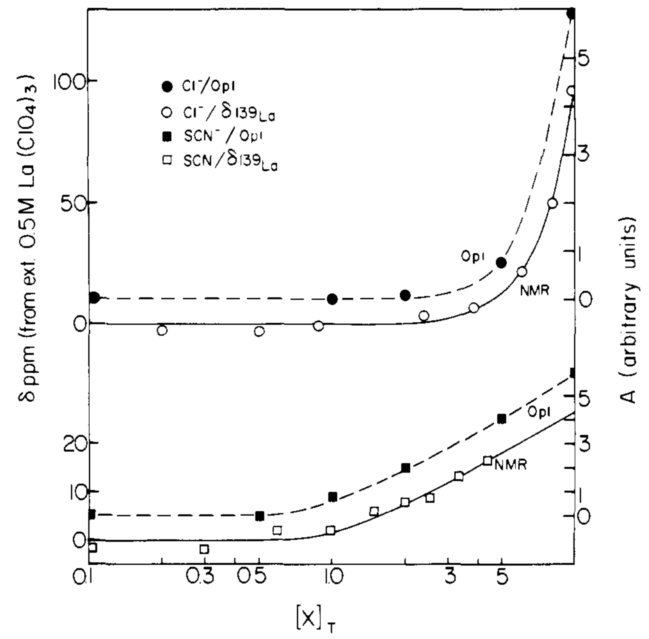

Figure 2. Correlation of the ^{139}La chemical shifts and optical spectra (oscillator strength) of Nd(III) in chloride and thiocyanate solutions. ^{139}La line widths show similar correlations, although not with the same degree of accuracy in the case of the thiocyanate system.

~0% for trichloroacetate. The values for $La(ClAc)^{+2}{}_{(aq)}$ are somewhat lower than the estimates from entropy data[4] and further work is necessary to evaluate the validity of our assumptions.

While the limiting chemical shifts in the series from LaX^{+2} to LaX_4^- may increase regularly, the line widths may behave differently. Formation of inner sphere LaX^{+2} introduces a large perturbation in the charge symmetry of the lanthanide complex, but formation of higher complexes may lead to species of higher symmetry causing a relative decrease in the line widths. Such is the case in the acetate system where a plot of δ vs. $\Delta\nu_{1/2}$ is linear below the concentration of acetate where $La(Ac)_2^+$ becomes significant. At higher acetate concentration, the line width no longer increases as rapidly as does the chemical shift.

Spectroscopic studies have indicated that both chloride and thiocyanate ions initially form outer sphere complexes with Nd(III).[7] At higher concentrations (1-2 M for SCN^- and 5-6 M for Cl^-), inner sphere complexation becomes significant, probably associated with formation of NdX_3 or NdX_4^-. This change in behavior is easily monitored in ^{139}La NMR studies of the La^{+3}/Cl^- and La^{+3}/SCN^- systems. Both the chemical shift and line width behavior of these systems exhibit no change until concentrations where inner sphere complexation is indicated by the optical spectra (Figure 2). In 10 M HCl the ^{139}La resonance is deshielded by ~100 ppm with a line width of 1300 Hz; in 5 M ammonium thiocyanate the resonance is deshielded by 36 ppm, and the observed line width is 1000 Hz.

In conclusion, chemical shifts of ^{139}La can serve as a valuable probe of the solution behavior of lanthanide ions. While line widths are useful when an equilibrium between two species is being observed, they are difficult to interpret with more complex equilibria, since line widths not only measure the relative amounts of species but also their electronic symmetries. Of course, it is possible in some cases that the spectrum observed may not be the time-averaged resonance of two or more species. Some complexed lanthanum(III) species will be long lived, with resonances obscured by relatively weak intensity and through extensive quadrupolar broadening. Such appears to be the case with certain chelating agents such as EDTA, where two ^{139}La signals are observed with chemical shifts of ~0 and 570 ppm, for uncomplexed and complexed La(III) respectively.

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High Resolution ^{13}C NMR Studies of Chemical Exchange Processes in the Solid State Using Magic Angle Spinning

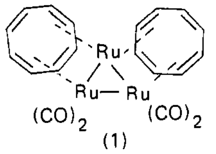
Sir:

Wide-line ^{1}H NMR has been widely used to investigate motional processes in solids, molecular motions partially averaging the proton-proton dipolar interactions and giving rise to line narrowing.[1] However, one cannot deduce *from these NMR measurements alone* whether chemical exchange processes are occurring along with or as part of overall molecular motions.

Techniques have recently been introduced for the measurement of "high-resolution" ^{13}C NMR spectra of solids.[2] In most cases, the measurements involve a combination of high-power decoupling of protons to remove dipolar broadening, cross-polarization schemes for signal enhancement,[3] and spinning of the sample rapidly (several kilohertz) about an axis aligned at an angle of 54° 44′ (the "magic angle") with respect to the dc field[2b] to remove broadening from the chemical shift anisotropy of the carbons. Spectra of moderate resolution are obtained by these techniques; line widths are in the range of 15-100 Hz and separate resolved signals are observed for most magnetically nonequivalent carbons in a molecule.[4-9]

An important feature of the spectra is that the signals observed occur at the isotropic shift values (as in solution) and are characteristic of the environment of the nucleus. As in solution, the observed averaging of signals from magnetically nonequivalent carbon atoms in a molecule should reflect the occurrence of a chemical exchange process. Therefore, high-resolution ^{13}C NMR should provide a direct probe to obtain incisive evidence for the occurrence of chemical exchange processes in the solid state.

To test the above ideas, we have investigated the solid-state behavior of a molecule known to exhibit a fast intramolecular chemical exchange process in solution. The molecule chosen was tetracarbonylbis(cyclooctatetraene)triruthenium(0) (**1**)



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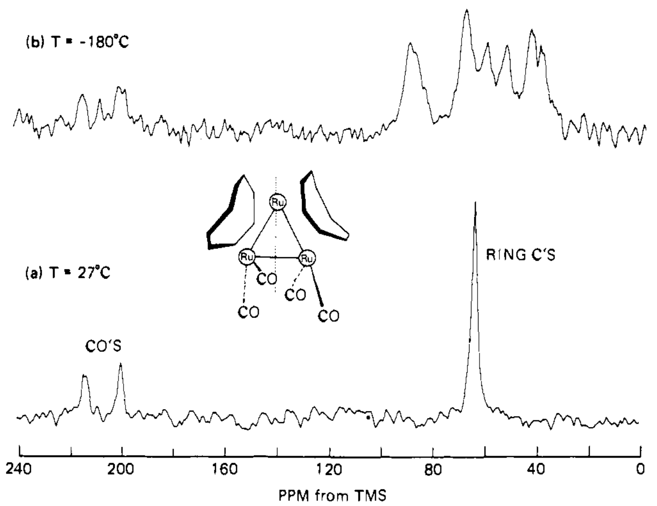

Figure 1. (a) Magic angle spinning (~4 kHz), cross-polarization ^{13}C NMR spectrum of **1** at 27 °C. Spectrum was obtained on a polycrystalline sample loaded in a hollow Kel-F rotor. The spectrum was obtained from a 2K FT of 1000 FID accumulations using a CP contact time of 5 ms and an experiment repetition time of 1 s. The proton decoupling field and Hartmann-Hahn matching conditions were ≈44 kHz. Inset: schematic representation of the molecular structure of tetracarbonylbis(cyclooctatetraene)triruthenium(0) in the solid state (adapted from ref 12). (b) ^{13}C NMR spectrum of **1** at −180 °C. Conditions were the same as in (a) except 2500 FID accumulations were obtained.

which belongs to the class of organometallics known as "fluxional".[10] The ^1H NMR spectrum in solution at room temperature shows only a single sharp signal for the sixteen ring protons which are rendered equivalent by a dynamic chemical exchange process. This process interchanges the points of "localized" bonding of the metal atoms to each ring.[11] The exchange process is thought to persist in the solid state.[12]

Figure 1a shows the molecular structure of the complex and the ^{13}C spectrum (15.08 MHz) obtained at 27 °C for the polycrystalline solid contained in a hollow Kel-F rotor[13] (volume ~60 μl) by using high-power proton decoupling, cross-polarization techniques, and 4-kHz spinning at the magic angle. The spectrum shows three clearly defined absorptions (64.1, 200.7, and 213.9 ppm downfield from Me_4Si) with line widths at half-height of 25 Hz (relative intensities 8:1:1, respectively). (The widths of the resonance lines are mainly due to broadening from incompletely decoupled protons, as well as residual chemical shift anisotropy arising from imprecise setting of the magic angle.) That these signals are characteristic of the entire crystalline sample and not a small amount of mobile material trapped in the lattice is indicated by the broadening (and eventual disappearance into the base line noise) of the resonance lines as the sample spinning axis is moved away from the magic angle. The resonance lines are assigned as indicated in Figure 1. Although the limited solubility of the complex made it impossible to obtain solution values of the ^{13}C chemical shifts, the assignments are entirely consistent with the body of literature on carbon resonances. The four carbonyl groups in the molecule are not equivalent, being related by an approximate C_2 axis as indicated by the dotted line in the structure inset in Figure 1. There are therefore two pairs of equivalent carbonyl groups, giving rise to the two low-field absorptions at 200.7 and 213.9 ppm. Additional evidence for the assignment of the carbonyl resonances is provided by the cross-polarization dynamics. Since the cross-polarization efficiency depends on the magnitude of the static C–H dipolar interactions,[3a] the carbonyl carbons would be expected to cross-polarize more slowly than the ring carbons. At contact times ≤2 ms, the two resonances at low field are indeed absent from the spectrum. Despite the fact that, in the absence of cross-polarization, carbon intensity buildup depends on carbon T_1's (expected to be impractically long in many crystalline solids),[3c] it proved possible to observe a spectrum of the complex with 90-τ-90 pulses, τ = 1–2 s, in which full intensities were obtained for all the carbons. The surprisingly short T_1 values inferred for the carbonyl carbons may be due to the presence of small amounts of paramagnetic impurities (an ESR spectrum of the solid material showed signals at $g \sim 2$ and 4).

The most important feature of the spectrum is that all 16 carbons from the two cyclooctatetraene rings contribute to the single sharp resonance at 64.1 ppm. The X-ray structure[14] shows clearly that the rings are nonplanar and would have magnetically nonequivalent carbons. Thus, if the structure were rigid in the solid state, one would expect a multiplicity of signals spread over a range of chemical shifts similar to the 60–70 ppm found for the rigid structures of such molecules in solution.[15] Indeed, the spectrum of the complex obtained at −180 °C (Figure 1b) shows the presence of at least six resolved lines, spread over ~50 ppm, for the COT ring carbons.[16] The degeneracy observed at ambient temperature is thus thought to be the result of a chemical exchange process in which the rings distort as they move so that the positions of "localized" bonding of the metal atoms to the rings are continually changing, resulting in exchange-averaged chemical shifts. This is exactly the process postulated to occur in solution. These processes are not detected by X-ray diffraction techniques which resolve only the positions of minimum potential for the atoms and do not detect dynamic processes unless disorder is introduced. Further, the result is in agreement with the conclusion previously reached from a comparison of wide-line NMR and X-ray diffraction data,[12] but, in the present work, this conclusion is reached very directly from a consideration of NMR data alone.

Thus, the concept of using high resolution ^{13}C NMR spectroscopy of solids as a tool to investigate *directly* chemical exchange processes which occur in the solid state has been shown to be valid. We are currently investigating exchange processes in other systems and also making measurements over a range of temperatures on the complex reported on here since the collapse of lines in the spectrum of the rigid molecule (with increasing temperature) could provide detailed information regarding the *mechanism* of the exchange process.

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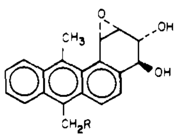
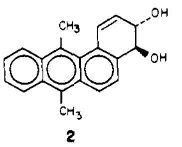
Synthesis of *trans*-3,4-Dihydroxy-3,4-dihydro-7,12-dimethylbenz[*a*]anthracene, a Highly Carcinogenic Metabolite of 7,12-Dimethylbenz[*a*]anthracene

Sir:

7,12-Dimethylbenz[*a*]anthracene (DMBA) is one of the most potent known carcinogenic hydrocarbons,[1,2] and DMBA-induced tumors are widely employed in cancer research. Recent studies have implicated the diol epoxide *trans*-3,4-dihydroxy-*anti*-1,2-epoxy-1,2,3,4-tetrahydro-DMBA (**1a**)[3,4] and/or the related triol epoxide **1b**[5] as the principal metabolically activated form(s) of DMBA which bind covalently to DNA in vivo.[6] The structures of these hypothetical intermediates were tentatively assigned on the basis of UV fluorescence and chromatographic data on the nucleic acid bound metabolites. Consistent with the hypothesis that **1a** and/or **1b** are the active carcinogenic forms of DMBA, the 3,4-dihydrodiol of DMBA (**2**), thought to be the metabolic precursor of **1a**, is found to undergo microsome-mediated transformation to a highly mutagenic intermediate presumed to be **1a**.[11] These findings are consistent with other evidence implicating diol epoxide metabolites as the principal (though not the sole)[9] active forms of other carcinogenic hydrocarbons.[7] Although synthesis of the 8,9,10,11-diol epoxide of DMBA has been described,[12] synthesis of **1a,b** remains a challenging objective.[13]



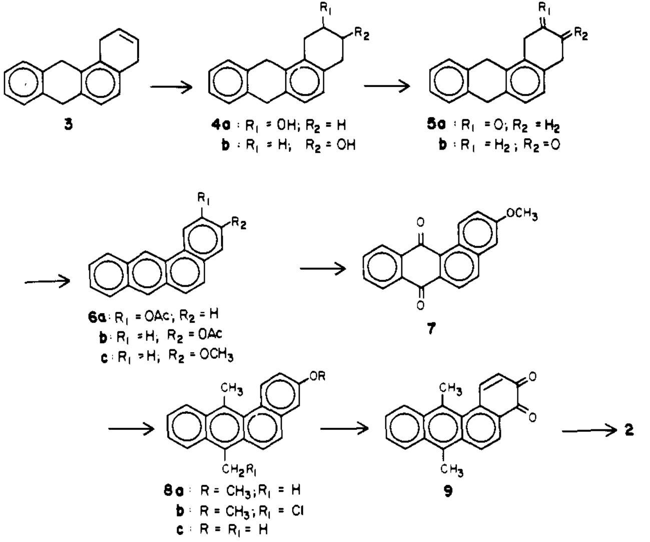
1a R = H
b R = OH



2

We now report efficient synthesis of **2** via a novel route. Attempts to adapt the synthetic approaches devised for the analogous dihydrodiols of unsubstituted polycyclic arenes[7a] were unsuccessful, principally owing to competitive side reactions on the reactive methyl groups. The method eventually devised (Scheme I) is potentially applicable with appropriate modification to the synthesis of many presently difficultly accessible analogous derivatives of other potent carcinogenic hydrocarbons (e.g., 7-methylbenz[*a*]anthracene and 3-methylcholanthrene).

Scheme I



Reduction of benz[*a*]anthracene (BA) with lithium in ammonia according to the published procedure[14] gave in two steps 1,4,7,12-tetrahydro-BA (**3**). The latter underwent reaction with diborane and alkaline H_2O_2[15] to a mixture of 2- and 3-hydroxy-1,2,3,4,7,12-hexahydro-BA (**4**).[16] Oxidation of the mixed alcohols with trifluoroacetic anhydride and Me_2SO according to the method of Swern[17] gave the mixed ketones **5a,b** where were separated by chromatography on Florisil. 3-Oxo-1,2,3,4,7,12-tetrahydro-BA (**5b**) underwent efficient conversion to 3-acetoxy-BA (**6b**) via formation of the enol acetate and dehydrogenation with *o*-chloranil by conventional procedures; methylation with dimethyl sulfate and sodium methoxide in methanol gave 3-methoxy-BA (**6c**).[18] 2-Acetoxy-BA (**6a**)[19] was obtained from the 2-keto compound **5a** through an analogous sequence of transformations. The synthesis of **6a–c** described constitute the first syntheses of A-ring substituted derivatives of BA directly from the parent hydrocarbon.[20]

Conversion of 3-methoxy-BA to 3-methoxy-DMBA (**8a**) was accomplished in high overall yield through initial oxidation of **6c** with sodium dichromate in acetic acid to the quinone **7**.[21] The latter underwent transformation to **8a** through reaction with methyllithium, followed by treatment with gaseous HCl by Newman's method[22] and reduction of the resulting 7-chloromethyl intermediate **8b** with $NaBH_4$.[23] Protection of the phenolic group as the methyl ether during reaction with methyllithium was found necessary, since attempted similar reactions on the free phenol or the acetate ester gave markedly diminished yields. Demethylation with lithium thiomethoxide[24] furnished the free phenol **8c** in 95% yield: mp 169 °C (benzene-hexane); NMR ($CHCl_3$) δ 3.05 (s, 3 H, 7-CH_3), 3.30 (s, 3 H, 12-CH_3), 7.0–8.5 ppm (m, 9 H, aromatic).

Oxidation of the phenol **8c** with Barton's reagent (benzeneselenic anhydride)[25] gave dark violet crystals of DMBA-3,4-dione (**9**) (80%), mp 181–183 °C dec. Compound **9** is apparently the first terminal ring *o*-quinone derived from a carcinogenic polyarene.[26] Reduction of **9** with $LiAlH_4$ afforded the *trans*-3,4-dihydrodiol **2**, mp 182–184 °C. The yield of **2** (43%) compares quite favorably with the 1–5% yields reported for analogous reductions of anthracene-1,2-dione and the phenanthrene-1,2- and -3,4-diones;[27] the improvement is at least partially a consequence of avoidance of acidic conditions during workup.

The integrated 270-MHz NMR spectrum of **2** was entirely

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