V



fluorenes involves holding at least one of the phenyl rings rigid and is expected to have a negative entropy of activation. However we are unable to explain the wide range of negative entropies of activation.

The divergent behavior of the ketones and carboxylic ester derivatives can be rationalized in terms of the relative charge delocalization into the phenyl rings or the carbonyl oxygen. Both cyclizations are analogous to the Woodward–Hoffman allowed electrocyclization (controtatory) of a pentadienyl cation to a cyclopentenyl cation.[24] The benzofuran cyclization can be regarded as an oxa equivalent of this type. It is conceivable that some positive charge is delocalized onto oxygen, and when an oxapentadienyl cation **17** is postulated as a representation of ion **6**, the formation of benzofuran results from electrocyclization and deprotonation of ion **17** (Scheme V). For the carboxylic acid derivatives the presence of an adjacent alkoxy or amido group renders the carbonyl oxygen more nucleophilic by the mesomeric effect and less prone to oxygen cyclization to benzofuran. Furthermore the larger inductive electron-withdrawing tendency of the carboxylic acid and carboalkoxy substituents (as is evident from σ_m-values) would tend to delocalize more positive charge into the aryl rings and favor fluorene cyclization.

The activation energies for decomposition of these ions are quite similar to ones reported by Sorenson for the electrocyclization of methyl-substituted pentadienyl ions[24] where a relationship between charge density, nonbonded interactions leading to nonplanarity of the dienyl system, and rate of the electrocyclization was observed. Assuming that the ions have perpendicular COR groups, i.e., in the plane of the empty p-orbitals as shown by CNDO/2 calculations, then it is appropriate to use the σ_m-values as a measure of the inductive effect. It is interesting that the relative activation energies of the decomposition of ions **6a,d,e–f** follow inversely the order of σ_m-values (σ_m: CF_3 (0.43), COOEt (0.40), COOH (0.36), $CONH_2$ (0.28)). Assuming that the nonbonded interaction is minimal and constant for all of these species the efficiency of fluorene cyclization is dependent on the extent of positive charge delocalization into the phenyl rings. For the ketone derivatives **6b** and **6c** the higher activation energies for oxygen cyclization can be attributed to the lack of symmetrical charge delocalization of such transition states. That these derivatives do not undergo fluorene cyclization implies an even larger activation barrier for this process and less positive charge delocalization into the phenyl rings for the ketone derivatives. The negative entropies of activation in all cases suggest an ordered transition state for decomposition consistent with a concerted electrocyclization. The acetyl group R = $COCH_3$ is inductively more electron withdrawing (σ_m = +0.38) than the amide substituent and about the same as the carboxyl group. However, the lack of oxygen cyclization in the case of the amide and the acid may be associated with neighboring-group interaction of the carbonyl oxygen with the adjacent positive charge, more predominant in the amide and acid than in the acetyl derivative, resulting in an unfavorable orthogonal geometry for oxygen cyclization.

Experimental Section

Melting points were determined on a Reichert melting point apparatus and were uncorrected. Infrared spectra were recorded on Pye Unicam SP1000 and SP3 200 instruments. A Hewlett-Packard 8451A Diode Array spectrophotometer was used to obtain UV spectra. NMR spectra were recorded on a Varian EM360 or CF-20 or a Brucker WH-400 or AM-300 spectrometer. The chemical shifts (ppm) were determined relative to Me_4Si as internal standard. Mass spectra were recorded on a V. G. Micromass 16F spectrometer. A Kiesegel PF_{254} was employed for preparative thin-layer chromatography. A 2-mm layer of adsorbent on a 20- × 20-cm plate was used, and 150–200 mg of material was applied to each plate. Bands were detected by exposure to short-wavelength UV light (254 nm). Benzilic acid was purchased from Aldrich Chemical Co. Tetrahydrofuran and ether were distilled from lithium aluminum hydride under dry nitrogen, and all other solvents were distilled before use.

Preparation of Carbocations. To a frozen (−198 °C) mixture of $ClSO_3H$ in CD_2Cl_2 was added a cooled (−78 °C; *i*-PrOH/dry ice) solution of diarylmethylcarbinol in CD_2Cl_2. The mixture was allowed to warm to −78 °C (*i*-PrOH/dry ice) with gentle mixing so as to obtain a clear solution of carbocations (15% final concentration).

The ^{13}C NMR spectra were recorded by using Brucker WH-400 and AM-300 spectrometers both equipped with a variable-temperature probe. The ^{13}C NMR chemical shifts are referenced to those of the internal Me_4Si or the solvent (CD_2Cl_2) set at 53.8 ppm.

Kinetic Procedure. Kinetic runs were carried out by mixing a few drops of dichloromethane solutions of the keto carbinols (10^{-4} M) with chlorosulfonic acid in dichloromethane (10% v/v) in a UV cuvette housed in a Dewar flask at a set temperature and monitoring the λ_{max} in the visible region with time by using a Carey 14 spectrophotometer. Correlation coefficients for Arrhenius plots were greater than 0.99. Maximum standard deviations for duplicate runs were ±2%.

Preparation of Diphenylmethylcarbinols. **α-Hydroxy-α-phenylbenzeneacetic acid methyl ester** was obtained from diazomethane esterification of the corresponding acid (64%): mp 75 °C;[26] IR (KBr) 1720 (C=O), 3500 cm^{-1} (OH); ^1H NMR ($CDCl_3$, 60 MHz) δ 7.2–7.6 (10 H, m), 4.2 (1 H, s, D_2O exchangeable), 3.8 (3 H, s); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 175.0 (C=O), 141.1 (ipso), 128.0, 127.2, 80.7, 54.0.

***N,N*-Dimethyl-α-hydroxy-α-phenylbenzeneacetamide** was prepared according to Scholkopf's[27] procedure in 80% yield after recrystallization: mp 135 °C; IR (KBr) 3310 (OH), 1625 cm^{-1} (C=O); ^1H NMR ($CDCl_3$, 60 MHz) δ 7.35 (10 H, s), 6.00 (1 H, s, D_2O exchangeable), 2.4–3.30 (6 H, br); ^{13}C NMR (CD_2Cl_2, 100 MHz) δ 172.1 (C=O), 140.9 (ipso), 127.9, 127.8, 127.5, 79.8, 38.9, 37.2.

2-Hydroxy-1,2,2-triphenylethanone was obtained in 80% yield according to the method of Greene:[28] mp 88 °C; IR (KBr) 3480 (OH), 1670 cm^{-1} (C=O); ^1H NMR ($CDCl_3$, 60 MHz) δ 7.7 (2 H, dd, *J* = 8, 2 Hz), 7.2–7.5 (13 H, m), 5.0 (1 H, s, D_2O exchangeable; ^{13}C NMR ($CDCl_3$, 100 MHz) δ 200.6 (C=O), 141.8 (ipso), 134.9 (ipso), 132.7, 130.6, 128.1, 128, 127.9, 84.6.

1-Hydroxy-1,1-diphenyl-2-propanone was made in 50% overall yield by the method of Ioffe:[29] mp 67 °C; IR (KBr) 3420 (OH), 1710 cm^{-1}

(26) *Dictionary of Organic Compounds*; Eyre and Spottiswoode: London, 1965; Vol. 2, p 335.
(27) Banhidai, B.; Scholkopf, U. *Angew. Chem., Int. Ed. Engl.* **1973**, *12*, 836.
(28) Greene, J. L. *J. Am. Chem. Soc.* **1958**, *80*, 3629.

(C=O); ^{1}H NMR ($CDCl_3$, 60 MHz) δ 7.3 (10 H, s), 4.85 (1 H, s, D_2O exchangeable), 2.15 (3 H, s); ^{13}C NMR (CD_2Cl_2, 100 MHz) δ 209.1 (C=O), 141.8 (ipso), 128.6, 128.4, 128.3, 85.9, 26.3.

1-Hydroxy-1,1-diphenyl-3,3,3-trifluoro-2-propanone. Diphenylmethanol trifluoroacetate (prepared from diphenylmethanol, trifluoroacetic anhydride, and pyridine in ether in 99% yield)[31] (2.8 g, 10 mmol) in dry tetrahydrofuran (25 mL) was added dropwise to a cold solution (−78 °C) of lithium diisopropylamide (11 mmol; 1.1 mL of a 10 M solution + 1.54 mL of *i*-Pr_2NH) in dry tetrahydrofuran under a blanket of dry nitrogen. The pale-green solution was allowed to gradually reach room temperature, the brown mixture was poured into aqueous saturated ammonium chloride, and the organic layer was separated, dried, and evaporated, leaving a brown viscous liquid. This was subjected to flash chromatography (10% ethyl acetate in petroleum ether, 60–68 °C), and 50-mL fractions were collected to a total solvent volume of 1000 mL. The desaired hydroxy ketone was eluted in fractions 11–16 contaminated with small amounts of impurities. Pure carbinol was obtained after preparatory thin-layer chromatography (silica gel/benzene) as a colorless oil (R_f 0.55 in benzene; 28%: IR (neat) 3560 (OH), 1760 cm^{-1} (C=O); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.3 (10 H, s), 4.3 (1 H, br, D_2O exchangeable); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 191.4 (q, $^2J_{C-F}$ = 33 Hz, C=O), 136.0 (ipso), 129.4, 128.6, 128.4, 116.4 (q, $^1J_{C-F}$ = 294 Hz, CF_3), 76.3; MS, *m/e* (relative intensity 280 (M^+), 183 ($M^+ - COCF_3$), 105 (100%), 77.

α-Hydroxy-α-(1-naphthyl)benzeneacetic Acid Methyl Ester. 1-Bromonaphthalene (2.07 g, 10 mmol) in dry ether (50 mL) was treated with *n*-butyllithium (10.5 mmol) in dry ether (10 mL) at −78 °C under dry nitrogen. The mixture was allowed to warm up to room temperature, and the white suspension of 1-naphthyllithium was added to methylbenzoyl formate (1.64 g, 10 mmol) in dry ether (20 mL) cooled in an ice bath. After 24 h, the brown mixture was poured into aqueous saturated ammonium chloride, and the ether layer was separated, washed with water, dried, and evaporated to give the hydroxy ester which was purified by recrystallization from ethyl acetate (68%): mp 153–155 °C; IR (KBr) 3530 (OH), 1725 cm^{-1} (C=O); ^{1}H NMR ($CDCl_3$, 60 MHz) δ 8.2–6.96 (12 H, m), 4.37 (1 H, s, D_2O exchangeable), 3.8 (3 H, s); ^{13}C NMR (CD_2Cl_2, 400 MHz) δ 175.4 (C=O), 140.4, 136.8, 133.7, 130.2, 129.4, 128.4, 127.9, 126.2, 125.8, 125.4, 125.3, 123.9, 81.1; MS, *m/e* (relative intensity) 292 (M^+), 233 ($M^+ - CO_2Me$, 100%), 105 (PhC^+O). Anal. Calcd for $C_{19}H_{16}O_3$: C, 78.06; H, 5.52. Found: C, 77.91; H, 5.64.

α-Hydroxy-α-(5-acenaphthyl)benzeneacetic acid methyl ester was prepared in the same manner as above (60%): mp 139–141 °C; IR (KBr) 3545 (OH), 1725 cm^{-1} (C=O); ^{1}H NMR ($CDCl_3$, 80 MHz) δ 7.56–7.06 (10 H, m), 4.20 (1 H, s, D_2O exchangeable), 3.80 (3 H, s), 3.34 (4 H, s); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 175.8 (C=O), 147.5, 146.2, 141.5, 140.2, 133.8, 129.9, 128.2, 128.0, 127.9, 127.2, 121.7, 119.4, 117.9, 81.8, 53.4, 30.5, 29.8; MS, *m/e* (relative intensity) 318 (M^+), 259 ($M^+ - CO_2Me$), 105 (PhC^+=O, 100%). Anal. Calcd for $C_{21}H_{18}O_3$: C, 79.23; H, 5.70. Found: C, 78.98; H, 5.73.

Preparation of ^{13}C-Enriched Diphenylmethylcarbinols. 2-Hydroxy-1,2,2-triphenyl[1-^{13}C]ethanone. Benzoic acid (^{13}C=O, 90%; 0.5 g, 4.1 mmol) was converted to its acid chloride by reaction with thionyl chloride. The crude acid chloride was added to diphenylmethanol (0.75 g, 4.1 mmol) in dry ether (30 mL) containing pyridine (0.35 mL). After 5 days the reaction mixture was applied on preparatory thin-layer chromatography plates (silica gel) and developed in benzene to give ^{13}C-labeled diphenylmethyl benzoate (^{13}C=O) (0.3 g, 25%; (R_f 0.85): mp 90 °C [lit. 92 °C[30]]; IR (Nujol) 1715 (C=O), 1670 cm^{-1} (^{13}C=O); ^{1}H NMR ($CDCl_3$, 60 MHz) δ 8.13 (2 H, dd, *J* = 7, 2 Hz), 7.6–7.1 (14 H, m); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 165.7 (^{13}C=O), 140.6, 133.4, 130, 128.8, 128.7, 128.2, 127.4, 77.7. The ^{13}C-labeled benzoate (170 mg) in dry tetrahydrofuran (1 mL) was added to a cold (−78 °C) solution of lithium diisopropylamide (1 equiv) in dry tetrahydrofuran (10 mL) under dry nitrogen. The dark-blue solution was stirred for 2 h at −78 °C and allowed to warm up to room temperature, and the reaction was quenched with saturated aqueous ammonium chloride. The organic layer was separated, dried, and evaporated to give, after preparatory thin-layer chromatography (silica gel/benzene; R_f 0.34), the labeled hydroxy ketone (44%): mp 88 °C;[28] IR (neat) 3440 (OH), 1640 cm^{-1} (^{13}C=O); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 200.7, 141.9, 132.9, 130.8, 128.3, 128.2, 128.1.

1-Hydroxy-1,1-diphenyl-2-[1-^{13}C]propanone was obtained in 50% overall yield by the literature method[29] using benzophenone (^{13}C=O) (90%): mp 67 °C; IR (neat) 3455 (OH), 1710 cm^{-1} (C=O); ^{1}H NMR ($CDCl_3$, 60 MHz) δ 7.30 (10 H, s), 4.85 (1 H, d, *J* = 2.5 Hz, D_2O exchangeable), 2.15 (3 H, very fine coupling); ^{13}C NMR (CD_2Cl_2/$CDCl_3$, 100 MHz, −80 °C) δ 208.9 (d, $^1J_{^{13}C-^{13}C}$ = 22 Hz), 140.5 (d, $^1J_{^{13}C-^{13}C}$ = 24 Hz), 128.4, 128.1, 128.0, 85.5, 25.9.

Rearrangement Products of Diphenylmethylcarbinols in Concentrated H_2SO_4. **α-Hydroxy-α-phenylbenzeneacetic acid** (1 g, 4.4 mmol) in chloroform (25 mL) was mixed with concentrated sulfuric acid (5 mL, 96%) at room temperature, and the mixture was left stirring overnight. The pale-pink mixture was poured onto crushed ice, and the organic layer was separated, combined with two washings of the aqueous layer, washed with water until neutral, dried, and evaporated, yielding a white solid (1.0 g). Recrystallization from ethanol gave the cyclic diester (11%): mp 195–196 °C [lit.[25] mp 193.5 °C]; IR (KBr) 1760 cm^{-1} (C=O); ^{1}H NMR ($CDCl_3$, 60 MHz) δ 7.2 (20 H, s). The mother liquor was evaporated, and the residue was recrystallized from benzene to give 9*H*-fluorene-9-carboxylic acid (73%): mp 225–227 °C [lit.[25] mp 223 °C]; IR (Nujol) 2300–3300 (OH), 1705 cm^{-1} (C=O); ^{1}H NMR[10] (Me_2SO-d_6, 60 MHz) δ 7.25–7.79 (9 H, m), 4.89 (1 H, s).

α-Hydroxy-α-phenylbenzeneacetic acid methyl ester (1 g, 4.1 mmol) in chloroform (25 mL) was stirred with concentrated sulfuric acid (5 mL, ~96%) at room temperature for 24 h. The pale-yellow mixture was worked up as above to give a colorless oil (1.00 g). Preparative thin-layer chromatography (silica gel/benzene) gave 27% of 9*H*-fluorene-9-carboxylic acid methyl ester (R_f 0.52): mp 63–64 °C [lit.[32] mp 63 °C] IR (KBr) 1735 cm^{-1} (C=O); ^{1}H NMR[10] ($CDCl_3$, 75 MHz) δ 7.77 (2 H, d, *J* = 7.6 Hz), 7.67 (2 H, d, *J* = 7.9 Hz), 7.43 (2 H, *J* = 7.6 Hz), 7.37 (2 H, t, *J* = 7.9 Hz), 4.86 (1 H, s), 3.70 (3 H, s). Starting material (12%; R_f 0.25) and 52% of 2-[2-oxo-2-methoxy-1,1-diphenylethyl]-9*H*-fluorene-9-carboxylic acid methyl ester[39] (R_f 0.36) as a colorless oil: IR (neat, FTIR) 1730.8 and 1738.1 cm^{-1} (C=O); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.67 (1 H, d, *J* = 7.6 Hz), 7.61 (2 H, d, *J* = 7.6 Hz), 7.51 (1 H, s), 7.30–7.20 (13 H, m), 4.77 (1 H, s), 3.76 (3 H, s), 3.60 (3 H, s); MS, *m/e* (relative intensity) 448 (M^+), 389 ($M^+ - CO_2Me$, 100%).

***N,N*-Dimethyl-α-hydroxy-α-phenylbenzeneacetamide** (160 mg, 0.63 mmol) in glacial acetic acid (5 mL) was treated with concentrated sulfuric acid (~96%) dropwise until no red coloration was observed. After an aqueous workup a yellow oil was obtained which on recrystallization (EtOH/pentane 1:1) yielded *N,N*-dimethyl-9*H*-fluorene-9-carboxamide (80g): mp 159–161 °C [lit.[33] mp 156.5–158.0 °C]; IR (KBr) 1640 cm^{-1} (C=O); ^{1}H NMR[10] ($CDCl_3$, 400 MHz) δ 7.76 (2 H, d, *J* = 7.1 Hz), 7.51 (2 H, d, *J* = 7 Hz), 7.39 (2 H, t, *J* = 7.1 Hz), 7.31 (2 H, t, *J* = 7.1 Hz), 5.08 (1 H, s), 2.95 (3 H, s), 2.35 (3 H, s); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 170.8 (C=O), 142.2, 140.9, 127.8, 127.6, 124.4, 120.4, 55.6, 36.6, 36.4; MS, *m/e* (relative intensity 237 (M^+), 192 ($M^+ - NMe_2$), 165 ($M^+ - CONMe_2$), 72 ($CNMe_2$, 100%).

2-Hydroxy-1,2,2-triphenylethanone (800 mg, 2.8 mmol) in chloroform (10 mL) was stirred with concentrated sulfuric acid (1 mL, ~96%) at room temperature for 24 h. The mixture was worked up as before to give a yellow oil which was separated by preparative thin-layer chromatography (silica gel/benzene) to give the following compounds. 2,3-Diphenylbenzo[*b*]furan (R_f 0.90; 20%: mp 124 °C [lit.[36] mp 123 °C]; IR (KBr) 1490, 1445, 1300, 1060, 1010, 990, 700 cm^{-1}; ^{1}H NMR[13] ($CDCl_3$, 75 MHz) δ 7.1–7.7 (multiplets); ^{13}C NMR ($CDCl_3$, 400 MHz) δ 141.9, 140.9, 132.8, 129.8, 129.2, 129.0, 128.4, 127.6, 127.2, 126.9, 125.9, 124.7, 122.9, 120.0, 111.1; MS, *m/e*[38] (relative intensity) 270 (M^+, 100%), 241 ($M^+ - HCO$), 239, 165 ($M^+ - PhCO$); UV λ_{max} (MeOH) 214, 304 nm. 6-[2-(1,2,2-Triphenylacetyl]-2,3-diphenylbenzo[*b*]furan[37] (R_f 0.79): mp 83–85 °C; IR (KBr) 1680 cm^{-1} (C=O); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.08–7.75 (several multiplets); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 198.5 (C=O), 143.3, 140.4, 132.6, 131.7, 131.0, 130.9, 129.6, 128.9, 128.4,

(29) (a) Ioffe, D. V. *Zh. Obshch. Khim.* **1965**, *35*, 1851; *Chem. Abstr.* **1966**, *64*, 3396g. (b) Upton, C. J.; Beak, P. *J. Org. Chem.* **1975**, *40*, 1094. (c) Koenig, K. E.; Weber, W. P. *Tetrahedron Lett.* **1974**, 2275. (d) Oakwood, T. S.; Weisgerber, C. A. *Org. Synth.*; Wiley: New York, 1955; Collect. Vol. III, p 114.

(30) Micha-Screttas, M.; Screttas, C. G. *J. Org. Chem.* **1977**, *42*, 1462.

(31) IR (neat) 1780 cm^{-1} (CF_3C=O); ^{1}H NMR ($CDCl_3$, 60 MHz) δ 7.20 (10 H, s), 6.87 (1 H, s).

(32) *Dictionary of Organic Compounds*; Eyre and Spottiswoode: London, 1965; Vol. 3, p 1440.

(33) Bavin, P. M. G. *Can. J. Chem.* **1964**, *42*, 1409.

(34) Bartle, K. D.; Jones, D. W. *J. Chem. Soc. B* **1971**, 388.

(35) This reaction was erroneously reported to give 3,3-diphenylazetidin-2-one under the same conditions. See: Petyunin, P. A.; Petyunin, G. P. *J. Org. Chem. USSR* (*Engl. Transl.*) **1972**, *8*, 373. An authentic sample of *N,N*-dimethyl-9*H*-fluorene-9-carboxamide was prepared by an independent method[33] and was shown by IR, ^{1}H NMR, and ^{13}C NMR spectroscopies and mixed melting point to be identical with our product.

(36) Arventi, B. I. *Bull. Soc. Chim. Fr.* **1936**, 598.

(37) Barboiu, V.; Wexler, H.; Arventiev, B. *Org. Magn. Reson.* **1974**, *6*, 327.

(38) Verbrel, J.; Roche, M.; Gore, J. *Org. Mass Spectrom.* **1977**, *12*, 751.

(39) Electrophilic substitution on fluorene occurs exclusively at the 2-position; for example, see: Brown, H. C.; Marino, G. *J. Am. Chem. Soc.* **1962**, *84*, 123.

127.8, 127.6, 127.2, 126.9, 119.0, 113.1; MS, *m/e* (relative intensity) 540 (M^+), 511 (M^+ - HCO), 435 (M^+ - PhCO, 100%); UV λ_{max} (MeOH) 214, 313 nm.

1-Hydroxy-1,1-diphenyl-2-propanone (0.5 g, 2.2 mmol) in chloroform (20 mL) was stirred with concentrated sulfuric acid (2 mL) at 0 °C for 4 h. After an aqueous workup a red oil was obtained which on preparative thin-layer chromatography (silica gel/benzene) gave the following compounds. 1,2-Diphenyl-2-propen-1-one (20%; R_f 0.79): mp 28 °C [lit. mp 28 °C];[40] IR (neat) 1680 cm^{-1} (C=O); ^1H NMR ($CDCl_3$, 60 MHz) 7.96 (2 H, d, J = 2.7 Hz), 7.27-7.64 (8 H, m), 6.07 (1 H, s), 5.64 (1 H, s); ^{13}C NMR ($CDCl_3$, 75 MHz) 197.4 (C=O), 148.2, 137.1, 133.0, 129.9, 128.6; 128.4, 127.00, 120.7.[41] 6-[1-(1,1-Diphenyl-2-oxopropyl)-2-methyl-3-phenylbenzo[*b*]furan (R_f 0.55; 20%): mp 153-155 °C; IR (neat) 1710 cm^{-1} (C=O); ^1H NMR ($CDCl_3$, 60 MHz) δ 7.15-7.50 (18 H, m), 2.46 (3 H, s), 2.12 (3 H, s); UV λ_{max} (EtOH) 210, 234 (sh), 262 nm; MS, *m/e*[42] (relative intensity) 386, 373 (M^+ - $COCH_3$), 295, 252, 165, 43. Bis[1-(1,1-diphenyl-2-oxopropyl)]-substituted 2-methyl-3-phenylbenzo[*b*]furan (R_f 0.24; 51%): mp 145-148 °C; IR (neat) 1715 cm^{-1} (br, C=O); ^1H NMR ($CDCl_3$, 400 MHz) δ 2.13 (3 H, s), 2.16 (3 H, s), 2.53 (3 H, s), 7.09-7.52 (27 H, m); UV λ_{max} (EtOH) 208, 234 (sh), 270 nm; MS, *m/e* (relative intensity) 581 (M^+ - CMe, 100%), 538 (M^+ - $2CCH_3$), 373, 165, 43.

α-Phenyl-α-(trifluoromethyl)benzenemethanol[43] (0.5 g, 2.00 mmol) in chloroform (50 mL) was stirred with concentrated sulfuric acid (2 mL) at 0 °C for 2 h. After an aqueous workup a yellow oil (0.5 g) was obtained which on preparative thin-layer chromatography ((silica gel/benzene)-hexane 1:1) gave 9-(trifluoromethyl)-9*H*-fluorene (25%; R_f 0.73): mp 95-97 °C [lit.[44] mp, 95.5-96.5 °C]; ^1H NMR ($CDCl_3$, 60 MHz) δ 7.10-7.73 (8 H, m), 4.54 (1 H, 9, $^1J_{F-H}$ = 9.5 Hz, CH-CF_3). Also obtained was unreacted starting material (50%; R_f 0.11).

Registry No. 6a, 89196-84-9; **6b**, 38252-89-0; **6c**, 87963-52-8; **6d**, 38252-97-0; **6e**, 38252-93-6; **6f**, 103192-03-6; 9-trifluoromethylfluorene, 1554-95-6; (2-oxo-1,1-diphenylpropyl)-2-methyl-3-phenylbenzofuran, 103150-67-0; bis(2-oxo-1,1-dimethylpropyl)-2-methyl-3-phenylbenzofuran, 103150-68-1; 1,2-diphenylprop-2-en-1-one, 4452-11-3; 2,3-diphenylbenzofuran, 13054-95-0; (2-oxo-1,1,2-triphenyl)-2,3-diphenylbenzofuran, 103150-69-2; 9-fluorenecarboxylic acid, 1989-33-9; 3,3,6,6-tetraphenyl-2,5-*p*-dioxanedione, 467-32-3; methyl 9-fluorenecarboxylate, 3002-30-0; 2-(α,α-diphenylacetic acid)-9-fluorenecarboxylic acid dimethyl ester, 103192-04-7; *N,N*-dimethyl-9-fluorenecarboxamide, 31859-84-4.

(40) Kopinski, R. P.; Pinhey, J. *Aust. J. Chem.* **1983**, *36*, 311.
(41) An authentic sample of 1,2-diphenyl-2-propen-1-one was obtained by phosphorus pentoxide dehydration of 2-hydroxy-1,2-diphenyl-1-propanone and was shown by ^1H NMR, IR, and ^{13}C NMR spectroscopies and TLC to be identical with our sample.
(42) Cardillo, G.; Cricchio, R.; Merlini, L. *Tetrahedron* **1971**, 1875.
(43) Olah, G. A.; Pittman, C. U., Jr. *J. Am. Chem. Soc.* **1966**, *88*, 3310.
(44) Streitwieser, A., Jr.; Marchand, A. P.; Pudjaatmaka, A. H. *J. Am. Chem. Soc.* **1967**, *89*, 693.

Mechanisms for the Removal of Benzyl Protecting Groups in Synthetic Peptides by Trifluoromethanesulfonic Acid-Trifluoroacetic Acid-Dimethyl Sulfide

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Abstract: The need to improve peptide synthesis has led to the development of less acidic and milder S_N2 deprotection conditions to remove benzyl protecting groups and to avoid reactive carbocations associated with the conventional S_N1 conditions. To further understand the relationships of both mechanisms and the acidity of the reaction, the S_N1 and S_N2 deprotection mechanisms for synthetic peptides with *O*-benzyl protecting groups were studied in a ternary mixture of trifluoromethanesulfonic acid (TFMSA)-trifluoroacetic acid (TFA)-dimethyl sulfide (DMS). Kinetic studies of the deprotection rate-acid profiles of *O*-benzylserine in sets of experiments containing predetermined amounts of DMS revealed sharp changeover points in the mechanism from S_N2 ($A_{AL}2$) to S_N1 ($A_{AL}1$) when the concentration of TFMSA in TFA was increased. Similar changeover points in mechanism were also found in the deprotection product-acid profiles of *O*-benzyltyrosine. The activities of DMS required for the S_N2 reaction were determined by ^1H NMR, and the acidities of the reaction media were calculated from the Yates-McClelland equation. The changeover points were found to be in the range where DMS activities were approaching zero. In general, the reaction mechanism depended on the activity of DMS and the acidity of the reaction mixture. The S_N1 deprotection mechanism predominated at high acidities and low DMS activities. S_N2 reaction mechanisms were observed at moderate acidities and high DMS activities. On the basis of the changeover points, a mechanism-reagent composition diagram could be constructed in the form of an equilateral triangle in which the S_N1 and S_N2 regions could be defined as a function of reagent composition. Furthermore, from the mechanistic considerations, a practical mixture for the S_N2 deprotection reaction was found to be TFMSA-TFA-DMS-*m*-cresol (10:50:30:10 (v/v)). For the deprotection of Trp(For)-containing peptides, the reagent was adjusted to TFMSA-TFA-DMS-*m*-cresol-ethanedithiol (10:50:30:8:2 (v/v)) so that the N^{in}-formyl could be removed concomitantly with other protecting groups. Both deprotection mixtures also converted Met(O) to Met efficiently.

The fundamental design of most protecting group strategies in peptide synthesis is based on the differential lability of protecting groups in acids.[1,2] A popular and widely used version is the combination of N^{α}-*tert*-butyloxycarbonyl and side-chain benzyl protection. Usually, a strong anhydrous acid in an S_N1 mechanism is employed in the final step to remove all the benzyl protecting groups.[3,4] Because of the strong acidity attendant with the S_N1

(1) Related papers of this work: (a) Tam, J. P.; Heath, W. F.; Merrifield, R. B. *Tetrahedron Lett.* **1982**, *23*, 2939-2942. (b) Heath, W. F.; Tam, J. P.; and Merrifield, R. B. *J. Chem. Soc., Chem. Commun.* **1982**, 896-897. (c) Tam, J. P.; Heath, W. F.; Merrifield, R. B. *Tetrahedron Lett.* **1982**, *23*, 4435-4438. (d) Tam, J. P.; Heath, W. F.; Merrifield, R. B. *J. Am. Chem. Soc.* **1983**, *105*, 6442-6455. (e) Tam, J. P.; Heath, W. F.; Merrifield, R. B. *Int. J. Peptide Protein Res.* **1983**, *21*, 57-65. (f) Tam, J. P.; Heath, W. F. In *Proceedings of the 7th American Peptide Symposium*; Hruby, V. J., Rich, D. H.; Ed.; Pierce Chemical Co.: Chicago, 1983; pp 83-86.

(2) (a) Merrifield, R. B. *J.* Am. *Chem. Soc.* **1963**, *85*, 2149-2154. (b) Merrifield, R. B.; Vizioli, L. D.; Boman, H. G. *Biochemistry* **1982**, *21*, 5020-5031. (c) Anderson, G. W.; Blodinger, J.; Welcher, A. D. *J. Am. Chem. Soc.* **1952**, *74*, 5309-5312. (d) Schwyzer, R.; Sieber, P. *Nature (London)* **1963**, *199*, 172-174.
(3) Sakakibara, S. In *Chemistry and Biochemistry of Amino Acids, Peptides, and Proteins*; Weinstein, B., Ed.; Dekker: New York, 1971; Vol. 1, pp 51-85.

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