cytochrome oxidase can be observed directly by CO-FTIR at $T \leq 180$ K.[2,4] Above this temperature Cu_B^+–CO has not been observed by conventional FTIR measurements, because the thermodynamically stable Fe_{a3}^{2+}–CO reforms too rapidly. Figure 2A shows the CO-FTIR absorbance difference spectrum (*before* minus *after* photodissociation) recorded at 127 K. The positive peaks represent CO bound to the heme a_3 (1963 and ca. 1949 cm^{-1}), and the negative peak at 2061 cm^{-1} represents CO bound to Cu_B^+. A minor Cu–CO peak, which decreases in intensity with increasing temperature,[2,4] is observed at ~2045 cm^{-1} at 127 K. The temperature invariance of the 2061 cm^{-1} frequency between 20 and 180 K[2,4] suggests that the frequency of the Cu_B^+–CO absorption at ambient temperature is close to this value. Accordingly, the time-resolved infrared absorption was followed at 2061 cm^{-1}, with control experiments at 2070 and 2042 cm^{-1} where the complex should not absorb (Figure 2B). The observation of the infrared transient at 2061 cm^{-1} and its absence at the higher and lower frequencies clearly demonstrate the room temperature binding of CO to Cu_B^+, following photodissociation of CO from the heme a_3. The Cu_B^+–CO intermediate subsequently decays to form the unliganded oxidase and free CO.

Our observations can be understood in the context of the following kinetics model of the mechanism of CO photodissociation and rebinding. In Scheme I pulsed illumination of the stable aa_3–CO complex yields the geminate photodissociated species, probably on subpicosecond time scale.[14] The k_3 and k_{-1} processes, which represent the formation of Cu_B^+–CO and the subsequent loss of CO into solution, respectively, are responsible for the infrared transient in Figure 2B. We have established in other work that the competing pathway (k_2) for decay of Cu_B^+–CO, the transfer of CO from Cu_B^+ to Fe_{a3}^{2+}, occurs on a much slower time scale with a half-life of 1 ms.[4] The apparent risetime of the Cu_B^+–CO transient, $t_{1/2} = 220$ ns, is equal to the effective time constant of our instrumentation. Hence, we cannot measure k_3 by using the present approach. Subsequent to its appearance Cu_B^+–CO decays with a first-order rate constant (k_{-1}) of $(4.7 \pm 0.6) \times 10^5$ s^{-1}, corresponding to a half-life of 1.5 ± 0.2 μs. The results obtained for glycerol- and non-glycerol-containing enzyme solutions were experimentally the same.

We emphasize the importance of the time-resolved infrared approach in establishing the precise chemical nature of the kinetics. Our measurements were made by following the infrared transient absorbance associated with a specific structural feature of the system, namely the C–O stretching frequency of the Cu_B^+–CO complex. Accordingly, there is no ambiguity in the assignment of the transient to the molecular phenomenon at issue, as there often is in kinetic UV–vis spectrophotometry.

These results provide the first direct evidence for a Cu_B^+–CO intermediate prior to the formation of the thermodynamically stable Fe_{a3}^{2+}–CO complex in eukaryotic cytochrome oxidase at room temperature. Details of the above reaction scheme will be reported elsewhere.[4] The lifetime of the Cu_B^+–CO complex is comparable to the time scale attributed to the formation of the Fe_{a3}^{2+}–O_2 intermediate in the flow-flash kinetics,[12] hence it is possible that the loss of CO by Cu_B^+ is the rate-determining step in the formation of the heme–O_2 adduct. Alternatively, the facts may indicate that the lifetime of Cu_B^+–CO is too short to interfere directly with the reaction of the oxidase with O_2. Even in the latter case, indirect effects upon the O_2 kinetics are possible. The room temperature observation of Cu_B^+–CO in the present study as well as in cytochrome ba_3[3] suggests the possibility that the binding of incoming ligands to Cu_B, and the "ligand shuttle" function, may be general mechanistic features of cytochrome oxidase reactivity.

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Registry No. Cu, 7440-50-8; CO, 630-08-0; cytochrome oxidase, 9001-16-5.

Exceptionally Stable Phenyldichlorocarbenium Ion as a Friedel–Crafts Intermediate: A High-Field Multinuclear NMR Study

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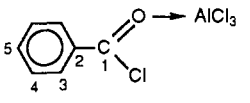
Halogenated carbocations play an important role as intermediates in a variety of organic reactions.[1-3] Nearly two decades ago, Olah and co-workers demonstrated that stable and long-lived halogenated alkylcarbenium ions could be obtained in strongly acidic media such as FSO_3H–SbF_5–SO_2, HF–SbF_5–SO_2ClF, and SbF_5–SO_2 at low temperatures ranging from −60 to −120 °C.[4-6] They have shown further that the halogenated arylcarbenium ions could also be directly observed by NMR spectroscopy under similar conditions at −30 to −80 °C.[4b,7] Interestingly, although many of the commercially important Friedel–Crafts syntheses[8] might actually involve the intermediacy of the halogenated arylcarbenium ions, their existence has never been proven under such conditions. Thus, nothing is known regarding the existence and stability of these ions is common organic solvents at 25 °C. We report here, for the first time, the intermediacy of an exceptionally stable phenyldichlorocarbenium tetrachloroaluminate complex (**4**) in the Friedel–Crafts reaction of acetanilide with benzotrichloride and $AlCl_3$ in ethylene dichloride at 25 °C and its characterization by the high field ^1H, ^{13}C, and ^{27}Al NMR spectroscopy.



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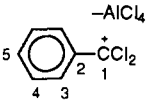

4

Methyl (5-benzoylbenzimidazol-2-yl)carbamate (known as Mebendazole) is an important human and veterinary broad spectrum anthelmintic drug.[9] As part of our research on the synthesis of potential anthelmintic drugs which are structurally analogous to Mebendazole, we needed to prepare 4-acetamidobenzophenone.[10] In this connection, we observed that while the

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Table I. The ^1H, ^{13}C, and ^{27}Al Spectral Data for **1–4**[a]

compd	^1H[b]	^{13}C[f] C_1	C_2	C_3	C_4	C_5	^{27}Al[i]
1	7.50 (dt, J = 1.5, 7.8 Hz, 2 H)	168.07	133.22	131.20	128.80	135.12[g]	
	7.67 (tt, J = 1.4, 7.5 Hz, 1 H)	167.51	132.60	130.72	128.46	134.88[h]	
	8.12 (m, 2 H)[c]						
2	7.75 (t, J = 8 Hz, 2 H)	192.05	130.53	135.71	130.74	143.73[g]	98[g]
	8.12 (t, J = 7.5 Hz, 1 H)	191.62	129.33	134.76	129.64	143.01[h]	99[h]
	8.44 (dd, J = 1.2, 8.5 Hz, 2 H)[d]						
3	7.42 (m, 3 H), 7.92 (m, 2 H)[c,e]	97.55	144.10	128.14	125.29	130.09[g]	
		97.32	143.65	128.00	124.94	130.01[h]	
4	8.02 (t, J = 8 Hz, 2 H)	209.76	140.53	144.08	134.11	160.00[g]	92[g]
	8.78 (t, J = 7.4 Hz, 1 H)	209.53	140.06	143.43	133.43	159.39[h]	93[h]
	8.86 (d, J = 7.8 Hz, 2 H)[d]						

[a] The ^1H NMR spectra were recorded in $CDCl_3$ only, whereas the ^{13}C and ^{27}Al spectra were recorded in both ethylene dichloride and $CDCl_3$. [b] The chemical shifts (in ppm) correspond to meta, para, and ortho protons, respectively. [c] Referred to internal TMS. [d] Referred to TMS of the corresponding uncomplexed parent compounds. [e] The meta and para protons are grouped together. [f] Referred to external capillary TMS. [g] Recorded in $CDCl_3$. [h] Recorded in ethylene dichloride. [i] ^{27}Al chemical shifts are with reference to $Al(H_2O)_6^{3+}$ at 0 ppm.

Friedel–Crafts acylation of acetanilide with benzoylchloride and $AlCl_3$ (3 equiv) in ethylene dichloride at 25 °C fails,[11] the Friedel–Crafts alkylation of acetanilide with benzotrichloride and $AlCl_3$ (3 equiv) under identical conditions provides 4-acetamidobenzophenone in a quantitative fashion.[12,13] Intrigued by this result, we decided to systematically establish the nature of the reaction intermediates by the high field multinuclear NMR spectroscopy.[14] Table I summarizes the ^1H, ^{13}C, and ^{27}Al NMR spectral data for benzoyl chloride (**1**), benzoyl chloride–$AlCl_3$ complex (**2**),[15] benzotrichloride (**3**), and benzotrichloride–$AlCl_3$ complex (**4**) in ethylene dichloride (EDC) or $CDCl_3$ at 25 °C.

A comparison of the ^1H NMR chemical shifts of benzoyl chloride (**1**) with those of benzoyl chloride–$AlCl_3$ complex (**2**) shows that the meta, ortho, and para protons of the complex **2** are deshielded, the difference being the following: $\Delta\delta^{1,2}$ (H_{meta}) = 0.25, $\Delta\delta^{1,2}$ (H_{para}) = 0.45, $\Delta\delta^{1,2}$ (H_{ortho}) = 0.32 ppm. These ^1H NMR chemical shift changes indicate the acquisition of positive charge by the carbonyl carbon of the complex **2** and the delocalization of the charge by mesomeric interaction. Similarly, a comparison of the ^1H NMR chemical shifts of benzotrichloride (**3**) and benzotrichloride–$AlCl_3$ complex (**4**) shows that the meta, para, and ortho protons of the complex **4** are deshielded[4b] even more significantly (2.5–3 times) than in the case of **2**: $\Delta\delta^{3,4}$ (H_{meta}) = 0.60, $\Delta\delta^{3,4}$ (H_{para}) = 1.36, $\Delta\delta^{3,4}$ (H_{ortho}) = 0.94 ppm. Evidently, the carbon atom bearing the ionizable chlorine substituents of complex **4** has acquired a significantly greater carbocation character compared to the carbonyl carbon of **3**. This phenomenon is even more explicit in the ^{13}C NMR spectral data.

The ^{13}C NMR spectra of **1–4** could be recorded in both $CDCl_3$ or EDC, and we found that solvent has no major effect on chemical shifts (Table I). However, for consistency, the chemical shifts in $CDCl_3$ will be used for discussion.

A comparison of the ^{13}C NMR spectral data of benzoyl chloride (**1**) and benzoyl chloride–$AlCl_3$ complex (**2**) reveals two important features: The carbonyl carbon C-1 of the complex **2** is deshielded, while the quarternary carbon atom C-2 is shielded. The differences in the ^{13}C chemical shift values are as follows: $\Delta\delta^{1,2}$ (C1) = 23.98, $\Delta\delta^{1,2}$ (C2) = −2.69, $\Delta\delta^{1,2}$ (C3) = 4.51, $\Delta\delta^{1,2}$ (C4) = 1.94, and $\Delta\delta^{1,2}$ (C5) = 8.61 ppm. Similarly, a comparison of the ^{13}C NMR spectra of benzotrichloride (**3**) and benzotrichloride–$AlCl_3$ complex (**4**, Figure 1) clearly reveals a remarkable deshielding experienced by the carbon atom C-1 of the complex **4**. Here the differences in the ^{13}C chemical shift values are as follows: $\Delta\delta^{3,4}$ (C_1) = 112.21, $\Delta\delta^{3,4}$ (C_2) = −3.57, $\Delta\delta^{3,4}$ (C_3) = 15.94, $\Delta\delta^{3,4}$ (C_4) = 8.82, and $\Delta\delta^{3,4}$ (C_5) = 29.91 ppm. A comparison of the differences in the ^{13}C chemical shift values $\Delta\delta^{3,4}$ (C_n, n = 1–5) with those of $\Delta\delta^{1,2}$ (C_n, n = 1–5) clearly indicates the much higher degree of positive charge associated with the carbon atom C-1 of the complex **4** as compared to C-1 of complex **2**.

This strongly supports the donor–acceptor structure[15] for **2** and the carbenium ion structure for **4**.[4b] Surprisingly, the ^{13}C spectrum of the complex **4** in EDC did not show any change, even after 2 weeks at 25 °C, demonstrating its unusually high stability.

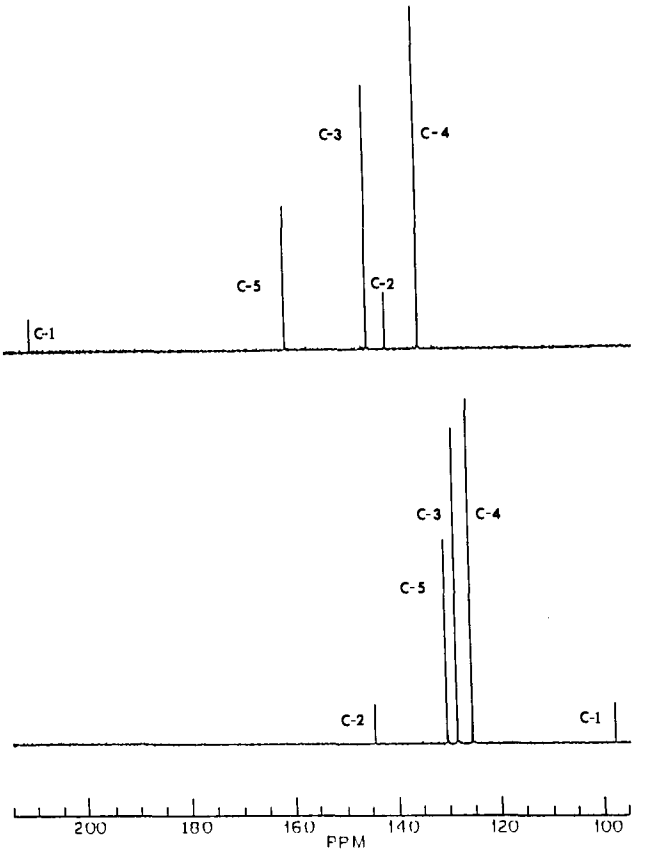

Figure 1. A comparison of ^{13}C NMR spectra of (a) benzotrichloride (**3**, below) and (b) benzotrichloride–$AlCl_3$ complex (**4**, above) in EDC at 25 °C.

(11) The experimental procedure is as follows: To a vigorously stirred mixture of aluminum chloride (20 g, 0.15 mol) in ethylene dichloride (75 mL) at 0 °C was added benzoyl chloride (7.10 g, 0.05 mol) dropwise over 0.5 h. Subsequently, acetanilide (6.8 g, 0.05 mol) was added portionwise, while the stirring was continued for 4 h at 25 °C. Finally, the reaction mixture was poured on ice, warmed to 70 °C for 0.5 h and worked up in the usual manner. Benzoic acid (4.6 g, 75%) and acetanilide were recovered.

(12) The procedure is as described in ref 11, except that benzotrichloride (10.8 g, 0.05 mol) was used instead of benzoyl chloride to obtain 4-acetamidobenzophenone (11.78 g, 98%).

(13) 4-Acetamidobenzophenone was obtained in poor yield when stoichiometric amount of aluminum chloride was employed. See ref 11.

(14) All NMR spectra were recorded on a Bruker MSL-300 MHz spectrometer.

(15) To the best of our knowledge, this paper reports for the first time the ^1H, ^{13}C, and ^{27}Al spectra for this particular complex. Previously, the structure of **4** was investigated by IR spectroscopy and X-ray analysis. See: (a) Susz, B. P.; Cassimatis, D. *Helv. Chim. Acta* **1961**, *44*, 395. (b) Rasmussen, S. E.; Broch, N. C. *Chem. Commun.* **1965**, 289. (c) Rasmussen, et al. *Acta Chem. Scand.* **1966**, *20*, 1351.

The ^{27}Al NMR spectra recorded for the complexes **2** and **4** in EDC or $CDCl_3$ (Table I) showed that the aluminum nucleus is more shielded in **4** than in **2**, in further support of the proposed structures shown above.[16] Thus, the NMR evidence clearly points out the intermediacy of **4** in the Friedel–Crafts reaction of acetanilide with benzotrichloride and $AlCl_3$ in EDC at 25 °C. While it is known that aryldihalocarbenium ions could be observed in SbF_5–SO_2ClF and SbF_5–SO_2 solutions at −30 to −80 °C,[4b,7] the present study demonstrates, for the first time, that it is possible to obtain exceptionally stable aryldihalocarbenium ions such as **4** under milder Friedel–Crafts reaction conditions in EDC at 25 °C.

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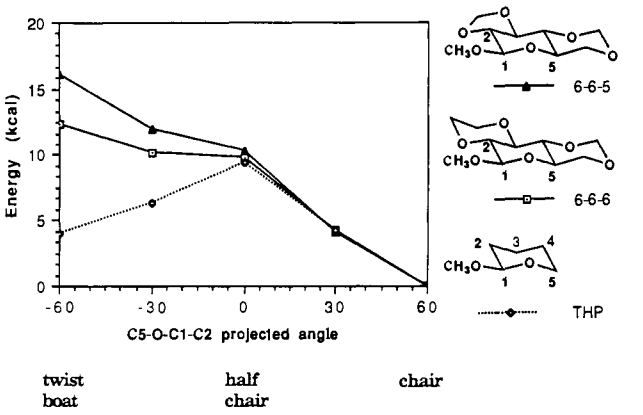
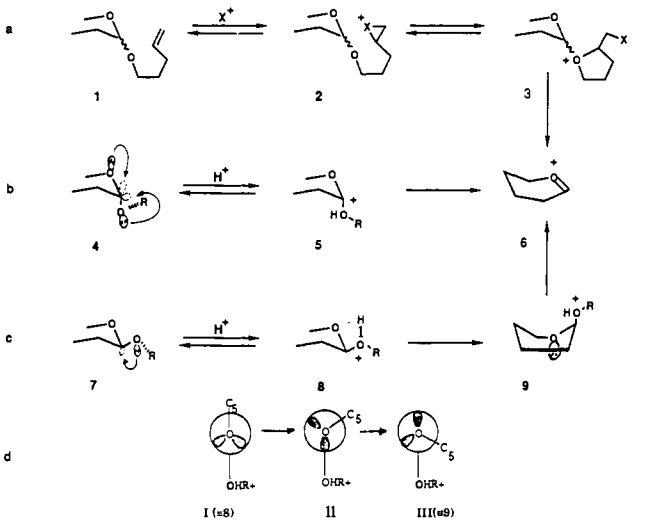


Figure 1. MM2 energies for chair → twist-boat changes.

Scheme I



Previous laboratory examination of the stereoelectronic requirements for glycoside hydrolysis have relied on kinetic isotope measurements,[18] the presence of "spontaneous" leaving groups at the anomeric center,[19,20] the study of conformationally biased systems,[20] and studies of sulfur analogues.[21] However, notably absent have been authentic carbohydrate derivatives that are so conformationally restrained that the stereochemical options available are unequivocally defined. In this manuscript, we describe our studies on such systems.

Questions of glycoside hydrolysis and stability of anomers are inevitably interwoven, and the unusual characteristics of the latter were captured in the term "anomeric effect", coined by Lemieux in 1958.[22] The phenomenon, originally attributed to dipole–dipole interactions,[23] was interpreted subsequently in terms of frontier orbital ($n\sigma^*$) perturbations by Altona.[24]

The latter description provided a launching point for the theory of "stereoelectronic control" in glycoside hydrolysis by Deslongchamps,[16] who postulated that an electron lone pair needs to be antiperiplanar to the bond being broken (i.e., the antiperiplanar lone pair hypothesis, ALPH). Thus, for α glycosides **4** (Scheme

Concerning the Antiperiplanar Lone Pair Hypothesis: Oxidative Hydrolysis of Conformationally Restrained 4-Pentenyl Glycosides[1]

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We recently reported that *n*-pentenyl acetals, **1**, can be readily hydrolyzed under neutral conditions with halonium ions,[4] and this discovery has been subsequently applied synthetically for chemospecific liberation of the anomeric center[5] and for the direct coupling of pentenyl glycosides to form oligosaccharides.[6–8] The reaction provides a novel opportunity to examine the mechanism of acetal hydrolysis without using acids, a matter which is of particular interest for laboratory[9–11] and enzymatic[12] studies of glycoside cleavage, where questions continue to be raised about the activation site[13–15] and the stereochemical requirements[16,17] of bond cleavage.

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