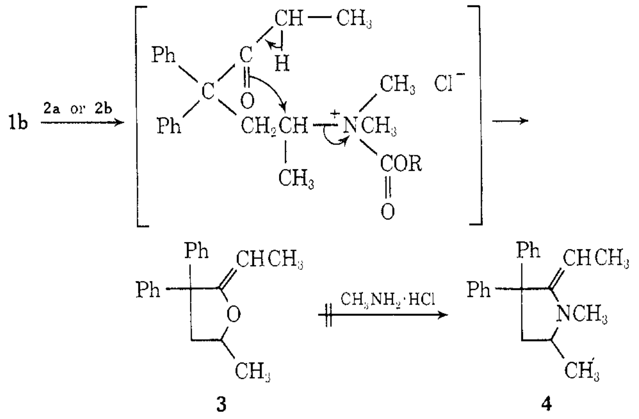
product containing nitrogen. The product **3** (Scheme I) was characterized by it smelting point and ir, nmr,[7] and mass spectra, and was found to be identical with the compound obtained by Easton and others on pyrolysis of the methiodide of methadone.[8] An attempt was made by us to convert **3** to **4** (by a variety of conditions; see Scheme I) which was unsuccessful. The compound **4** is a primary metabolite of methadone, which results from demethylation and cyclization.[1,2] However, it is not known whether **3** could result from the biotransformation of methadone, in view of its facile formation, under such mild conditions as employed in our attempted demethylation reaction.

SCHEME I



Experimental Section

Melting points of compounds were determined on a Thomas-Hoover apparatus and are uncorrected. Infrared spectra were obtained with a Perkin-Elmer Infracord (KBr disk). Proton magnetic resonance spectra were obtained with a Varian XL 100 instrument (CDCl$_3$, TMS). Mass spectra were obtained with a Du Pont 492 mass spectrometer. Thin layer chromatography was performed on Analtech plates with florescent indicator. Methadone hydrochloride (racemic) was obtained from Eli Lilly and Co., Indianapolis, Ind. Phenyl chloroformate was obtained from Eastman Kodak Co., Rochester, N. Y. Ethyl chloroformate was obtained from J. T. Baker and Co., Phillipsburg, N. J.

Reaction of Methadone Hydrochloride with Phenyl Chloroformate. Formation of 3.—To a suspension of racemic **1b** hydrochloride (346 mg, 1 mmol) in 25 ml of tetrahydrofuran was added NaHCO$_3$ (2 g, 6 mmol) and **2b** (1.4 g, 8.9 mmol). The resulting mixture was magnetically stirred at room temperature for 24 hr. The reaction mixture was then treated with NaOH (50% solution) until alkaline in pH (about 11) and the solvent was carefully evaporated *in vacuo*. The residue was extracted with chloroform and aqueous NaOH (pH 11) and the chloroform extract was chromatographed preparatively on precoated silica plates (solvent benzene). Some unreacted methadone was found to be present at the origin.[9] The major band close to the solvent front was eluted with chloroform and the extract was evaporated *in vacuo*. A syrupy residue was obtained. This syrupy residue was treated with the minimum of ethanol and water, and allowed to stand overnight at room temperature. The following day, 132 mg (yield 50%) of white crystals, mp 79–81° (lit.[5] mp 78–80°), of **3** was obtained by filtration.

Reaction of Methadone Hydrochloride with Ethyl Chloroformate (2a). Formation of 3.—To a suspension of racemic **1b** hydrochloride (346 mg, 1 mmol) in 20 ml of tetrahydrofuran was added NaHO$_3$ (2 g, 6 mmol) and **2a** (0.8 g, 7.4 mmol). The resulting mixture was magnetically stirred at room temperature for 24 hr. Then the mixture was worked up as in the previous experiment to give 69 mg (25%) of **3**, mp 79–81°.

Acknowledgment.—This research was supported in part by the Narcotic Antagonist Research Program of the New York City Department of Health and Grant No. DA-00297.

Registry No.—(±)-**1b** HCl, 297-88-1; **2a**, 541-41-3; **2b**, 1885-14-9; **3**, 17494-37-0.

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(8) We are thankful to Dr. N. R. Easton for kindly sending us the ir and nmr spectra of the compound.

(9) No effort was made to quantitatively estimate the minute amounts of starting material in this reaction.

Conformations of Carbon-13-Labeled Phenylsuccinic Acid

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Received November 13, 1972

Various papers have commented upon the apparent relationship between vicinal ^{13}C–H nmr coupling constants and the geometry of these groups.[1-4] Roughly, the relationship appears to be analogous to the well-known Karplus relationship describing the dependence of H–H coupling constants on dihedral angle.[5] Similar relationships have been postulated for the interaction of ^{31}P–H, ^{31}P–^{13}C, and F–H pairs of nuclei.[6-13] Recently, the effect of molecular geometry on ^{13}C–^{13}C coupling constants has been reported.[14]

From the plot of $J_{^{13}\mathrm{CH}}$ *vs.* dihedral angle, given by Lemieux and coworkers, a coupling constant of *ca.* 1 Hz would be expected for gauche ^{13}C–H groups, and *ca.* 8 Hz for trans groups. Somewhat earlier, Perlin and Casu had given values of 0.7 Hz for gauche and 7.8 Hz for trans groups. Lemieux and coworkers caution that ^{13}C–H couplings are quite sensitive to certain structural parameters, including electronegativity of groups, carbon hybridization, and steric relationships.

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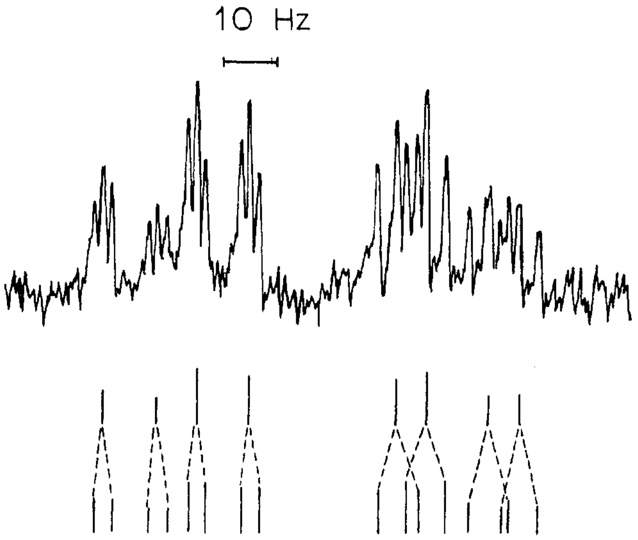
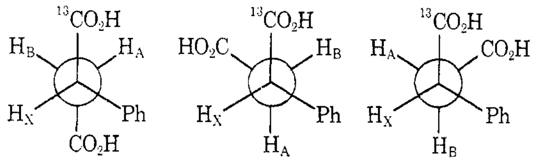


Figure 1.—Partial nmr spectrum of the labeled phenylsuccinic acid in acetone-d_6 (protons B and A).

Considering only proton couplings, a common finding in ABX systems might be a large J_{AX} and a small J_{BX}. Unfortunately, these findings do not indicate which conformer (*e.g.*, **1** or **2**, Chart I) is predominant, unless some independent means exists of identifying which proton is A and which is B. One technique used to circumvent this difficulty is isotopic labeling.[15] This work describes the use of ^{13}C labeling in the molecule of interest, phenylsuccinic acid. Molecular models suggest that the phenyl and carbonyl groups have roughly similar size at their points of attachment to the ethanic skeleton. However, work in other types of molecules has indicated that phenyl is more space demanding than carbonyl.[16] It is of interest to see which group demands the more unhindered position in phenylsuccinic acid, and if the conformation is dependent upon the state of ionization of the carboxylates.[17]

Chart I



1 **2** **3**

The spectrum of unlabeled phenylsuccinic acid at pH 6 (at which ~30% of the molecules are in the monoanion form)[18] showed the expected ABX pattern, from which the following couplings were calculated: $J_{AB} = -15.1$, $J_{AX} = 9.0$, and $J_{BX} = 6.9$ Hz. A similar spectrum (Figure 1) of the material having about 60% enrichment of ^{13}C in one carbonyl group showed that each spectral line of the unlabeled material is almost symmetrically flanked by two new lines, which are the absorptions of the labeled material. Computer simulation of the spectra gave $J_{^{13}C\text{-}A} = 4.3$ and $J_{^{13}C\text{-}B} = 2.5$ Hz Using reasonable values for the limiting coupling constants for trans hydrogens ($J_T = 13.5$ Hz) and gauche hydrogens ($J_G = 2.8$ Hz),[19] the populations of the three conformers are calculated to be 0.58, 0.38, and 0.04. These values are probably good to ±5–8%.[20] Because of large steric effects, conformer **3** probably has the smallest population[21] (4%), but the weights of conformers **1** and **2** cannot be assigned. However, the fact that $J_{^{13}C\text{-}A}$ is larger than $J_{^{13}C\text{-}B}$ suggests that the labeled carbon and proton A are gauche in the major conformer and trans in the next most highly populated conformer, whereas the labeled carbon and proton B are very likely gauche in both principal conformers. This is consistent with **1** being the major conformer and **2** the next most highly populated conformer. For the populations of **1**, **2**, and **3** indicated above, limiting coupling constants for the ^{13}C–H couplings of $J_T \cong 11$ and $J_G \cong 2$ Hz would be required in order to fit the observed data. The alternate and probably incorrect assignment of conformers (**2**, 58%; **1**, 38%) would demand limiting ^{13}C–H values of $J_T \cong 1$ and $J_G \cong 4$ Hz, which is quite distant from the data given by Lemieux and Perlin, *et al.*

Varying the pH from 5 or 6 to 9 (at which the dianion form is strongly predominant)[18] had very little effect on the general appearance of the spectra, or the derived parameters (Table I). Thus, the preference for conformer **1** appears quite independent of monoanion or dianion character in this particular case. In contrast, the spectra of malic acid[22] and several halosuccinic acids[23] showed a substantial pH dependence. Erickson[23] assigned a value of 500 cal as an approximate indication of the greater repulsion of gauche carboxylates (dianion form) compared to the corresponding free

Table I
100-MHz Spectral Parameters

	Coupling constants, Hz					Chemical shifts,[a] ppm		
Solvent	J_{AB}	J_{AX}	J_{BX}	$J_{^{13}C\text{-}A}$	$J_{^{13}C\text{-}B}$	δ_A	δ_B	δ_X
D$_2$O, pH 6	−15.1	9.0	6.9	4.3	2.5			
D$_2$O, pH 9	−15.2	9.0	7.0	4.3	2.6			
Pyridine[c]	−16.8	5.2	9.9	7.5	3.1	3.16	3.85	4.8
Acetone-d_6[b]	−17.0	5.3	10.0	7.5	3.2	2.67	3.16	4.09
Acetic acid-d_4	−17.3	5.4	9.9	7.5	3.0	2.76	3.25	4.14

[a] A deuterum lock was used for the D$_2$O solutions; no internal standard was present. [b] These data are similar to the proton couplings reported by M. Brink, *Tetrahedron*, **24**, 7005 (1968). [c] In the organic solvents, the concentration was 2.5% (w/v), rather than *ca.* 1%, which was used for the aqueous solutions.

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[17] The dihedral angles in **1** and **2** are shown as 60° purely for convenience. Substantial deviations from this value are probable so that the most comfortable fit of groups may be achieved; see J. E. Mark and C. Sutton, *J. Amer. Chem. Soc.*, **94**, 1083 (1972).

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acids. In other work, very large values for the ratios of the ionization constants of diacids, K_1/K_2, were explained by a stabilization of the monoanion by intramolecular hydrogen bonding and by an enhanced coulombic interaction in cases where the COO^- and COOH groups were held near one another.[24,25] In a recent study on the thermodynamics of ionization of dicarboxylic acids, Purdie and Tomson indicated some reservations about the hydrogen-bonding theory.[26] The ionization of several diacids was shown to be dominated by entropy effects, which suggests that solvation of the charged center(s) is of prime importance. "Cooperative solvation" of the COO^- and COOH groups by a set of solvent molecules was mentioned as a possible alternative to intramolecular hydrogen bonding in the monoanion. In phenylsuccinic acid (like succinic acid itself), the magnitudes and the differences between the first and second acid dissociation constants are closer to those of fumaric acid, in which the carboxylates are held remote from one another, than to those of maleic acid. Thus, neither conformation nor acidity of this particular molecule seems to be affected by intramolecular hydrogen bonding or cooperative solvation to any great extent. It is noteworthy, however, that the monoesters of phenylsuccinic acid are between two and four times less acidic than the diacid, and that the COOH group adjacent to phenyl is about two times more acidic than the other COOH group, perhaps owing to the inductive effect of phenyl.[27]

In pyridine solution, the carboxylic acid groups are hydrogen bonded to solvent, but not ionized.[28] Significantly different nmr parameters result in this solvent: $J_{AB} = -16.8$, $J_{AX} = 5.2$, $J_{BX} = 9.9$, $J_{^{13}C\text{-}A} = 7.5$, and $J_{^{13}C\text{-}B} = 3.1$ Hz. These data suggest that conformer **2** is the dominant species in this solvent (~60%). The coupling constants in acetone-d_6 were quite similar to those in pyridine. Acetic acid-d_4 was tested to see if the coupling constants observed in this solvent would be similar to those found in aqueous solvents, since both are hydroxylic, or similar to the other organic solvents. As Table I indicates, all organic solvents are similar. Thus, the phenyl group prefers the least hindered position, trans to COOH, in the organic solvents tested, but the labeled COO^- group prefers the least hindered position in aqueous solvents.[29]

^{13}C spectra were obtained using the usual Fourier transform technique. The one-bond coupling constant between the labeled carbon and the carbon bearing phenyl was 55 Hz, approximately the same as that observed in acetic acid.[30] No splitting of the methylene carbon resonance was observed, and thus $^2J_{CC} \leqslant 3$ Hz, which is also close to literature values.

Experimental Section

The spectra of labeled and unlabeled phenylsuccinic acid were taken on a Varian XL-100 nmr instrument at 500 and at 100 sweep widths, using frequency counter calibration of resonances. The concentration of the solutions was 1.0–1.5% (w/v). Spectra at both sweep widths were simulated using the LAOCOON III program adjusted to provide a computer-generated plot of the spectrum.[31] The parameters were adjusted until the computer-generated plot was superimposable over the observed spectrum. In some cases the iterative operation was used, which led to root mean square errors of 0.08–0.1 between the calculated and observed data sets. Usually the data generated by the iterative procedure required one or two more trial-and-error adjustments before the computer plot and the observed spectrum were identical. The ^{13}C spectra were taken on an acetone-d_6 solution (2% w/v) using a 1K filter, and a 1500-Hz noise band width at 80% high power operation of the decoupler; 11,000 transients were taken using an acquisition time of 1.3 μsec and a 40-μsec pulse width. Under these conditions, little or no interference of the signal of the labeled carbonyl was observed. The synthesis of the substrate has been reported earlier.[32] In this work, signs of coupling constants are not implied unless expressly stated.

Acknowledgment.—Partial funds for the purchase of the XL-100 were provided by NSF Grant GP-10293, which is gratefully acknowledged.

Registry No.—Carbon-13 phenylsuccinic acid, 37729-65-0.

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A New Method for the Preparation of 4-Methylene-1-cyclohexenes

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Received June 19, 1973

The direct synthesis of 4-methylene-1-cyclohexenes *via* the Diels–Alder reaction, using allene as a dienophile and dienes such as 1,3-butadiene, substituted butadienes, and cyclic dienes, is possible only in special cases.[2,3] 4-Methylene-1-cyclohexenes are usually made by modification of other Diels–Alder adducts. For example, pyrolysis of 3-cyclohexenylmethyl acetate gave a 60% yield of 4-methylene-1-cyclohexene contaminated with toluene.[4] Treatment of the adduct of cyclopentadiene and methyl α-bromovinyl sulfone with sodium methoxide in dimethyl sulfoxide afforded 5-methylene-2-norbornene.[5] Finally, addition of methyllithium to the Diels–Alder adduct of 1,3-butadiene with 3-chloro-2-(trichlorosilyl)propane gave 4-methylene-1-

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