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(6) 7 is the acid moiety of the pyrethroids NRDC-143 or Permethrin (ester with 3-phenoxybenzyl alcohol) and NRDC-149 or Cypermethrin (ester with (±)-α-cyano-3-phenoxybenzyl alcohol).[3]
(7) **2**: IR ($CHCl_3$) ν 1790 cm^{-1} (CO); ^1H NMR ($CDCl_3$) δ 3.28 (dd, J = 4 and 16 Hz, H_a C_3), 3.82 (dd, J = 7.5 and 16 Hz, H_b C_3), 5.09 (dd, J = 4 and 7.5 Hz, H C_2).
(8) **4**: mp 75–76 °C; IR ($CHCl_3$) ν 1805 cm^{-1} (CO); ^1H NMR ($CDCl_3$) δ 1.42 (s, CH_3), 1.45 (s, CH_3), 3.00 and 3.14 (AB, J = 16 Hz, H_2 C), 3.45 and 3.60 (AB, J = 16 Hz, CH_2 CCl_3); ^{13}C NMR ($CDCl_3$) δ 196.6 (s, C_1), 95.3 (s, CCl_3), 80.8 (s, C_2), 57.0 and 56.4 (2t, $2CH_2$), 37.9 (s, C_3), 25.1 and 23.8 (2q, $2CH_3$).
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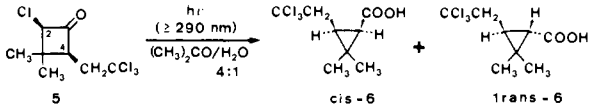
(10) **5**: mp 56–57 °C; IR ($CHCl_3$) ν 1795 cm^{-1} (CO); ^1H NMR ($CDCl_3$) δ 1.14 and 1.63 (2s, $2CH_3$), 2.87 (dd, J = 6 and 15 Hz, H_aC CCl_3), 3.15 (dd, J = 4 and 15 Hz, H_bC CCl_3), 3.47 (m, J = 2, 4, and 6 Hz, H C_4), 4.76 (d, J = 2 Hz, H C_2); ^{13}C NMR ($CDCl_3$) δ 197.0 (s, C_1), 97.8 (s, CCl_3), 69.4 (d, C_2), 60.6 (d, C_4), 49.5 (t, CH_2CCl_3), 36.8 (s, C_3), 27.4 (q, CH_3 trans), 18.6 (q, CH_3 cis).
(11) After separation on silica gel (hexane–ether). *cis*-**6**: mp 92–93 °C; IR ($CHCl_3$) ν 1695 cm^{-1} (CO); ^1H NMR (360 MHz, $CDCl_3$) δ 1.23 and 1.26 (2s, $2CH_3$),1.60 (ddd, J = 5, 7, and 9 Hz, H C_2), 1.69 (d, J = 9 Hz,[12] H C_1), 3.00 (dd, J = 7 and 15 Hz, CH_a CCl_3), 3.15 (dd, J = 5 and 15 Hz, CH_b CCl_3); ^{13}C NMR ($CDCl_3$) δ 178.5 (COO), 99.8 (CCl_3), 49.2 (CH_2 CCl_3), 30.6 and 28.7 (C_2 and C_1), 28.6 (*r*-1-CH_3 trans), 26.5 (C_3), 14.7 (*r*-1-CH_3 cis). *trans*-**6**: mp 132–133 °C; IR ($CHCl_3$), ν 1695 cm^{-1} (CO); ^1H NMR (360 MHz, $CDCl_3$) δ 1.23 and 1.32 (2s, $2CH_3$), 1.48 (d, J = 5.5 Hz,[12] H C_1), 1.85 (br q with J = 6.5 Hz, H C_2), 2.70 (dd, J = 6.5 and 14.5 Hz, CH_a CCl_3), 2.86 (dd, J = 6.5 and 14.5 Hz, CH_b CCl_3); ^{13}C NMR ($CDCl_3$) δ 178.5 (COO), 99.0 (CCl_3), 53.4 (CH_2 CCl_3), 32.5 and 30.7 (C_1 and C_2), 28.0 (C_3), 22.0 (*r*-1-CH_3 trans), 20.4 (*r*-1-CH_3 cis).
(12) Since no photo-Favorskii rearrangement of an α-halocycloalkanone[13] leading to a carboxylic acid has yet been described, it is worth mentioning that the photo-Favorskii rearrangement **5** → **6** exhibits a lower degree of retention of configuration than the base-induced rearrangement. Thus the irradiation of an 80% acetone–water (v:v) solution of 2,4-*cis*-**5** (125-W high-pressure Hg lamp, Pyrex, 20 °C, 44 h) afforded a 1:2 mixture of cis and trans isomers of **6** in 97% yield. Since **6** does not absorb above 290 nm, no isomerization was observed when an acetone–water solution of either *cis*- or *trans*-**6** was irradiated through Pyrex glass.



(13) Examples of photo-Favorskii rearrangement of α-chloro ketones in methanol have been reported: (a) Kaplan, B. E.; Hartwig, A. L. *Tetrahedron Lett.* **1970**, 4855. (b) Givens, R. S.; Strekowski, L. *J. Am. Chem. Soc.* **1975**, *97*, 5867. (c) Jones, G., II; McDonnell, L. P. *Ibid.* **1976**, *98*, 16203.
(14) For melting point and ^1H NMR of both stereoisomers of 7, see: M. Elliott, *Pestic. Sci.* **1974**, *5*, 791.
(15) For comparison, the following yields of [2 + 2] cycloadducts were found using **3** or dichloroketene (both generated in situ by dehydrohalogenation of the corresponding acid chlorides by NEt_3): with methylenecyclobutane, 49 and 33%,[16] respectively; with cyclopentadiene, 89 and 77%,[17] respectively; with indene, 58 and 48%,[18] respectively.
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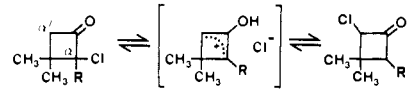
(18) Potts, T. R.; Harmon, R. E. *J. Org. Chem.* **1969**, *34*, 2792.
(19) Chloro(2,2-dichlorovinyl)ketene, prepared in situ from 2,4,4-trichlorobut-3-enoic acid chloride, gives the [2 + 2] cycloadduct with isobutylene in only 17% yield.
(20) The name *"cine rearrangement"* is used here with reference to *"cine substitution"*, a commonly used term for α′ substitution of α-halocyclobutanones by external nucleophiles (Nu ≠ halogen). Cf. Conia, J. M.; Robson, M. J. *Angew. Chem.* **1975**, *87*, 505, and references cited therein. The distribution of products of the "cine rearrangement" was found to depend on the nature of the second α substituent. These product distributions, which are found starting from either i or iii, indicate a transition state with a high degree of ionic character, e.g., ion pair ii (cf. Bordwell, F. G.; Carlson, M. W. *J. Am. Chem. Soc.* **1970**, *92*, 3377), since the α substitution by electron-withdrawing groups such as CH_2CCl_3 or Cl clearly destabilizes the positive charge in the α position of the allyl cation, thus directing the chlorine anion into the α′ position and vice versa. We should note here, that the "cine rearrangement" is not restricted to α-chlorocyclobutanones. 2-Bromo-2-(2′,2′,2′-tribromoethyl)-3,3-dimethylcyclobutanone readily underwent (HBr, EtOH, 70 °C) catalyzed rearrangement to give 4-bromo-2-(2′,2′,2′-tribromoethyl)-3,3-dimethylcyclobutanone. The latter compound is a convenient precursor for the biologically very active *cis*-2,2-dimethyl-3-(2′,2′-dibromovinyl)cyclopropane-1-carboxylic acid esters.[3]



R = CH_2CCl_3	0 %	100 %
R = Cl	0 %	100 %
R = CH_3	57 %	43 %
R = $(CH_2)_2CH(CH_3)_2$	15 %	85 %

(21) From the economic point of view, it is noteworthy that in the present synthesis of 7 only cheapest and readily available substances are used; e.g., triethylamine represents the most expensive substance used in a molar equivalent amount!

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Selection of Nonprotonated Carbon Resonances in Solid-State Nuclear Magnetic Resonance

Sir:

Procedures that simplify NMR spectra are important when studying complex molecules, especially when resonance assignments result from the physical basis of a selection process. Among the most useful spectroscopic techniques of high resolution ^{13}C NMR of liquids is the application of weak modulated proton decoupling to selectively broaden those resonances from carbons with directly bonded protons;[1] additional manipulations[2,3] result in a carbon spectrum with narrow lines from only the nonprotonated carbons. This communication describes a method for obtaining the analogous nonprotonated carbon spectrum for solid samples where the signals from carbons with attached protons are suppressed.

In both solids and liquids the much stronger ^{13}C-^1H interaction for carbons with bonded protons is utilized for selection of the nonprotonated carbons. However, the heteronuclear spin interactions that are effective are different in the two cases: with scalar spin-spin coupling operative in liquids and static dipole-dipole coupling in both amorphous and polycrystalline solids.

Proton-enhanced NMR[4] is combined with magic angle sample rotation[5] to give natural abundance ^{13}C spectra of complex molecules in the solid state. The strongest spin in-

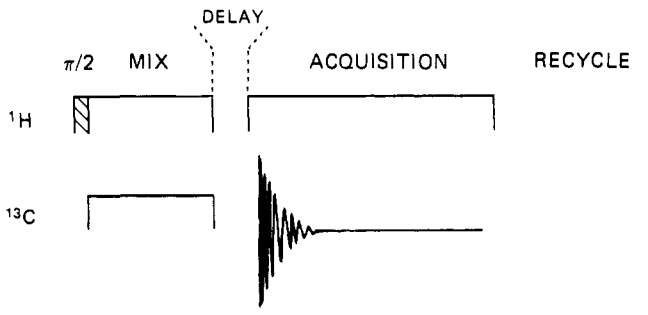

Figure 1. Pulse sequence used to suppress signals from protonated carbons in solid samples. $\pi/2$ represents the initial 90° ^1H pulse. The mix period consists of a long ^1H irradiation that is phase shifted 90° from the initial pulse to spin lock the protons and ^{13}C irradiation that is adjusted in strength to allow magnetization transfer (see ref 4). The delay interval is without any applied radio frequency fields to allow ^{13}C spins to precess in their local ^1H dipolar fields. Proton irradiation is reapplied during the acquisition period to give decoupled carbon signals. Proton magnetization recovers in the static magnetic field during the recycle delay.

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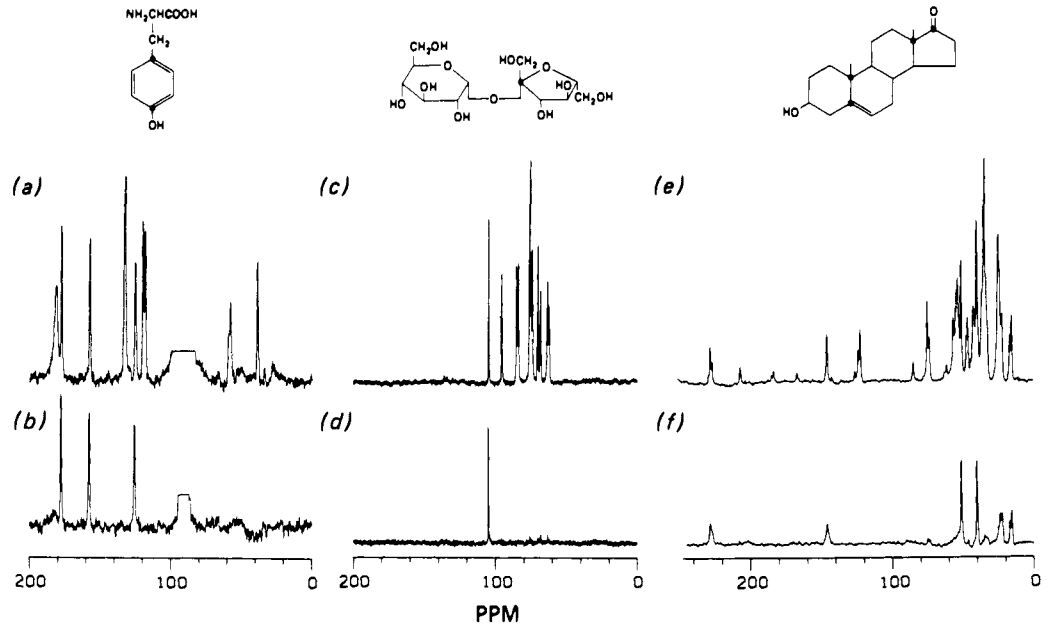

Figure 2. ^{13}C NMR spectra of polycrystalline organic molecules. Spectra were obtained on a home-built double-resonance spectrometer with ^{13}C resonance frequency of 37.83 MHz. The proton-decoupling field was 1.5 mT. Samples consisted of ~300 mg of material packed in Andrew-type rotors. All spectra were obtained with cross-polarization mix times of 1 ms and systematic phase inversions to remove artifacts. Chemical shifts are reported to external Me_4Si. Pairs of spectra are plotted on the same scale. (a) Tyrosine: complete spectrum from 300 accumulations with a 3.5 recycle delay and 0.1-s acquisition time; the Delrin rotor contributes the large peak at 90 ppm and the spinning side band at 182 ppm. (b) Tyrosine nonprotonated carbon spectrum: obtained under the same conditions as (a) except for a 40-μs period without proton decoupling prior to data acquisition (carbonyl, 178; C_ζ, 158; C_γ, 129; Delrin, 90 ppm). (c) Sucrose: Complete spectrum from 1000 accumulations with a 20-s recycle delay and a 0.8-s acquisition time in a Kel-F rotor. (d) Sucrose nonprotonated carbon spectrum: obtained under the same conditions as (c) except for a 45-μs period without proton decoupling prior to data acquisition (C-2, 104 ppm). (e) Δ^5-Androster-3-ol-17-one. Complete spectrum from 1,000 accumulations with a 12 s recycle delay and a 0.4-s acquisition time in a Kel-F rotor. (f) Δ^5-Androster-3-ol-17-one nonprotonated carbon spectrum. Obtained under the same conditions as (e) except for a 40-μs period without proton decoupling prior to data acquisition (C-17, 225 ppm; C-5, 143 ppm; C-13, 48 ppm; C-10, 39 ppm).

teraction for most carbons is dipolar coupling to protons. The cross-polarization of carbons from protons relies on this mechanism, while proton decoupling during data acquisition removes the severe dipolar broadening. The magic angle spinning removes the chemical-shift anisotropy to give a spectrum with a relatively narrow resonance for each carbon in the sample. The ^{13}C-^1H dipolar interaction has a $1/r^3$ dependence, where r is the internuclear distance; therefore, the coupling is much greater for carbons bonded to protons ($r \approx 1.1$ Å) compared with those carbons with protons only on nearest neighbor carbons ($r > 2.0$ Å). This substantial difference can used to differentiate between these two classes of carbons. Experimentally this can be accomplished with a slight modification of the normal proton-enhanced NMR pulse sequence. As outlined in Figure 1, a brief delay without proton decoupling is inserted between the development of ^{13}C magnetization with the mix pulse and data acquisition with full proton decoupling. This procedure has been used for two-dimensional separated local field experiments[6] by incrementing the delay interval; it has also been used for T_2 measurements of ^{13}C in plastic crystals.[7] The sequence can be modified for multiple-contact cross-polarization.[8]

Separated local field spectroscopy[9] has characterized the nature of the ^{13}C-^1H dipolar fields. There are several effects that can mitigate the selective dipolar effect of bonded protons. Spin diffusion among the protons and the cumulative influence of more distant protons were anticipated as problems for isolation of local field effects.[9] Experiments on crystals and oriented materials[6,8,10] have demonstrated that spin diffusion is not a severe problem in most cases and the bonded protons are enough closer to the attached carbon to clearly dominate over the effects of neighboring protons. Molecular motion can reduce the strength of dipolar coupling; thus a rapidly rotating group could appear as if its protons were farther away.

In polycrystalline samples all angles are present; therefore both dipolar and chemical-shift powder patterns are present. The sample spinning brings all chemical-shift components to the ^{13}C isotropic resonance position which then would have all ^{13}C-^1H dipolar splitting frequencies associated with it in a powder average.[11] The destructive interference of the collection of dipolar splittings causes a rapid loss of ^{13}C magnetization during the delay period without proton irradiation. This provides the temporal resolution between classes of carbons.

Figure 2 contains natural abundance ^{13}C NMR spectra of three types of polycrystalline organic molecules: sucrose, tyrosine, and Δ^5-androster-3-ol-17-one. For rigid molecules a delay time of 40-100 μs without decoupling provides excellent resolution between protonated and nonprotonated carbons. A representative sampling of organic molecules from this Department of Chemistry have been run and the selection for nonprotonated carbons has always worked. In some cases there is a moderate loss in intensity of nonprotonated carbon resonances owing to the effect of neighboring protons and in others small out-of-phase contributions from protonated carbons remain. Because oscillations of carbon magnetization are occurring during the time period without decoupling, imperfections can be reduced by adjusting the delay interval. Some methyl carbon resonances are difficult to eliminate entirely, presumably because rapid methyl group rotations reduce the proton-carbon dipolar couplings; however, since they usually are far upfield resonances, no confusion results. An additional advantage of the procedure is that it significantly reduces interference from Delrin or other rotor materials.

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Detection of Individual Carbon Resonances in Solid Proteins

Sir:

Natural abundance ^{13}C nuclear magnetic resonance spectroscopy is one of the most informative NMR approaches for the study of proteins.[1,2] A significant number of new ideas on the chemistry, structure, and dynamics of individual residues and the peptide backbone have resulted from ^{13}C NMR of proteins in solution. There are a number of reasons to expect NMR spectroscopy of proteins in the solid state will be of even greater value than the solution studies. The anisotropic character of nuclear spin interactions is retained in the absence of molecular motion;[3] therefore angular and distance parameters can be extracted with a variety of experiments. The ultimate ^{13}C resolution in solids may be significantly better than in solution because the isotropic chemical-shift dispersion is the same and experimental procedures can remove static line-broadening mechanisms but not relaxation-induced widths.[4] The relatively small globular proteins that are most amenable to high resolution solution NMR are exactly the same ones that crystallize most conveniently for X-ray diffraction analysis; so NMR of polycrystalline proteins will be complementary to diffraction studies. More importantly those proteins not readily crystallized and not water soluble can be studied as amorphous materials. A variety of structural, mechanical, and intrinsic membrane proteins fall in this category; thus solid-state NMR of proteins offers the promise of extending the range of the method.

There are formidable problems of sensitivity and resolution associated with natural abundance ^{13}C NMR of molecules as large and complex as proteins. The procedures that deal with the fundamental static nuclear spin interactions are now established experimental methods. These include the cross-polarization of carbon magnetization from protons and the decoupling of ^{1}H–^{13}C dipolar interactions during data acquisition.[5] Mechanical sample rotation at the magic angle removes the ^{13}C chemical-shift anisotropy.[6] A spectrum results with single resonance lines of approximately equal area, height, and width for each carbon.

Because of the large number of overlapping protein resonances, resolution enhancement is needed for both solution and solid-state studies to work with individual carbon signals. The aromatic amino acids are the focus of attention because they are relatively few in number with high functionality both chemically and biologically with resonances that appear in an uncluttered spectral region. In solution the nonprotonated aromatic carbons are narrower than the others, although this advantage is lost for solids; however, in both cases this restricted class of resonances can be selected experimentally. The solution studies of proteins rely on modulated off-resonance proton decoupling to broaden the protonated carbons.[7] A selection procedure for nonprotonated carbons of solids is described in the preceding paper that uses the stronger dipolar coupling of bonded protons to carbon to remove those resonances.[8] Not only do these selection procedures increase resolution by having 7 instead of 23 lines in the region 110–160 ppm from Me_4Si, they also provide partial assignments of resonances.

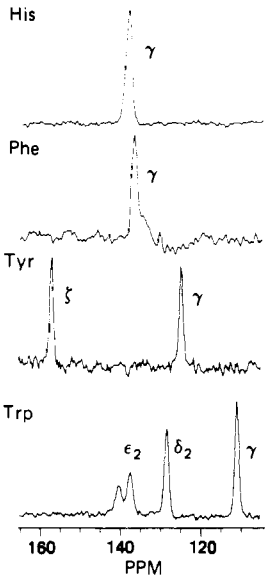

Figure 1. ^{13}C spectra of the nonprotonated ring carbons of the polycrystalline aromatic amino acids. All were obtained using the procedure of ref 8 with 1-ms mix time, 3-s recycle delay, 0.1-s acquisition time, and 300 acquisitions. The delay prior to data acquisition without decoupling to remove the protonated carbon resonances was 40 μs for His, Tyr, and Trp and 90 μs for Phe. All chemical shifts are relative to external Me_4Si.

Figure 1 contains the nonprotonated carbon spectra of the four polycrystalline aromatic amino acids. The assignments are readily made by comparison with the solution spectra. The line width of the aromatic resonances of amino acids is ~0.5 ppm (20 Hz) compared with 0.01 ppm for the same molecules in solution. This substantial line width remains in the presence of 3.0-mT ^{1}H decoupling and 4.0 kHz magic angle sample spinning and is a major limitation for ^{13}C NMR of solid proteins. Resonances from some carbons of amino acids have narrower lines (5–10 Hz), especially methyls of aliphatic side chains and carbonyl carbons. In general those carbons bonded to one nitrogen are split into an asymmetric doublet (e.g., Trp C_{ϵ_2} in Figure 1) in a 3.5-T field because the magic angle spinning does not completely average the dipolar coupling between the spin $\frac{1}{2}$ ^{13}C nucleus and the ^{14}N nucleus with its substantial quadrupole moment.[9] An exception is His C_γ (Figure 1) which is apparently unperturbed.

The solid-state spectra were obtained on a home-built double-resonance spectrometer with a 3.5-T magnet with ^{13}C resonance frequency of 37.83 MHz. The ^{1}H decoupling field used for the spectra shown was 1.5 mT. Magic angle spinning at 3.2 kHz was performed in 10-mm sample chamber Andrew rotors holding ~300 mg of material.[10] The solution spectrum was taken on a Nicolet NT-150 spectrometer with ^{13}C resonance frequency of 37.74 MHz.

We are investigating the bacteriophage fd by NMR, particularly the major coat protein.[11] This structural protein resides within the cell membrane during part of the virus life cycle and is completely intractable and insoluble when isolated. Without detergents or lipids the coat protein can only be studied in the solid state. The protein has 50 amino acids with

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