Lanthanide Chemical Shift Reagents as Tools for Determining Isomer Distributions in 2,4-Hexadienoates and Related Compounds

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Abstract-Quantitative analysis of geometrical isomers of unsaturated esters and alcohols is facilitated with Eu(fod)$_3$. Commercial sorbic acid exists in the all-*trans* form, while sorbyl alcohol contains c. 10% of the *cis*-4,5 isomer.

NMR CHEMICAL shift reagents continue to find widening application in elucidating coupling constants and geometric configurations[1] of organic molecules. Esters,[2] alcohols and ketones[3] give greatly simplified spectra with Eu(fod)$_3$ 1 at Eu/substrate concentrations c. 0·2 to 0·5. Recently Swern and Wineburg[4] demonstrared the utility of **1** in elucidating possible branching in the structures of long chain fatty acids. We wish to report that 1 is a useful reagent for qualitative and quantitative estimations of isomer distributions in sorbate esters and sorbyl alcohol.

In a related study[5] we wished to determine the isomer distribution of 2,4-hexadienoic (sorbic) acid obtained from various natural and commercial sources. Since acids decompose shift reagents,[6] commercial sorbic acid (Aldrich) was treated with diazomethane. The resulting ester gave a complex, non-analyzable olefinic NMR pattern. Addition of **1** to CH$_3$CH=CHCH=CHCO$_2$Me (2) gave a first-order spectrum at a c. 0·4 l/ester molar ratio, the spectrum showing six cleanly separated resonances consistent with the all-*trans* configuration: (OCH$_3$, s), (H$_\alpha$, d, $J_{\alpha\beta}$ = 16 Hz), (H$_\beta$, d of d, $J_{\beta\gamma}$ = 10 Hz), (H$_\gamma$, d of d, $J_{\gamma\delta}$ = 15 Hz), (H$_\delta$, six lines, $J_{\delta-CH3}$ = 6 Hz), (CH$_3$, d). The same spectrum was obtained from ester prepared from sorbic acid, methanol and sulfuric acid. However, when ester prepared from sorboyl chloride and methanol was so analyzed, new multiplets appeared in the spectrum, indicating the presence of another isomer. A second OCH$_3$ singlet appeared upfield together with second upfield patterns for both H$_\alpha$ and H$_\gamma$. These exhibited the same multiplicity and coupling constants as above. However, the H$_\gamma$ and H$_\delta$ patterns still overlapped with those from all-*tram* isomer. The terminal CH$_3$ showed a new doublet downfield from the corresponding all-trans isomer doublet, with long range doublet splitting,[7] in accord with H$_\gamma$ and H$_\delta$ being *cis*. Integration showed a 17 % concentration of the 2-*trans*-4-*cis* isomer.

The induced shift ratio concept elaborated by Swern and Wineburg[4] is of utility in analyzing these data. The induced shift ratio Ξ is independent of shift reagent concentration, and depends only on the relative shifts of a particular proton H$_x$ and a standard proton H$_\alpha$ in

the same molecule, which in esters, alcohols and ketones is defined as the proton most proximate to the functional group. $\Xi_x = (\delta_{Eu} - \delta_0)_x/(\delta_{Eu} - \delta_0)_\alpha$, where δ_{Eu} and δ_0 are respectively the chemical shifts with and without the presence of shift reagent. The induced shift ratios of the two sorbic acid isomers, together with the relative chemical shifts of the protons in the two isomers, are given in Table 1.

TABLE 1. INDUCED SHIFT RATIOS FOR ALL-*trans* (2a) AND 2-*trans*-4-*cis* (2b) METHYL SORBATE[a,b]

	H$_\alpha$	OCH$_3$	H$_\beta$	H$_\gamma$	H$_\delta$	C-CH$_3$
δ $_b/\delta_{2a}$	0.93	0·89	0·97	0.98	1·00	1·18
Ξ_{2a}[c]	1·0	1.05	0.99	0.22	0.11	0·04
Ξ_{2b}[d]	1·0	1·01	1·08	0.18	0.07	0.15

[a] At 60 MHz, CCl$_4$ solution. [b] Relative to H$_\alpha$ = 1·0. [c] Average of 8 runs with Eu/ester molar ratio 0·03 to 0·4. [d] At Eu/ester = 0·35.

As Ξ in long chain alcohols and esters is a function monotonically decreasing with increasing distance from the complexation site,[4] it is of interest to note the inversion of $\Xi_{H\delta}$ and Ξ_{C-CH3} in the isomers **2a** and 2b. Examination of structure diagrams shows that H$_\delta$ and C—CH$_3$ exchange their spatial locations relative to the ester function as the 4,5-double bond inverts configuration.

Although the criteria of lanthanide induced shifts obeying a r^{-3} 'distance only' relationship has been substantially refuted,[8] it is conceded **that** shift reagents will associate with substrates so as to minimize steric interaction, and that only molecules in which the substrate is forced (by steric constraints) to envelop the metal ion will be expected to show large variations of Φ in the pseudo-contact shift equation, $\Delta H/H = K(3 \cos^2 \Phi - 1)/r^3$. The noncyclic materials used in this study are expected to closely approximate the 'distance only' criterion of induced shift.

2-*cis*-4-*trans*-Hexadienoic acid is known to be an unstable, readily polymerizing compound[5] and the all-*cis* isomer is unknown, hence Eu(fod)$_3$ spectra of these compounds were not obtained. Quantitative analysis of mixtures containing these isomers should be possible, as $\Xi_{H\beta}$ and $\Xi_{H\gamma}$ should behave as ΞH_δ and ΞH_{CCH} did when the 4,5 double bond reversed configuration: moving the H$_\beta$ and H$_\gamma$ resonances to unobscured regions of the spectrum.

Although definite proof awaits further study, we speculate that the 4-*cis*-sorbate produced in the thionyl chloride mediated esterification is formed via a Diels-Alder reaction with SO$_2$, enolization and retro-Diels-Alder reaction sequence.

Commercial 2,4-hexadienol (Eastman) (3), treated with 1, gave a first-order 60 MHz spectrum at Eu/ester $= 0\cdot4$, which indicated a predominantly all-*trans* configuration: H^1, d, $J_{12} = 5$; H^2, t of d, $J_{23} = 14$; H^3, d of d, $J_{34} = 10$; H^4, d of d, $J_{45} = 14$; H^5, q of d, $J_{56} = 5\cdot5$; H^6, d. The induced shift ratios Ξ: H^1, $1\cdot0$; H^2, $0\cdot56$; H^3, 0.53; H^4, 0.22; H^5, $0\cdot11$; H^6, 0.05; OH, $3\cdot96$ supported this conclusion. However, the H^6 region of the spectrum showed a downfield second doublet with long range doublet splitting. The long range splitting[7] and Ξ value of this doublet implied that it arose from the 4,5-*cis* isomer of sorboyl alcohol. From peak height measurement the concentration of 4,5-*cis*-2,4-hexadienol in commercial sorbyl alcohol can be estimated as 10%.

Several other commercial materials were analyzed by this technique for geometric isomers, including 4-phenyl-3-buten-2-one and methyl cinnamate. These compounds all gave first-order spectra at Eu/substrate $=$ $0\cdot4$ or less. The spectra indicated the presence of only the *trans* isomer. We estimate that the $Eu(fod)_3$ method would detect the presence of c. 2% of a *cis* isomer. Further applications of shift reagents to structural problems are under investigation.

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