Tetrahedron Letters No. 44, pp 4197 - 4200, 1971. Pergamon Press. Printed in Great Britain.

# CARBON-13 PSEUDO-CONTACT SHIFTS IN STRUCTURE DETERMINATION: THE HEMIKETAL DIMER FROM 2-HYDROXY-2-METHYLCYCLOBUTANONE.

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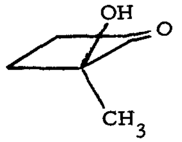
(Received in USA 29 July 1971; received in UK for publication 1 October 197.)

The dimer that crystallizes from the viscous mixture that develops as 2-hydroxy-2-methylcyclobutanone 1 stands has been found to be a dioxolane 2a, rather than the dioxane 3a originally proposed.[1] The decisive evidence came from a study of the effect of the paramagnetic shift reagent[2] tris-(2, 2, 6, 6-tetramethyl-3, 5-heptanedionato)europium(III) on the $^{13}C$ nmr spectrum of 2b, the monoacetate of 2a. This is the first structure elucidation based upon $^{13}C$ pseudo-contact shifts.



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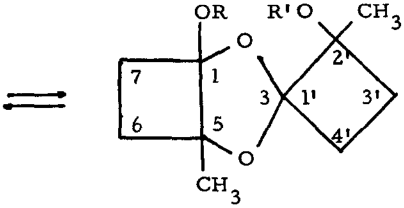
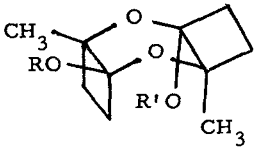


2a, R = R' = H
b, R = $CH_3CO$, R' = H
c, R = $CH_3CO$, R' = $C_6H_5CO$
d, R = $C_6H_5CO$, R' = $CH_3CO$



3a-d

Prior to the insight from this valuable new tool and before experiments described below, structure 3a was compatible with all known properties of this dimer, and with history. Its mass spectrum was in accord with fragmentations known for dioxane[3] and cyclobutane derivatives. Its nmr spectra showed that it has no elements of symmetry. The $^1H$ nmr had two hydroxyl, and two methyl, singlets. The $^{13}C$ nmr[4] of this 10-carbon molecule showed nine lines with one of double intensity ($\delta_c$ 29.7, Table 1). It was assumed that boat-to-boat interconversion between the enantiomers of 3a was slow on the nmr time scale.[1] The infrared spectrum showed two hydroxyl and strong C-O stretching bands, but no carbonyl.

Table 1. Spectra of 2a and 2b.

| Mass spectra[a] | | | $^{13}$C nmr[b] | | | $^{1}$H nmr[c] | |
|---|---|---|---|---|---|---|---|
| 2a | 2b | Composition | 2a[d] | 2b[d] | Slope[e] | 2a | 2b |
| 183 (0.5) | 183 (1) | $M^+$ - RO | | 167.4 | 9.0 (C=O) | 6.49[f] | 2.04[g] |
| 172 (4) | 214 (1) | $M^+$ - $C_2H_4$ | 113.9 | 116.2 | 7.4 (C-1) | 4.85[f] | 5.04[f] |
| | 172 (4) | $M^+$ - $C_4H_6O$ | 106.5 | 105.1 | 7.4 (C-3) | 2.5-1.4[h] | 2.5-1.4[h] |
| 142 (20) | 184 (12) | $M^+$ - $C_3H_6O$ | 85.8 | 86.0 | 5.2 (C-5) | 1.22[g] | 1.34[g] |
| 101 (15) | 143 (5) | $M^+$ - $C_5H_7O_2$ | 79.1 | 78.5 | 34.0 (C-2') | 1.16[g] | 1.18[g] |
| | 101 (8) | $M^+$ - $C_7H_9O_3$ | 31.4 | 31.2 | 13.4 (C-3') | | |
| 100 (14) | 142 (5) | $M^+$ - $C_5H_8O_2$ | 29.7 | 30.0 | 4.6; [C-6, | | |
| | 100 (11) | $M^+$ - $C_7H_{10}O_3$ | 29.7 | 29.0 | 6.6; C-7, or | | |
| 99 (20) | 99 (51) | $C_5H_7O_2$ | 28.4 | 28.8 | 4.6; C-4'] | | |
| 84 (19) | 84 (15) | $C_5H_8O$ | 23.0 | 21.9 | 16.8 (2' $CH_3$) | | |
| 83 (16) | 83 (23) | $C_5H_7O$ | | 21.0 | 4.6 ($\underline{C}H_3CO$) | | |
| | | | 18.9 | 18.3 | 3.1 (5 $CH_3$) | | |

a) m/e of larger fragments (intensity as percent of base peak m/e 43). Compositions by exact mass measurement. AEI MS9 at 70 eV, direct inlet. Molecular ions ($M^+$): 2a m/e 200, $C_{10}H_{16}O_4^+$ (not detected); 2b m/e 242, $C_{12}H_{18}O_5^+$ (detected at 12 eV and low resolution). b) Bruker HFX in pulsed mode at 22.6 MHz; proton noise decoupling; probe 40°. c) Chemical shifts (δ) in dimethylsulfoxide-$d_6$ at 32°; 60 MHz; internal TMS. d) Chemical shifts in ppm downfield from external TMS, ± 0.1 ppm. Solvents: pyridine (2a) and carbon tetrachloride (2b). e) Slope of plot of paramagnetic shift in ppm versus [$Eu(thd)_3$]/[2b] (assignment). f) s, 1, OH. g) s, 3, $CH_3$. h) m, 8, $CH_2$.

Since dioxadiene was converted to a dibromodioxane that was in turn converted to a diacetate,[5] identical with that prepared from glycolaldehyde dimer;[6] such crystalline hemiacetals from α-aldols and hemiketals from α-ketols have been assumed to be dioxanes.[7] More recent physical evidence supports such structures for all of them that have been studied.[8]

Although 2a has a novel structure, its chemistry parallels that of the others. In all cases, a single dimer crystallizes from the complex mixture of such substances[8b] that is formed as the monomer is stored. All dissociate in solution, but 2a is surprisingly stable. For example, the acetoin dimer dissociates in a day, but this reaction of 2a to give 1 requires months, in dimethylsulfoxide. The latter reaction is rapid when 2a is heated, and it is catalyzed by acids and bases.

Doubts about structure 3 developed during studies on the esterification of the dimer. Its reaction with excess acetic anhydride in pyridine for 48 hr at 25° gave *only* a single monoacetate 2b (mp 57-58°). Conversion to the diacetate required further reaction at 90° for 72 hr. A comparison of the infrared, mass, $^{1}$H nmr, and $^{13}$C nmr spectra of 2a and 2b (Table 1) confirms that the two have the same skeleton. Also, the $^{1}$H nmr spectrum of 2b in isoquinoline was unchanged, except for indications of minor decomposition, after the solution had been held at 240° for 18 hr. These results might have been due to the conformer 3b having a much lower free energy than the alternative one (3, R = H, R' = $CH_3CO$). However, treatment of 2b with equimolar benzoyl chloride in pyridine gave the acetate-benzoate 2c (mp 89-90°), and the reverse order of esterification gave the benzoate-acetate 2d (mp 96-97°). These diesters were different substances; and their nmr spectra were virtually unchanged (again limited decomposition occurred) after 18 hr at 240°. One likely, and two unlikely, possibilities remained: the dimer had some other structure, such as 2a; the structure 3 was rigid; or the compounds were stereoisomers of 3 with one *cis* and one *trans* ring junction.

Definitive evidence that the structure is 2 came from the observation that the largest $^{13}$C pseudo-contact shift induced by incremental addition of Eu(thd)$_3$ to solutions of 2b in carbon tetrachloride involved its line at $\delta_c$78.5 (Table 1), obviously then due to its hydroxyl-bearing carbon atom.[2] Noise off-resonance decoupling experiments[9] with 2a showed that the four carbons that absorb at lowest field are quaternary. Also, those of 2b giving the lines at $\delta_c$116.2 and 105.1 are attached to two oxygen atoms while those at $\delta_c$86.0 and 78.5 are linked to one. Therefore, since the carbon atom of 2b that bears it hydroxyl group has no other oxygen attached, 3b and its stereoisomers are eliminated. Except for structure 2b, all others that have been visualized fail to account for the $^{13}$C nmr spectra and pseudo-contact shifts observed. Of course, the chemistry and other physical properties of the dimer are consistent with 2. However, a decision between the four *cis*-fused *dl* pairs of stereoisomers of 2 is not permitted by the present evidence.

Dioxolane dimers from five other 2-hydroxycyclobutanones have been isolated. Most, like 2a, are insoluble in solvents in which the shift reagent is effective, but the dimer from 2-hydroxy-2, 3, 3-trimethylcyclobutanone 4 is soluble in carbon tetrachloride. However, Eu(thd)$_3$ excessively broadened its $^1$H nmr signals and catalyzed its dissociation to 4, and the ketol rearrangement of 4.[10] The $^1$H paramagnetic shifts of 2b were measured without such difficulties but did not permit structural conclusions.

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