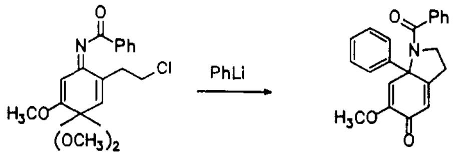
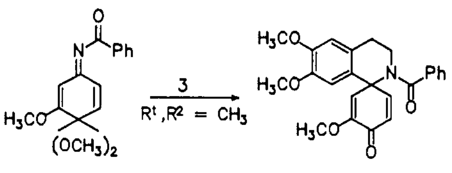
available compounds. Thus, 4,5-dimethoxy-2-(2-chloroethyl)aniline, the key intermediate for the preparation of **4a,b**, was prepared by nitration of 3,4-dimethoxyphenylacetic acid, followed by diborane reduction of the acid to the alcohol (99%) and conversion of the alcohol to the chloride (triphenylphosphine, carbon tetrachloride, 95%). Hydrogenation of this nitro compound afforded the above aniline, which was immediately reacted with benzoyl chloride (77% over two steps). Anodic oxidation[4] of the benzanilide furnished **4a** (90%).

The addition reactions of phenyllithium with **4a** and also **3** (R^1, R^2 = CH$_3$, X = Cl)[6,7] with **6** were conducted at −78 °C for 0.5 h. The reaction mixtures were then warmed to room temperature and heated to reflux for 1 h to effect the intramolecular cyclization. The resulting ketals were purified by chromatography on activity III neutral alumina and hydrolyzed with 5% aqueous acetic acid to give **5** (65% overall) and **7** (67% overall) after recrystallization. This chemistry demonstrated that both the B and C rings of the *Erythrina* skeleton could be formed via intramolecular cyclization. However, all attempts to hydrolyze the amide linkages of **5** and **7** led either to no hydrolysis or to destruction of the dienone unit.



4a **5** (65%)



6 **7** (67%)

The most direct method for effecting the final ring closure to the *Erythrina* tetracyclic skeleton would be hydrolysis of the amide group and intramolecular ring closure of the resulting amine with a side-chain having a leaving group. The *tert*-butoxycarbonyl group was chosen as the protecting group for the imide nitrogen in the hope that the subsequent deprotection of the amine could be effected without competing dienone–phenol rearrangement. The required precursor to **4b** was prepared by reaction of 4,5-dimethoxy-2-(2-chloroethyl)aniline with phosgene to form the isocyanate (70%), followed by reaction with *tert*-butyl alcohol to give the respective urethane (90%). Anodic oxidation of this urethane gave the quinone imide ketal **4b** in 90% yield.

Reaction of **3** (R^1, R^2 = CH$_3$, X = Cl) with **4b** essentially as outlined in the model studies afforded a crystalline product (70%) (Scheme II). However, spectroscopic data did not allow a clear choice between the two possible structures **9** and **10** (X = Cl). In simple systems, formation of a pyrrolidine is usually faster than ring closure to afford a piperidine;[8] however, it was desirable for future work to establish unequivocally the initial product from the addition. Reaction of the fluoro derivative **3** (R^1, R^2 = CH$_3$, X = F) with **4b** gave **9** (30%) in addition to the fluoro compound **10** (X = F, 40%).[9] This experiment established **9** as the product from reaction of **4b** with **3** (R^1, R^2 = CH$_3$, X = Cl). Thus, the intermediate amide anion **8** undergoes preferred closure to the six-membered ring. Reaction of **9** with trifluoroacetic acid/*p*-toluenesulfonic acid at room temperature deblocked the *tert*-butoxycarbonyl derivative to give the crude amine, which underwent cyclization to form **11** (80%), thus completing the sequence.

This chemistry comprises a new, convergent approach to the synthesis of the *Erythrina* alkaloids. The route is especially convenient since both segments of the *Erythrina* skeleton derive from 3,4-dimethoxyphenylacetic acid. In addition, this synthetic strategy could be adapted to the synthesis of the homoerythrinans and other biologically interesting nitrogen-containing spiro ring systems.

Acknowledgment. We thank the National Science Foundation for partial support of this work.

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(6) The lithium compound **3** was prepared via reaction of 2-(2-chloroethyl)-3,5-dimethoxybromobenzene with 2 equiv of *tert*-butyllithium at −78 °C. Although this reagent is known to form the corresponding benzocyclobutene on reaction at room temperature, successful annelation of this organolithium with benzonitrile has been reported.[7]

(7) Jakiela, D. J.; Helquist, P.; Jones, L. D. *Org. Synth.* **1984**, *62*, 74. Ponton, J.; Helquist, P.; Conrad, P. C.; Fuchs, P. L. *J. Org. Chem.* **1981**, *46*, 114.

(8) Knipe, A. C.; Stirling, C. J. M. *J. Chem. Soc. B* **1968**, 67.

(9) This product showed in the ^{1}H NMR spectrum the lowest field methylene group as a doublet of triplets with J_{HH} = 5.8 Hz and J_{HF} = 47.3 Hz and in the ^{19}F NMR spectrum the fluorine resonance at δ −218.4 as a triplet of triplets (J = 47.3 and 25.6 Hz).

(10) Part of this work was presented at the 19th Central Regional Meeting of the American Chemical Society, June 24–26, 1987, paper no. 282. The structural assignments were supported by the usual spectroscopic properties and exact mass measurements or combustion analyses. The following compounds were crystalline and had the indicated melting points: **4b**, 100 °C (dec); **5**, 223–225 °C; **5** (dimethyl ketal), 161–163 °C; **6**, 66–69 °C; **7**, 223–226 °C; **9**, 143–145 °C; **10** (X = F), 138–140 °C; **11**, 161–162 °C (dec).

NMR of Di-^{13}C-Labeled Compounds: Insights into the Effect of Alkylation, Ionization, and Micellization on Conformation†

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Received June 18, 1987

We have recently exploited a method[1,2] for detecting chain folding based on long-range coupling between two ^{13}C atoms spaced four carbons apart ($-{}^*CH_2-CH_2-CH_2-{}^*CH_2-$).[3] Thus, ^3J decreases from 3.5–4.0 to 1.5 Hz when a trans conformation about the central bond rotates into a gauche conformation (as was observed, for example, in the binding of an inhibitor to an enzyme).[3] The method is nondisruptive and works equally well for ordered and disordered systems. In the present communication, the power of the method is demonstrated with several dilabeled molecules whose conformations are affected by alkylation, ionization, and micellization. Information was obtained that is impossible to secure by any other means.

[1,4-^{13}C$_2$]Myristic acid, synthesized according to Scheme I, has ^3J = 3.5 ± 0.1 Hz which is independent of (a) the solvent (25 mM in chloroform, tetrahydrofuran, acetone, acetonitrile, and dimethyl sulfoxide), (b) the temperature (25–65 °C in dimethyl sulfoxide), (c) the particular doublet under scrutiny (namely that of the carbonyl or methylene carbon), and (d) the spectral mode (traced normally or with the aid of a 32-phase INADEQUATE sequence[4]). Since 3.5 Hz falls close to the value expected for a trans disposition,[5-7] myristic acid must be "linear", or nearly so, under all the above conditions (structure I). When, however,

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† Dedicated to Professor Ye Xui-Lin, Peking University, author of *Stereochemistry* (PRC, 1983).

(1) Phillippi, M. A.; Wiersema, R. J.; Brainard, J. R.; London, R. E. *J. Am. Chem. Soc.* **1982**, *104*, 7333.

(2) Marshall, J. L. *Carbon–Carbon and Carbon–Proton NMR Couplings: Applications to Organic Stereochemistry and Conformational Analysis*; Verlag Chemie: Deerfield, FL, 1983.

(3) Menger, F. M.; Carnahan, D. W. *J. Am. Chem. Soc.* **1986**, *108*, 1297.

(4) Bax, A.; Freeman, R.; Kempsell, S. P. *J. Am. Chem. Soc.* **1980**, *102*, 4849.

(5) Marshall, J. L.; Miiller, D. E. *J. Am. Chem. Soc.* **1973**, *95*, 8305.

(6) Barfield, M.; Burfitt, I.; Doddrell, D. *J. Am. Chem. Soc.* **1975**, *97*, 2631.

(7) Wehrli, F. W.; Wirthlin, T. *Interpretation of Carbon-13 NMR Spectra*; Heyden: New York, 1976; p 59.

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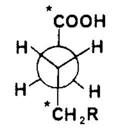
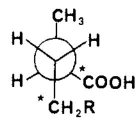


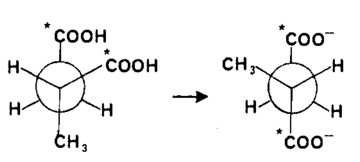
I



II

myristic acid is methylated at the 2-position, ^3J diminishes to 2.1 Hz. One can calculate from this coupling constant, along with $^3J_{trans} = 4.0$ Hz and $^3J_{gauche} = 1.0$ Hz for $-{}^*CO-CH_2-CH_2-{}^*CH_2-$ relationships,[5-7] that about two-thirds of the conformer population now has its carbonyl gauche to the hydrocarbon chain (structure II).[8] The di-^{13}C-labeling method should prove generally useful for detecting conformational changes, as occurs with this methyl-induced twist, in both chemical and biochemical systems.

[1,4-$^{13}C_2$]Methylsuccinic acid[9] in D_2O has $^3J = 2.1$ Hz at pD 1.0 (where both carboxyls are protonated) but $^3J = 4.2$ Hz at pD 12 (where both carboxyls are anionic).[10] Since the monomethyl ester of [1,4-$^{13}C_2$]succinic acid was found to have ^3J values in acidic and basic water differing by only 0.3 Hz, ionization per se has little if any effect upon the coupling constants. Therefore, the observed increase in ^3J from 2.1 to 4.2 Hz when methylsuccinic acid forms a dianion must reflect a gauche to trans rotation (eq 1).

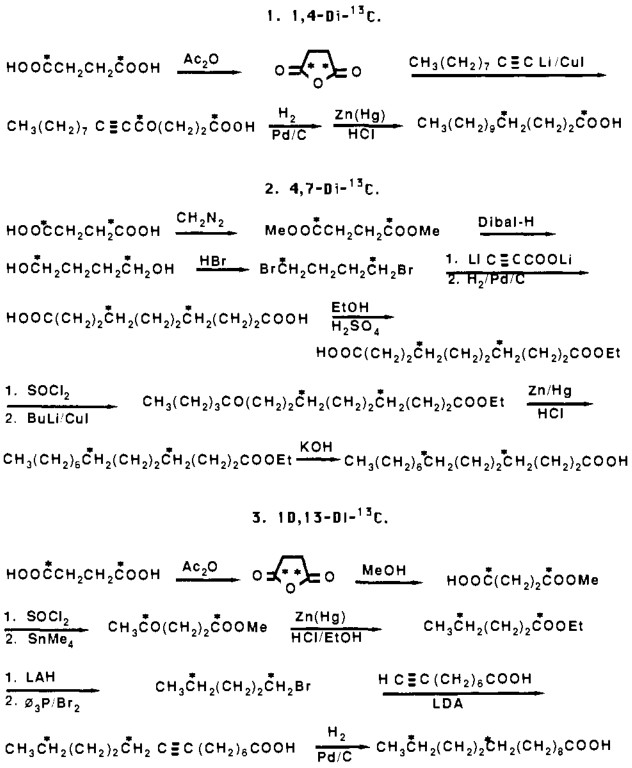


(1)

The di-^{13}C-labeling method was next applied to an ongoing and contentious issue in the field of colloid chemistry: micelle structure. Years ago we proposed that surfactant molecules within micelles are folded and disorganized.[11,12] Evidence in support of this concept includes the observation that (a) chain termini are in contact with the micelle periphery owing to chain looping[13] and (b) chains can bind nonradially to micelles.[3] Attempts to evaluate theoretically the extent of chain folding in micelles have led to diverse conclusions. Fromherz[14] endowed micelles with a crystal-like packing in which linear chains lie parallel to one another. Molecular dynamics computer simulations by Woods, Haile, and O'Connell[15] showed that about 28% of all bonds possess a gauche conformation. Gruen[16] calculated that the probability of a gauche linkage jumps from 0.28 near the micelle surface to about 0.36 near the chain termini (values that approximate those of a randomly coiled chain in a bulk *n*-alkane).

In order to determine experimentally the time-averaged conformations of micellized chains, we synthesized myristic acid dilabeled at three positions: 1,4, 4,7, or 10,13 (Scheme I). At concentrations of 0.01–0.10 M in 0.2 M KOD/D_2O (well above the cmc),[17] the potassium salt of [1,4-$^{13}C_2$]myristic acid displays $^3J = 3.7 \pm 0.1$ Hz. This coupling constant approximates the value expected for a linear molecule. Similarly, $^3J = 3.7$ Hz for micellar myristate labeled at the 4,7- and 10,13-positions. Therefore, we are forced to conclude that the micellized soap molecules assume largely transoid conformations at three different loci distributed across the chain. Our "brush heap" micelle model, replete with kinks and loops,[11,12] seems disallowed by the NMR data. As will be shown in the next paragraph, however, matters are not quite so simple (or unpleasant!).

Scheme I



[4,7-$^{13}C_2$]Myristic acid was converted into sodium [4,7-$^{13}C_2$]tetradecyl sulfate and [3,6-$^{13}C_2$]tridecylammonium chloride.[18]

$$CH_3(CH_2)_6{}^*CH_2(CH_2)_2{}^*CH_2(CH_2)_3OSO_3^-$$
$$^3J = 2.6 \text{ Hz}$$
$$CH_3(CH_2)_6{}^*CH_2(CH_2)_2{}^*CH_2(CH_2)_2NH_3^+$$
$$^3J = 2.0 \text{ Hz}$$

Monomeric [3,6-$^{13}C_2$]tridecylamine in chloroform has $^3J = 3.8$ Hz. But in D_2O at concentrations many-fold higher than the cmc's,[19] the anionic and cationic detergents have $^3J = 2.6$ and 2.0 Hz, respectively. As can be readily seen from $^3J_{trans} = 4.0$ Hz and $^3J_{gauche} = 1.5$ Hz,[5-7] the majority of C_5–C_6 or C_4–C_5 linkages are gauche when micellized. In other words, the detergent molecules, unlike the soaps, bend appreciably in the micellar state. The reason for the dependence of conformation upon head group is not understood. Perhaps only the carboxylate head group has a hydrated radius sufficiently small to permit packing into nonspherical aggregates (e.g., unilamellar disks originally proposed by Harkins[20] and Debye[21] but later discounted). In any event, theoretical approaches to micelle structure, which to date have not differentiated among head group types, can clearly no longer afford this luxury.

Acknowledgment. This work was supported by the National Institutes of Health.

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[8] The lifetime of a trans state is approximately 10^{-10} s. Since rotation is fast relative to the NMR time scale, $^3J_{obsd}$ is a weighted average of $^3J_{trans}$ and $^3J_{gauche}$. Uncertainty in the coupling constants for "pure" trans and gauche limits, of course, the accuracy of trans/gauche ratios. See: London, R. E.; Avitabile, J. *J. Am. Chem. Soc.* **1977**, *99*, 7765.

[9] This compound was prepared by treating dilabeled diethyl succinate with 2 equiv of LDA and 1 equiv of methyl iodide followed by hydrolysis.

[10] The Karplus curve for $-\underline{C}O-CH_2-CH_2-\underline{C}O-$ has not been established as it has[3-5] for $-\underline{C}H_2-CH_2-CH_2-\underline{C}H_2-$ and $-\underline{C}O-CH_2-CH_2-\underline{C}H_2-$. We are currently carrying out calculations to fill this void.

[11] Menger, F. M. In *Surfactants in Solution*; Mittel, K. L., Lindman, B., Eds.; Plenum: New York, 1984; p 347.

[12] Menger, F. M. *Nature (London)* **1985**, *313*, 603.

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[14] Fromherz, P. *Chem. Phys. Lett.* **1981**, *77*, 460.

[15] Woods, M. C.; Haile, J. M.; O'Connell, J. P. *J. Phys. Chem.* **1986**, *90*, 1875.

[16] Gruen, D. W. R. *J. Phys. Chem.* **1985**, *89*, 153.

[17] The cmc of potassium myristate is 7 mM. Osipow, L. I. *Surface Chemistry*: Reinhold: New York, 1962.

[18] Unfortunately, we lacked sufficient material to carry out analogous conversions with [1,4-$^{13}C_2$]- and [10,13-$^{13}C_2$]myristate.

[19] The cmc of tridecylammonium chloride, determined tensiometrically in 0.01 N HCl, equals 4 mM.

[20] Harkins, W. D. *J. Chem. Phys.* **1948**, *16*, 156.

[21] Debye, P. *Ann. N.Y. Acad. Sci.* **1949**, *51*, 575.