

Communications to the Editor

Reactions in Inclusion Molecular Complexes. 2.¹ A Topochemical Solid-State Photoaddition of Acetone to Deoxycholic Acid

Sir:

The advantages of utilization of molecular crystals for the performance of topochemical biomimetic functionalization have been demonstrated recently in the one-step regioselective and stereospecific hydroxylation of deoxycholic acid.¹

Remote oxidations of steroids via photoaddition reactions of ketones in solutions have been successfully accomplished by Breslow et al.² Extension of these reactions to organic crystals might lead to cleaner and more stereospecific transformations. However, exploitation of this approach demands a better understanding of the detailed conditions required for their successful accomplishment.

As convenient models we have selected the molecular complexes of deoxycholic acid (**1**) and apocholic acid (**7**) with aliphatic and aromatic ketones. Recent studies by Scheffer, Trotter, et al.³ have demonstrated the occurrence of intramolecular lattice-controlled photoinduced abstraction of allylic hydrogens by a keto group in the solid state. Here we wish to report the first successful intermolecular topochemical photoaddition of acetone to **1** in the crystalline phase.

1 forms a well-defined 2:1 molecular complex with acetone, mp 170–175 °C. Irradiation of the solid leads to the formation of the three major products, as shown in Scheme I:⁴ **2** (20%), mp 177–180 °C; **3** (4%), mp 213–215 °C; and **4** (2%), 218–221 °C.

The stereochemistries of these products follows from comparison of their ¹³C NMR spectra with that of **1** previously assigned by Leibfritz and Roberts.⁵ The ¹³C chemical shifts of compounds **1–4**⁶ are summarized in Table I. A careful assignment of the spectra clearly demonstrates that no change had occurred at ring C,D and at the side chain, suggesting that the addition has occurred in the region of ring A or B with conservation of the A/B cis junction in all three products.

The structure of **4** could be assigned as resulting from addition of acetone to position 5β of **1**, since the reaction is as-

Scheme I

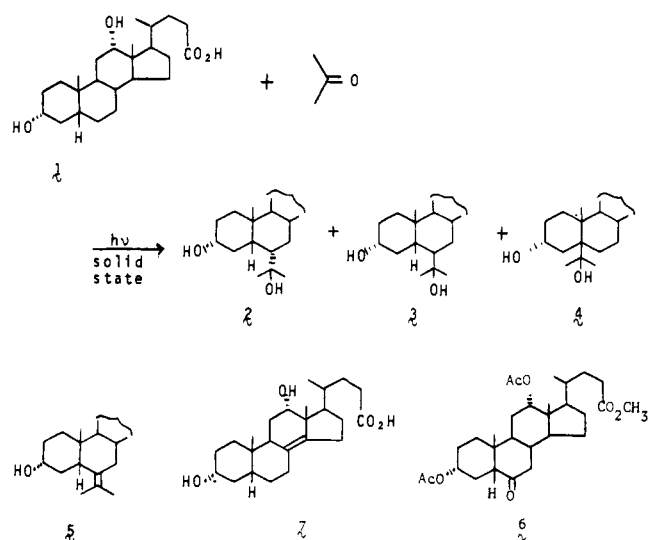


Table I. ¹³C Chemical Shifts of Compounds **1–4**^a

	1 (CD ₃ OD)	2 (CD ₃ OD)	3 (CD ₃ OD)	4 (CD ₃ COOD) ^b
C ₁	36.5	36.7	36.5	32.1
C ₂	30.9	30.7	30.5	29.0
C ₃	72.5	72.6	71.4	69.4
C ₄	37.4	45.7	36.0	37.3
C ₅	43.6	46.3	42.9	48.5
C ₆	27.4	32.7	34.0	28.5
C ₇	28.4	28.0	30.5	28.1
C ₈	37.2	37.9	36.0	37.6
C ₉	34.7	35.0	34.4	36.4
C ₁₀	35.2	36.3	35.4	41.0
C ₁₁	29.8	30.1	30.1	30.2
C ₁₂	74.0	74.0	74.1	75.1
C ₁₃	47.5	47.8	47.5	46.8
C ₁₄	49.1	49.4	50.0	49.3
C ₁₅	24.8	24.8	24.8	24.7
C ₁₆	28.5	28.6	28.7	28.5
C ₁₇	48.0	48.2	48.2	47.9
C ₁₈	13.3	13.3	13.4	13.1
C ₁₉	23.7	24.3	24.8	19.9
C ₂₀	36.6	36.7	36.9	36.9
C ₂₁	17.6	17.7	17.8	17.6
C ₂₂	32.2	32.4	33.1	31.7
C ₂₃	32.0	32.2	33.0	31.7
C(CH ₃) ₂ -OH		73.5	73.9	80.5
C(CH ₃) ₂ -OH		{ 29.7	29.8	31.6
		{ 27.9	29.6	31.5

^a The spectra were measured in perdeuterated methanol, except for **4**,^b and the chemical shifts are relative to Me₄Si used as an internal standard. The assignment of the chemical shifts was carried out by single-frequency off-resonance proton decoupling and partially relaxed T₁ experiments. ^b See note 6.

sociated with the formation of two new quaternary carbons (C-5 at 48.5 ppm and HO-CMe₂ at 80.5 ppm) and with the shift of C-19 by -4 ppm and C-10 by +6 ppm relative to **1**.⁵

2 and **3** lose water under the mass spectrometric conditions and demonstrate an identical mass spectrum. Similarly treatment of both compounds with SiO₂-supported FeCl₃ leads to the loss of one molecule of water and formation of the same product **5**:⁷ mp 212–214 °C; *m/e* 432. These observations demonstrate that **2** and **3** are generated by addition of acetone to the same carbon. Oxidation of the diacetylated methyl ester of **5** with RuO₄ yields the 6-keto deoxycholic acid homologue **6**, as could be demonstrated by the characteristic mass spectrometric degradations.⁸

The ¹³C NMR spectrum and partially relaxed T₁ measurements of **2** and **3** indicate that C-6 changes its multiplicity in both compounds from secondary to tertiary, and shift from 27.4 in **1** to 32.7 and 34.0 ppm for **2** and **3**, respectively, demonstrating again that the addition of acetone has occurred at C-6. From Dreiding models it can be seen that in the 6 equatorial isomer there is a strong interaction between the isopropyl group with C-4 and weak one with C-7, whereas in the axial isomer these interactions are reversed. This is nicely reflected in the ¹³C NMR spectrum (see Table I), leading us to suggest that the major product **2** is the equatorial isomer, whereas **3** is the axial one.⁹

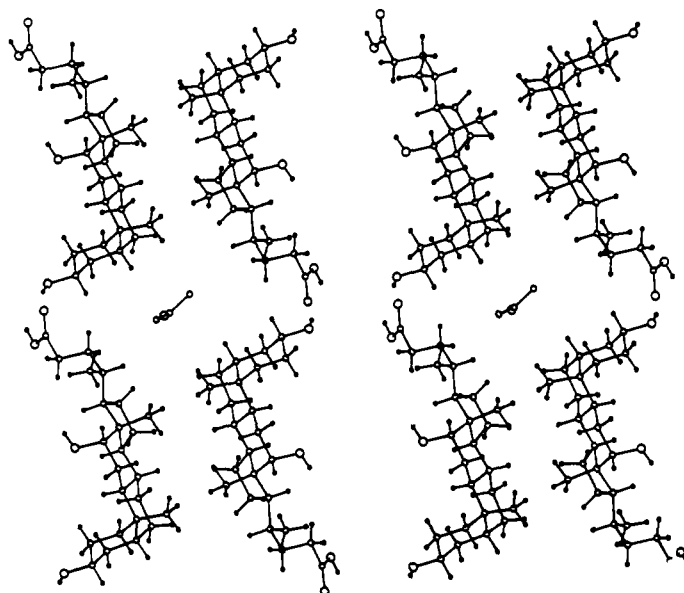


Figure 1. Stereoscopic view of the host-guest packing relation in DCA-acetone complex—viewed along c axis.

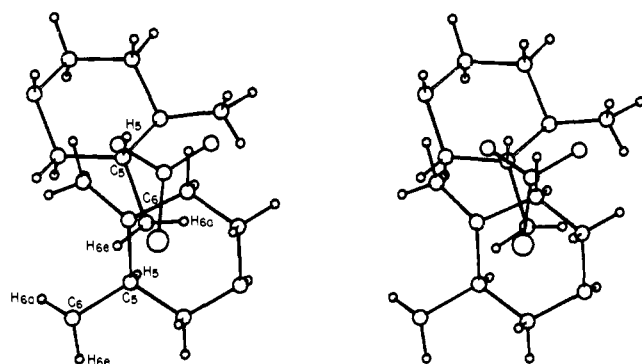
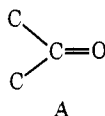


Figure 2. Stereoscopic view of the host-guest packing arrangement of DCA-acetone complex—viewed perpendicular to the best plane of the acetone molecule.

In order to correlate between the structure of the complex with the stereochemistry of products formed, the x-ray crystal structure of the complex has been carried out.¹⁰ From the packing (Figure 1) it can be seen that the hydrogen-bonding structures of the steroid are similar to those of other reported inclusion complexes of 1.^{1,11,12} The channel has dimensions of $\sim 4 \times 6$ Å. Steric contacts prevent adjacent acetone molecules from being related by the 2_1 axis and this results in population of only half of the sites. Thus in any given channel the acetone molecules are essentially related by translation of 7.2 Å and are sandwiched between two host molecules. From this structure it follows that the abstractable hydrogens C_5 H and C_6 H_{eq} and H_{ax} lie below the plane of the A group (Figure 2). The distances from the oxygen (ketone) to the nearest hy-



drogens, H_5 , H_{6eq} , and H_{6ax} , are 3.8, 3.4, and 3.4 Å, respectively.¹³ The distances from C (ketone) to C_5 and C_6 are 3.88 and 3.87 Å, respectively. The distances to all other carbons are greater than 4.0 Å.¹⁴

The topochemical nature of these reactions are further supported by the results obtained on the 1:1 complex of apocholic acid (7) with acetone which upon irradiation under argon forms only traces of products (<1%).

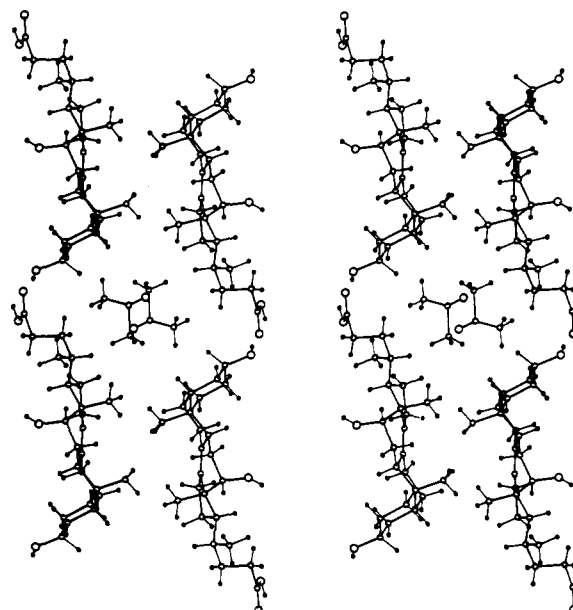


Figure 3. Stereoscopic view of the host-guest packing relation in apocholic acid-acetone complex—viewed along c axis.

From the packing arrangement of this system,¹⁵ we can see that the sole short contact is between the carbonyl oxygen with the hydrogen of C_{20} (2.9 Å) directed along the axis of the carbonyl group (Figure 3). Despite the fact that this distance is significantly shorter than the distances of the abstractable hydrogens discussed above, no addition product was isolated, suggesting that either the hydrogen is not appropriately oriented for abstraction¹⁶ or steric hindrance avoids addition of the carbonyl carbon to the C_{20} of the steroid separated by 4.85 Å. The answer to this question and the exact orientational conditions required for these reactions to take place must await examination of additional solid-state regiospecific oxidations both in the choleic acids as well as in linear paraffins currently in progress.

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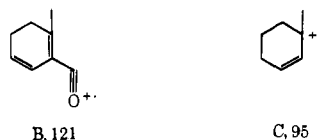
Supplementary Material Available: Fractional coordinates and thermal parameters of deoxycholic acid-acetone complex and fractional coordinates and thermal parameters of apocholic acid-acetone complex (4 pages). Ordering information is given on any current masthead page.

References and Notes

- (1) For part 1 in this series, see N. Friedman, M. Lahav, L. Leiserowitz, R. Popovitz-Biro, C. P. Tang, and Z. (V. I.) Zaretskii, *J. Chem. Soc., Chem. Commun.*, 864 (1975). Part of the present work has been presented at the Israel Crystallographic Society Meeting, Jerusalem, June 1977, and the Fourth European Crystallographic Meeting, Oxford, Aug 1977.
- (2) R. Breslow, *Chem. Soc. Rev.*, 1, 553 (1972); R. Breslow, S. Baldwin, T. Fletcher, P. Kalicky, S. Liu, and W. Washburn, *J. Am. Chem. Soc.*, 95, 3251 (1973), and references cited therein.
- (3) S. E. V. Phillips and J. Trotter, *Acta Crystallogr., Sect. B*, 33, 996 (1977), and references therein; A. A. Dzakpasu, S. E. V. Phillips, J. R. Scheffer, and J. Trotter, *J. Am. Chem. Soc.*, 98, 6049 (1976).
- (4) In a characteristic experiment 10 g of the sample was irradiated with Westinghouse sun lamps (290 nm). The products were detected by TLC with R_f values as follows: 1 (0.6), 2 (0.25), 3 (0.45), and 4 (0.35). The reaction mixture was recrystallized from acetone. Most of the products remained in solution, whereas the deoxycholic acid-acetone complex precipitated and was further irradiated. This procedure was repeated five times. Finally the reaction products were separated by chromatography on silica gel 1:100 and eluted with $CH_2Cl_2/CH_3OH/HAc$ in the ratio of 94.5:5:0.5; >70% 1 could be recovered. Irradiation of 1 in acetone solution yields a

complex mixture; the products of the solid-state reaction could not be detected by the TLC analysis.

- (5) D. Leibfritz and J. D. Roberts, *J. Am. Chem. Soc.*, **95**, 4996 (1973).
- (6) The ^{13}C NMR spectrum of **4** was carried out in perdeuterated acetic acid, because of its low solubility in methanol. However differences in chemical shifts between the two solvents are not exceeding 0.1–0.6 ppm, except for C_3 , C_{12} , and $\text{HO}(\text{CH}_2)_2$ carbons (0.5–1.5 ppm). This could be demonstrated from comparative studies of **2** and **3** in both solvents.
- (7) The dehydration was carried out according to the procedure of E. Kelnan and Y. Mazur, private communication: 3% FeCl_3 supported on SiO_2 was suspended with 0.5% **2** and **3** in methanol and dried under vacuum for 1 h; this was followed by extraction of the steroid with methanol and precipitation of the FeCl_3 with Na_2HCO_3 .
- (8) The oxidation was performed as described by Donald G. Lee in "Oxidation", Vol. 1, R. L. Augustine, Ed., Marcel Dekker, New York, N.Y., 1969, p 17. The high resolution mass spectrometric analysis is consistent with structure **6**. The two most characteristic fragments obtained in addition to the mo-



lecular peaks are B and C. See Z. V. Zaretskii in "Mass Spectrometry of Steroids", Wiley, New York, N.Y., 1976, p 11.

- (10) The complex **1** ($2\text{C}_{24}\text{H}_{40}\text{O}_4 - \text{C}_3\text{H}_6\text{O}$) crystallizes in space group $P2_12_12_1$; $a = 25.809$ (5), $b = 13.610$ (2), $c = 7.233$ (1) Å; $Z = 4$ molecules of **1** and 2 molecules of acetone; $D_c = 1.102$ g cm^{-3} . The crystal structure was determined with an R factor of 0.10 for 2505 reflections.
- (11) P. B. M. Craven and G. T. DeTitta, *J. Chem. Soc., Chem. Commun.*, 530 (1972).
- (12) S. C. De Sanctis, E. Gliglio, V. Pavel, and C. Quaglata, *Acta Crystallogr., Sect. B*, **28**, 3656 (1972).
- (13) Because of the change in hybridization and bond length of the carbonyl group upon excitation, a slight difference of the geometrical picture as described by the x-ray analysis of the ground state is expected. For a discussion, see J. C. D. Brand and D. G. Williams, *Adv. Phys. Org. Chem.*, **1**, 365 (1963).
- (14) In the intramolecular hydrogen abstractions described in ref 3, the allylic abstractable hydrogens are in the plane of the keto group.
- (15) The crystal structure of $\text{C}_{24}\text{H}_{38}\text{O}_4 - \text{C}_2\text{H}_6\text{O}$ was measured in a closed capillary saturated with acetone vapor. It crystallizes in a space group $P2_12_12_1$; $a = 24.47$, $b = 14.26$, $c = 7.50$ Å; $Z = 4$ molecules of **8** and 4 molecules of acetone; $D_c = 1.129$ g cm^{-3} . The crystal structure was determined with an R factor of 0.08 for 2579 reflections.
- (16) For a discussion of the conditions on hydrogen abstractions in rigid cyclic systems, see F. D. Lewis, R. W. Johnson, and R. A. Ruden, *J. Am. Chem. Soc.*, **94**, 4292 (1972).

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Hydride Donation Reactions of Transition Metal Formyl Complexes

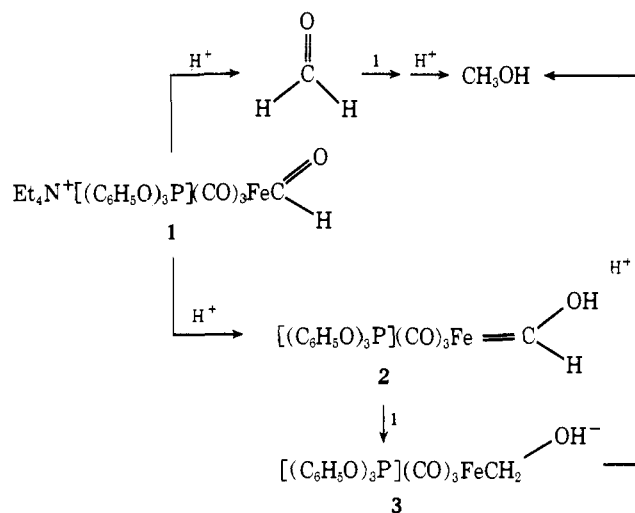
Sir:

We recently developed a new synthesis of metal formyl complexes,¹ which have been proposed as important intermediates in the metal catalyzed reduction of CO by H_2 .² The availability of metal formyl complexes has allowed us to study their kinetic and thermodynamic stability and their chemical reactivity. Here we report that metal formyl complexes can act as hydride donors to electrophiles such as ketones, alkyl halides, and metal carbonyls.

Whereas Et_4N^+ *trans*- $[(\text{C}_6\text{H}_5\text{O})_3\text{P}](\text{CO})_3\text{FeCHO}^-$ (**1**) decomposes to $\text{Et}_4\text{N}^+(\text{CO})_4\text{FeH}^-$ and $(\text{C}_6\text{H}_5\text{O})_3\text{P}$ with a half-life of ~ 1 h at 67 °C in tetrahydrofuran,³ attempts to obtain a ^1H NMR spectrum of **1** in acetone- d_6 at ambient temperature led to disappearance of the formyl hydrogen resonance at δ 14.9 within 25 min and suggested that **1** had reacted with acetone. Reaction of **1** with 2-butanone overnight at ambient temperature followed by acid hydrolysis gave a 95% yield of 2-butanol, as determined by gas chromatography.⁴ The

possibility that 2-butanone is reduced by $(\text{CO})_4\text{FeH}^-$ formed in situ is excluded since **1** reacts with 2-butanone much faster than it decomposes to $(\text{CO})_4\text{FeH}^-$ and since no reaction between $(\text{CO})_4\text{FeH}^-$ and 2-butanone was observed by infrared spectroscopy.

Reaction of a THF solution of **1** (0.346 mmol) with $\text{CF}_3\text{CO}_2\text{H}$ (10 equiv) led to the formation of CH_3OH (0.095 mmol, 27%) and no observable formaldehyde (<5%).^{5,6} Methanol might arise from acid cleavage of **1** to give formaldehyde which is subsequently reduced to methanol by hydride donation from a second equivalent of **1**.⁸ Alternatively, methanol could arise via O protonation of **1** to give hydroxycarbene complex **2**, which is subsequently reduced to hydroxymethyl complex **3** by a second equivalent of **1**; cleavage of **3** by acid would give methanol. Either of the two routes leads to a maximum 50% yield of methanol.



Collman and Winter have reported that $[(\text{C}_6\text{H}_5)_3\text{P}]_2\text{N}^+(\text{CO})_4\text{FeCHO}^-$ reacts with 1-iodooctane to give octane (75%) and a trace of nonanal; octane formation was attributed to decarbonylation of $[(\text{C}_8\text{H}_{17})(\text{CHO})\text{Fe}(\text{CO})_4]$, followed by hydride migration and reductive elimination of octane.⁹ We have found that Et_4N^+ *trans*- $[(\text{ArO})_3\text{P}(\text{CO})_3\text{FeCHO}^-$ (Ar = 3,5-dimethylphenyl) reacts with $n\text{-C}_7\text{H}_{15}\text{I}$ when stirred overnight at ambient temperature in THF to give $n\text{-C}_7\text{H}_{16}$ (71%) and $(\text{CO})_4\text{FeP}(\text{OAr})_3$; <0.2% $n\text{-C}_7\text{H}_{15}\text{CHO}$ was observed.¹⁰ Since formyl complexes appear to function as hydride donors, we propose that heptane is formed by nucleophilic displacement of iodide by the formyl hydrogen atom.

Metal formyl complexes can transfer hydride to metal carbonyl compounds to produce new metal formyl complexes.¹¹ These "transformylation" reactions can be used to determine the relative stability of a series of metal formyl complexes. The reaction of **1** with $\text{Re}_2(\text{CO})_{10}$ in THF- d_8 was followed by ^1H NMR. The characteristic doublet at δ 14.9 due to **1** is rapidly replaced by a singlet at 16.04 attributed to Et_4N^+ *cis*- $(\text{CO})_9\text{Re}_2\text{CHO}^-$ (**4**) formed in 82% yield as determined by NMR integration.¹² $(\text{CO})_4\text{Fe}[\text{P}(\text{OC}_6\text{H}_5)_3]$ was detected by IR as a co-product of the reaction.

4 was independently synthesized by reaction of $\text{K}^+\text{HB}(\text{O}-i\text{-Pr})_3^-$ with $\text{Re}_2(\text{CO})_{10}$ in THF at 0 °C, followed by aqueous basic workup and cation exchange with $\text{Et}_4\text{N}^+\text{Br}^-$. **4** was recrystallized from THF-hexane, and isolated in 32% yield as a yellow, air-stable solid.^{13,14} **4** was characterized spectroscopically: ^1H NMR (THF- d_8) δ 1.32 (tt, $J = 7.2$, $J_{\text{NH}} = 1.5$ Hz, 12 H, NCH_2CH_3), 3.40 (q, $J = 7.2$ Hz, 8 H, NCH_2CH_3), 16.04 (s, 1 H, ReCHO); IR (THF) 2084 (w), 2066 (m), 2015 (s), 1979 (s), 1949 (w-m), 1899 (w-m, MCO), 1559 (w, $\text{MCH}=\text{O}$) cm^{-1} ; IR (KBr) 2089 (vw), 2068 (m), 2009 (s), 1890 (s, sh), 1936 (w-m), 1884 (m), 1734 (m), 1602 (m), 1493