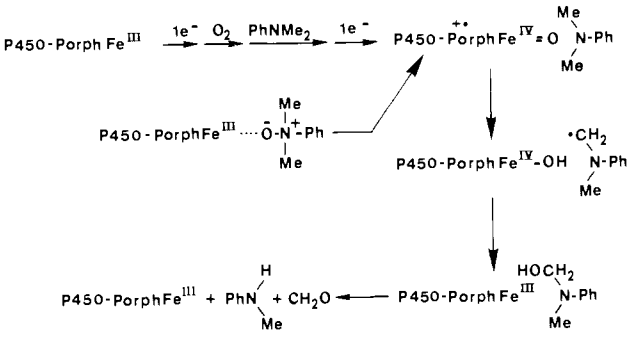
Scheme I



lecular isotope effect is defined as the preferential removal of the protio- vs. the deuteriomethyl group when both are present in the same molecule of aniline. Intermolecular isotope effects occur as the result of preferential N-demethylation of the d_0 vs. the d_6 substrate when both substrates are present in the reaction mixture, i.e., an isotope competition experiment. Demethylation of both DMANO and *p*-CNDMANO proceeded with a significant intramolecular isotope effect with both cytochrome $P450_{CAM}$ and $P450_{LM2}$, suggesting that carbon–hydrogen bond breaking is contributing to the rate-limiting step of demethylation. The porphyrin model system showed comparable intramolecular isotope effects.[2,9] It is also evident that $P450_{CAM}$ displays a larger preference for hydrogen abstraction from CH_3 vs. CD_3 than does $P450_{LM2}$. Small but significant intermolecular isotope effects were observed with $P450_{CAM}$, while this is effectively masked in the $P450_{LM2}$ reactions.

Cytochrome $P450_{LM2}$ will also catalyze the oxidative demethylation of dimethylaniline (K_m = 126 μM, V_m = 16.3 nmol/min/nmol P450) and *p*-cyanodimethylaniline (K_m = 50 μM, V_m = 7.7 nmol/min/nmol P450) in the presence of NADPH, molecular oxygen, and saturating amounts of NADPH–cytochrome P450 reductase. Both the intra- and intermolecular isotope effects observed with these reactions are similar to those seen with the corresponding *N*-oxides, suggesting that the active hydrogen-abstracting species generated in both cases are similar. These results are also consistent with those reported for the demethylation of *N*,*N*-dimethylphentermine by purified rat liver P450.[10] If the observed intramolecular isotope effects for the demethylation of DMA and *p*-CNDMA by cytochrome P450, through the pyridine nucleotide/O_2 dependent reaction, vs. the *N*-oxide-supported case had been substantially different it would imply that the *N*-oxide could not be an intermediate prior to hydrogen abstraction in the reaction path. The fact that these two isotopes effects are of the same magnitude does not preclude the formation of an *N*-oxide intermediate in the normal NADPH/O_2 reaction, but neither does it require such an intermediate. It does suggest that the species active in carbon–hydrogen bond scission is similar in both cases. Thus, these studies point to reaction of exogenously supplied *N*-oxide via oxygen atom transfer to the heme iron, followed by abstraction of a methyl hydrogen and subsequent oxygen radical capture to generate a carbinolamine intermediate, which decomposes to the observed products. The lack of significant intermolecular isotope effects in demethylation of dimethylanilines by the reconstituted cytochrom P-450 systems and in demethylation of dimethylaniline *N*-oxides by the iron(III) cytochrome P450's must be due to a commitment to reaction that occurs prior to C–H bond breaking. These commitment steps may involve (Scheme I) the formation of the reactive cytochrome P450 species following the second $1e^-$ transfer from reductase and oxygen transfer from *N*-oxide to P450-PorphFe^{III}. The significant intramolecular isotope effects show that bond breaking is at least partially rate determining in the demethylation step. The inability of either *N*-oxide to support normal substrate oxygenation is probably related to the proximity and orientation effects common to all enzymes, which would produce an enormous enhancement of the rate of N-demethylation relative to the rate of dissociation of the heme/oxygen–dimethylaniline complexes.

Acknowledgment. This study was supported by a National Institutes of Health grant to S.G.S. (GM31756) and an American Cancer Society grant to T.C.B. (0843983); S.G.S. is a Career Development Awardee (AM01160), and M.W.N. received support as an NIH postdoctoral fellow.

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Two-Dimensional Exchange NMR in Static Powders: Interchain ^{13}C Spin Exchange in Crystalline Polyethylene

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Two-dimensional (2D) NMR spectroscopy has established itself as a valuable method for the study of exchange processes. In solution,[1] in powdered solids under magic angle spinning conditions,[2] and in single or plastic crystals[3] exchange is measured between well-resolved peaks. We here want to demonstrate the application of 2D exchange NMR to a powdered solid with chemical shielding anisotropy (2DECSA). The experiment exploits the dependence of the nuclear resonance frequency on the molecular orientation. The time dependence of spin exchange or molecular jumps and the change in orientation of the chemical shielding tensor can be studied on a time scale of the order of 10^{-2}–10^2 s.

A detailed description of 2D exchange NMR can be found elsewhere.[1,2,4] The pulse sequence used is shown in Figure 1. The measured 2D NMR spectrum $F(\omega_1,\omega_2;\tau)$ represents the correlation function between the NMR resonance frequencies ω_1 before and ω_2 after an exchange time τ. Any exchange process that couples different resonance frequencies ω_1 and ω_2 will manifest itself by off-diagonal signal intensity in the 2D spectrum.

In the case of anisotropic chemical shielding the nuclear resonance frequency depends on the molecular orientation and is given by

$$\omega = \omega_0(1 - \lambda_{11}^2\sigma_{11}^2 - \lambda_{22}^2\sigma_{22}^2 - \lambda_{33}^2\sigma_{33}^2) \qquad (1)$$

where ω_0 is the chemical shift reference frequency, the σ_{ii} are the principal elements of the chemical shielding tensor, and the λ_{ii} are the direction cosines of the angles between the magnetic field and the tensor principal axes. In a powder all orientations contribute to the spectrum, which shows a characteristic line shape (Figure 2a) with discontinuities at frequencies ω_{ii} that correspond to the σ_{ii} values. An exchange process involving a change in molecular orientation alters the resonance frequency. The resulting 2D powder spectrum[4] typically contains a large signal along the diagonal from molecules that are in the original orientation, whereas exchange is reflected by off-diagonal ridges and humps. The off-diagonal pattern is specific for the change in orientation of the shielding tensor and allows for a detailed characterization of the exchange process.

2DECSA NMR spectra for the ^{13}C methylene resonance of polyethylene are shown in Figure 2. The spectra reflect mainly

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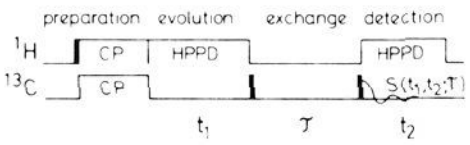

Figure 1. 2D exchange NMR pulse sequence used. 90° pulses (5 μs) are in black. Cross-polarization (CP; 1.5 ms), high-power proton decoupling (HPPD), and proton spin-temperature alternation were used.[9] The experiment is repeated for a number of t_1 values. Fourier transform of $S(t_1,t_2;\tau)$ gives the 2D spectrum $F(\omega_1,\omega_2;\tau)$.

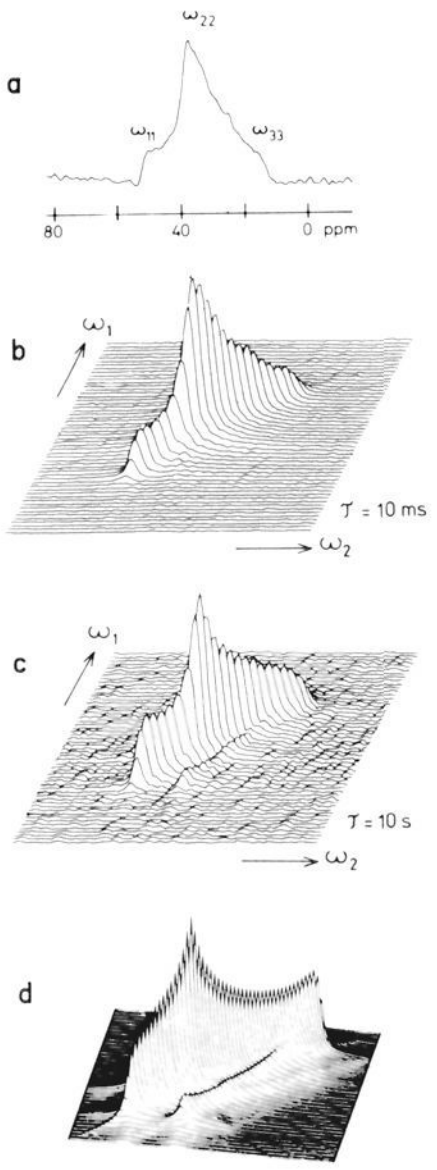

Figure 2. ^{13}C exchange NMR of the methylene resonance in the crystalline fraction of polyethylene (DOWLEX 2045) at room temperature, ^{13}C resonance frequency 75.43 MHz. The instrument was a Bruker CXP 300. (a) Normal spectrum. The singularities at ω_{ii} in the powder line shape are indicated. The spectral width is 7 kHz. (b,c) Stacked plots of the 2DECSA spectra after exchange times τ of 10 ms and 10 s. The spectral width is 7 kHz in both directions; 64 t_1 values were used with an increment of 60 μs. For each t_1, 400 sweeps were averaged. (d) Simulated 2DECSA spectrum for exchange between shielding tensor orientations that are rotated by 0°, 90°, 180°, and 270° around the σ_{33} axis. In this case, 0° and 180° give the same spectrum, as do 90° and 270°. Exhange is assumed to be complete; i.e., all orientations contribute equally. Appropriate line broadening has been added.

the crystalline fraction of the polymer. The signal from the amorphous fraction is strongly suppressed by the relatively short cross-polarization time used (Figure 1). In addition, the fast spin–lattice relaxation of the amorphous fraction ($T_1 \approx 0.3$ s) ensures that it does not contribute to the exchange spectrum after 10 s.[9c] The spectra obtained after exchange times of 10 ms and 10 s are strikingly different: a pronounced ridge appears on both sides of the diagonal for the longer exchange time. In Figure 2c, the posterior ridge is hidden behind the diagonal peaks. The ridges are the manifestation of exchange. In this case, we can obtain the change in orientation of the shielding tensor in a fairly simple way. The ridges begin at the intersection of ω_{11} and ω_{22} and converge toward ω_{33}, indicating that the exchange leaves the direction of σ_{33} unaltered whereas σ_{11} and σ_{22} are interchanged. This corresponds with two possible tensor reorientations: (1) a rotation by 90° around the σ_{33} axis or (2) a rotation by 180° around the axis bisecting the σ_{11} and σ_{22} directions. (1) and (2)

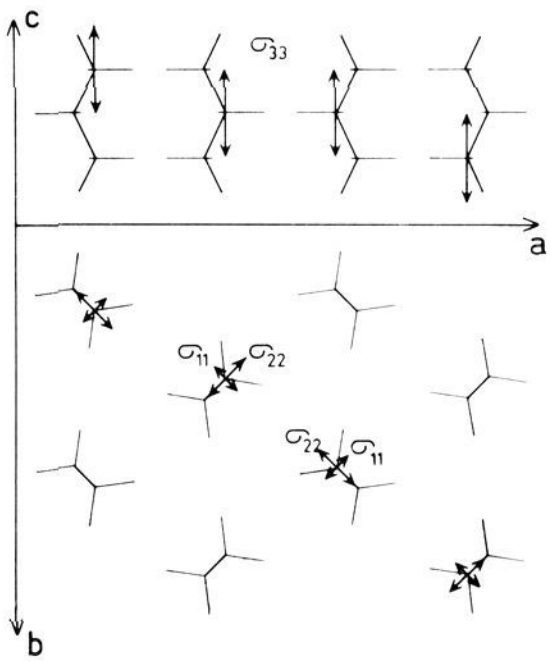

Figure 3. Crystalline structure of polyethylene and the orientation of the ^{13}C methylene shielding tensor. The molecular projections on two crystal planes are shown. The orientation of the shielding tensor is shown for the four different methylene groups in the unit cell.

give the same 2D exchange spectrum. The simulated spectrum (Figure 2d) indeed reproduces the measured one accurately. Simulations with rotation angles deviating more than 10° never matched with the measured spectrum.

We now must determine which physical process explains the observed exchange. The crystalline structure of polyethylene[5] and the orientation of the ^{13}C shielding tensor[6] are known and are shown in Figure 3. The molecular chain axes are parallel, but two orientations of the molecular planes occur that are approximately perpendicular to each other. σ_{33} lies parallel to the chain axis. First, we can exclude reorientation 2: an upside-down jump of the polymer chain is physically impossible, whereas molecular symmetry makes cases 1 and 2 equivalent for spin exchange. For reorientation 1 two processes can be envisaged: (a) a molecular jump by 90° of the polymer around the chain axis or (b) interchain spin exchange between ^{13}C nuclei located on neighboring molecules with mutually perpendicular orientation. The jump process (1a) cannot a priori be excluded. It might arise when lattice defects move through the crystal, leaving behind a structure in which all chains have changed their orientation by 90°. However, interchain spin exchange (1b) is the most plausible explanation. It is supported by additional experiments. We found that a raise in temperature does not increase the rate of exchange, whereas partial proton decoupling does. The latter is expected for spin exchange between weakly coupled nuclei in the presence of strong proton dipolar fields. ^{13}C spin exchange then is proportional to the probability that two exchanging nuclei have the same resonance frequency.[7] Without decoupling this probability is low because the proton local fields cause a large spread in ^{13}C resonance frequencies. The probability increases when the spread is narrowed by incomplete proton decoupling. If the nuclei have different chemical shifts, complete proton decoupling quenches the probability of spin exchange.[7c] In that case, maximum spin exchange is expected when the residual broadening from the protons is comparable to the chemical-shift difference. The intensity of the ridges indicates that interchain spin exchange is fairly complete after 10 s. The existence of 180° jumps of the molecules around the chain axis has been proposed. For that case, and also for intrachain spin diffusion, the shielding tensor is invariant under the reorientation and both exchange processes are unobservable in the 2DECSA spectrum.

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In conclusion, with the 2DECSA experiment slow spin exchange or molecular jumps can be measured for exchange times τ in the range $t_1 < \tau \lesssim T_1$, where t_1 is the preparation time of the 2D experiment (of the order of ms), and T_1 is the spin–lattice relaxation time, which for ^{13}C can be longer than 100 s. The method is an addition to the few NMR techniques by which very slow motions can be detected in solids.[8] Naturally, spin exchange between different chemical shielding tensors can be studied in the same way.

Acknowledgment. The polyethylene sample, DOWLEX 2045, was provided by Dr. Th. Scholte (D.S.M., Geleen, The Netherlands) as Chairman of the IUPAC Working Party on the Molecular Characterization of Commercial Polymers. Prof. Dr. E. de Boer and Dr. W. S. Veeman gave valuable support.

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Double β-Addition of Electrophiles to Acetylide Ligands[1]

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The majority of metal carbyne complexes have been prepared by pathways involving removal of substituents from metal-bonded carbon atoms (α-carbon atom), e.g., alkoxide abstraction from alkoxycarbene complexes[2] or α-hydrogen abstraction[3] from alkylidene ligands. Other carbyne complex syntheses are based on the addition of substituents to atoms that are separated from the metal by two bonds (β-atom), e.g., alkylation or protonation of carbonyl,[4] thiocarbonyl,[5] and isocyanide[6] ligands. One of the more recently developed routes of the latter type is β-protonation or β-alkylation of terminal[7] or bridging[8] vinylidene ligands. The vinylidene complexes employed in these investigations were synthesized by isomerization or transformation of acetylene complexes or derived from carbonyl complexes. Vinylidene complexes can also be prepared from acetylide complexes by β-electrophile addition.[9] Since acetylide complexes are available in large numbers,[10] we became interested in the possibility of a new generally applicable carbyne complex synthesis starting from acetylides.

According to a recent molecular orbital study,[11] the gross atomic charge (Mulliken population analysis) at the β-carbon atom of an acetylide ligand is not changed significantly by the addition of an electrophile to give a vinylidene ligand (eq 1). Thus, a

$$[L_nMC{\equiv}CR]^x \xrightarrow{E^+} [L_nM{=}C{=}CRE]^{x+1} \quad (1)$$

second electrophile possibly could add to the same carbon atom (eq 2) provided the additional positive charge (of the first electrophile) on the vinylidene complex does not cause a sharp decrease of the reactivity toward electrophiles. This work describes the transformation of acetylide ligands into carbynes via vinylidene intermediates by double β-addition of electrophiles to acetylide ligands.

$$[L_nM{=}C{=}CRE]^{x+1} \xrightarrow{E^+} [L_nM{\equiv}CCRE_2]^{x+2} \quad (2)$$

Alkylation of the tetraethylammonium salt of the anionic pentacarbonyltungsten *tert*-butylacetylide complex[12] **1a** with FSO_3Me or $[Et_3O][BF_4]$ in CH_2Cl_2 (−70 to 20 °C) gives the deep green vinylidene complexes $(CO)_5W{=}C{=}C(CMe_3)R'$ (**2a**, R′ = CH_3; **2b**, R′ = C_2H_5) (eq 3). After chromatography on silica/hexane at 10 °C (or below), compounds **2** are isolated in 40–60% yield as moderately stable oils; they have been characterized by mass spectrometry and by spectroscopic means.[13] Complexes **2** are the first isolable pentacarbonyl tungsten vinylidene complexes.[14]

$$[NEt_4][(CO)_5WC{\equiv}CCMe_3] \xrightarrow[CH_2Cl_2,\ -70\text{ to }20\ ^\circ C]{FSO_3Me\text{ or }[Et_3O][PF_6]} (CO)_5W{=}C{=}C(CMe_3)R' \quad (3)$$

1a → **2a**, R′ = CH_3; **2b**, R′ = C_2H_5

The vinylidene complexes **2** do not undergo further alkylation, however, protonation in CH_2Cl_2 (−70 to 0 °C) with a slight excess of CF_3SO_3H in the presence of iodide ions (NMe_4I) provides the carbyne complexes *trans*-$I(CO)_4W{\equiv}CCH(CMe_3)R'$ (**3a**, R′ = CH_3; **3b**, R′ = C_2H_5) in almost quantitative spectroscopic yield (IR) (eq 4). After neutralization of the excess acid with Na_2CO_3, the solvent is removed, and the products are recrystallized from CH_2Cl_2/hexane (50–70% isolated yield). Due to the thermal lability of the tetracarbonylcarbyne complexes **3**, all procedures have to be performed at temperatures at or below 0 °C. The complexes are easily characterized by their spectroscopic data[15]

$$\mathbf{2} \xrightarrow[CH_2Cl_2]{CF_3SO_3H/NMe_4I} \underset{\mathbf{3}}{I(CO)_4W{\equiv}CCH(CMe_3)R'} \quad (4)$$

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(13) **2a**: MS (m/e, ^{184}W) 420; IR cm^{-1}, cyclohexane) ν_{CO} 2088 (w), 1986 (sh, w), 1977 (vs), 1969 (s), $\nu_{C=C}$ 1664 (w); ^{13}C NMR (ppm, $CDCl_3$) 376 (C_α), 211 (trans CO), 194 (cis CO), 128 (C_β). **2b**: MS (*m/e*, ^{184}W) 434; IR (cm^{-1}, cyclohexane) ν_{CO} 2088 (w), 1986 (sh,w), 1978 (vs), 1970 (sh,s), $\nu_{C=C}$ 1653 (w); ^{13}C NMR (ppm, $CDCl_3$) 382 (C_α), 210 (trans-CO), 194 (cis-CO), 134 (C_β).

(14) (a) The complex $(CO)_5W{=}C{=}CH_2$ is proposed to be formed as a reactive intermediate in the reaction of $(CO)_5W{=}C(OCH_3)CH_3$ with $LiCH_3$ and subsequent protonation: Levisalles, J.; Rudler, H.; Jeannin, Y.; Dahan, F. *J. Organomet. Chem.* **1978**, *178*, C8–C12. (b) Stable, phosphine-substituted tungsten vinylidene complexes, $(CO)_3(Ph_2PCH_2CH_2PPh_2)W{=}C{=}CHR$, have been prepared by isomerization of the corresponding acetylene complexes.[7c] (c) Homologous pentacarbonyl tungsten alleneylidene complexes, $(CO)_5W{=}C{=}C{=}CR_2$, have been synthesized: Berke, H.; Härter, P.; Huttner, G.; Zsolnai, L. *Chem. Ber.* **1982**, *115*, 695–705.

(15) ^{13}C NMR (ppm, $CDCl_2$) **3a**, 297 (C_α), 190 (CO), **3b**, 298 (C_α), 190 (CO).

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