CONFORMATION OF SUCCINIC ACID DERIVATIVES BY DOUBLE ^{13}C-LABELLING

F. M. Menger* and L. H. Lee

Department of Chemistry, Emory University, Atlanta, Georgia 30322

Summary: Three-bonded carbon/carbon couplings ($^3J_{cc}$) are used, in conjunction with MM2 calculations, to examine conformational equilibria in several di-^{13}C-labelled succinic acid derivatives.

Three-bonded carbon/carbon couplings ($^3J_{cc}$) respond to dihedral relationships in a typical Karplus fashion (i.e. maxima near 0° and 180° and a minimum near 90°).[1,2] For example, in $\underline{C}$-C-C-$\underline{C}$=O systems, $^3J(0°)$ = 2 Hz, $^3J(60°)$ = 0.5 Hz, $^3J(90°)$ = 0 Hz, and $^3J(180°)$ = 4-5 Hz, as illustrated by the two ^{13}C-carboxyl-labelled compounds below.[3] We have recently examined conformations among acyclic compounds possessing two ^{13}C atoms spaced four atoms apart ($\overset{*}{C}$-C-C-$\overset{*}{C}$).[4] Although synthesis of compounds with two ^{13}C labels is often tedious, the effort
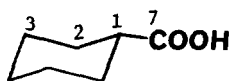

$J_{7,3}$ = 4.10 Hz
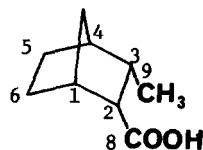
$J_{8,9}$ = 1.9 Hz

$J_{8,4}$ = 0.5 Hz

is worthwhile because interpreting the NMR spectra then becomes trivial. Instead of deciphering a composite of couplings (e.g. $^2J_{8,1}$, $^1J_{8,2}$, $^2J_{8,3}$, $^3J_{8,6}$ etc. for the norbornyl derivative above), one simply measures the separation between members of the two doublets looming above the "natural abundance" peaks.

In the course of synthesizing chains containing two ^{13}C atoms, we obtained a variety of di-^{13}C-labelled succinic acid derivatives (Scheme) that readily lent themselves to NMR

examination. Moreover, since succinic acid serves as substrate[5] and inhibitor[6] for certain enzymes, $^3J_{cc}$ data on succinic acid derivatives could provide the basis for stereochemical studies at active sites. We therefore report here on conformational equilibria on these materials; supportive MM2 calculations are also included.

<u>Scheme</u>
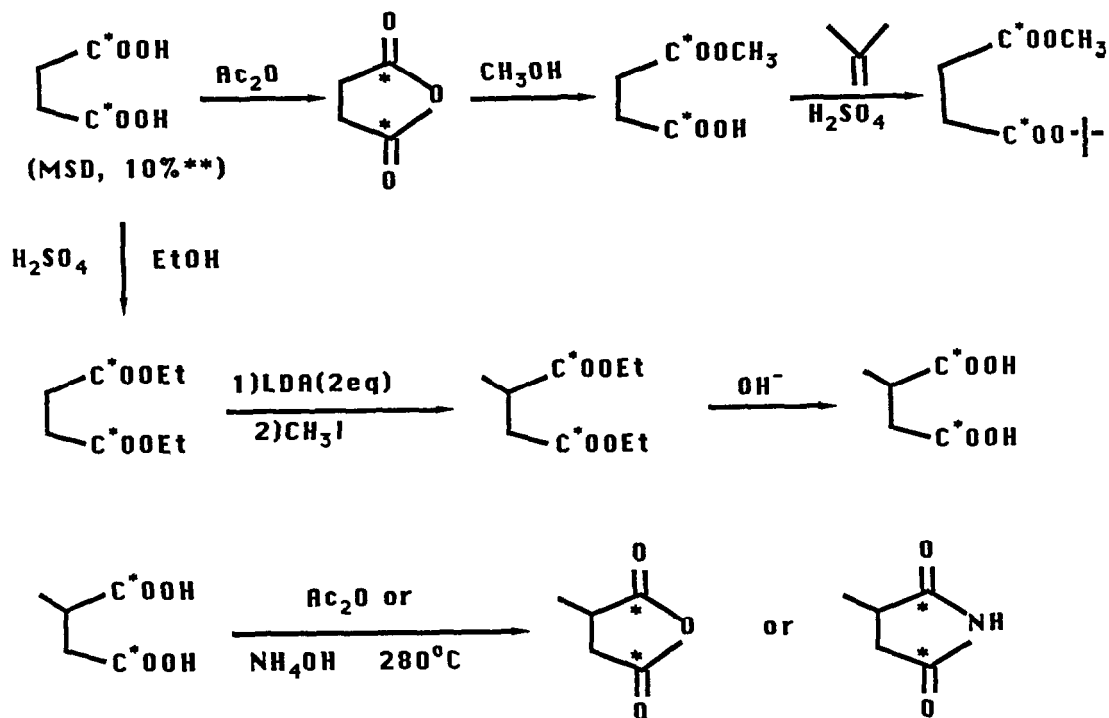
All NMR spectra were obtained at 23 ± 0.5°C using an IBM-WP-200-SY spectrometer. A typical run had 50 mg 10% di-labelled compound in 3 ml deuterated solvent (5000 scans, SW = 5000, PW = 6). No dependence of $^3J_{.cc}$ was observed on concentration or spectral mode (traced normally or with the aid of a 32-phase INADEQUATE sequence). Uncertainty in the coupling constants is ±0.1 Hz.

Monomethyl succinate, $HOO\overset{*}{C}(CH_2)_2\overset{*}{C}OOCH_3$, displayed $^3J_{cc}$ values of 2.3, 2.4, 2.5, 2.6, and 2.7 Hz in acidic D_2O, DMSO, benzene, acetone, and chloroform, respectively. Only dioxane ($^3J_{cc}$ = 3.0 Hz) fell out of the 2.5 ± 0.2 Hz range, showing that conformation is rather insensitive to solvent polarity. Apparently, specific solvent-solute complexation (<u>e</u>.<u>g</u>. H-bonding of donor

solvents to the carboxyl proton) is too far removed to contribute substantially to intramolecular interactions.

In order to determine experimentally the trans/gauche ratios from coupling data, one needs to know $^3J_{cc}$ values for "pure" trans and gauche. The $^3J_{cc}$ for "pure" gauche was obtained from the fact that, according to MM2 calculations, methyl succinic acid is 96% gauche.
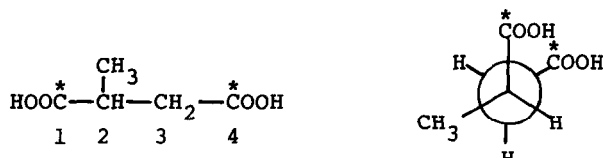
96%

This percentage was deduced in the following manner: The dihedral angle was rotated about the 2-3 bond from -180° to + 180° to locate energy minima that appeared at 60° and 179°. The dihedral angle was then fixed at 60°, and the 1-2 and 3-4 bonds were rotated in a "3-dimensional" dihedral driver analysis to find the energy of the global minimum. A similar procedure was applied to a central dihedral angle of 179°. In this way, gauche was found to be more stable than trans by 1.92 kcal/mol, signifying a 96-to-4 preponderance of gauche. Since the observed $^3J_{cc}$ for methyl succinic acid is 2.1 Hz, "pure" gauche is associated with a $^3J_{cc}$ = 2.0 Hz.[7]

$^3J_{cc}$ for "pure" trans was estimated as 3.6 Hz. This was obtained from the $^3J_{cc}$ = 4.2 Hz for methyl succinic acid at high pH where, it was assumed, the carboxylates are totally trans. Since it was found that $^3J_{cc}$ for monomethyl succinate increases from 2.3 to 2.6 Hz as it passes from acid to base, we subtracted 2 x 0.3 Hz = 0.6 Hz from the observed value of 4.2 Hz as a rough correction for inductive effect differences between carboxyl and carboxylate.

MM2 calculations on monomethyl succinate, performed as described for methyl succinic acid, showed that the monoester is 64% gauche and 36% trans.[8] It can thus be estimated from Eq. 1 that $^3J_{cc}$ equals 2.6 Hz (compared to 2.5 ± 0.2 Hz that was, as cited above, found in most solvents). Conversely, one can calculate trans/gauche ratios using observed $^3J_{cc}$ values. For

$$^3J_{cc} = 0.64 \times 2.0 + 0.36 \times 3.6 = 2.6 \text{ Hz} \qquad (1)$$

example, the two diesters below have $^3J_{cc}$'s in acetone of 2.4 Hz and 2.5 Hz, corresponding to 75% and 69% gauche, respectively (values that are within experimental error of one another).

Two interesting facts are revealed by the diesters: (a) The t-butyl group plays a minor role in

$$^3J_{cc} = 2.4 \text{ Hz} \qquad ^3J_{cc} = 2.5 \text{ Hz}$$
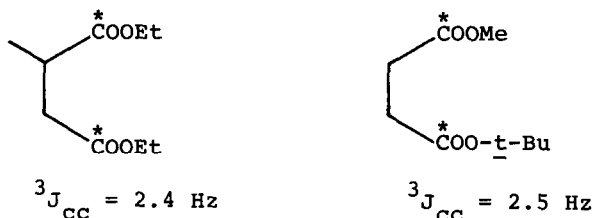
determining conformation (no doubt stemming from the same reason advanced for a lack solvent effects). (b) The slight preference for gauche carbonyls persists even when intramolecular hydrogen bonding, possible in methyl succinic acid[9], is definitely not a factor.

Zetta and Gatti[10] studied succinic and methyl succinic acids via analysis of AA'BB'X and ABCD$_3$ ^{1}H NMR spectra. They concluded that substantial amounts of trans and gauche conformers are present. Our method is far less complicated and provides a more quantitative assessment of rotamer populations. A wealth of useful conformational information lies in wait for anyone willing to synthesize di-^{13}C-labelled materials.[11]

References

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7. Calculated from $2.1 = 0.96J_g + 0.04J_t$ where $J_t = 3.6$ Hz as given in the next paragraph.

8. These percentages incorporate the fact that monomethyl succinate has two enantiomeric gauche conformers.

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11. $^3J_{cc} = 8.9$ Hz (CDCl$_3$) for the cyclic anhydride in the Scheme. The cyclic imide has coupling constants of 12.1 Hz in DMSO-d$_6$ and 13.0 Hz in acidic D$_2$O.

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