be applied in a much smaller dimensional regime to achieve specific functions where the molecule-based material is the active element.

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Registry No. SiO_2, 7631-86-9; silicon, 7440-21-3; gold, 7440-57-5; polypyrrole (homopolymer), 30604-81-0.

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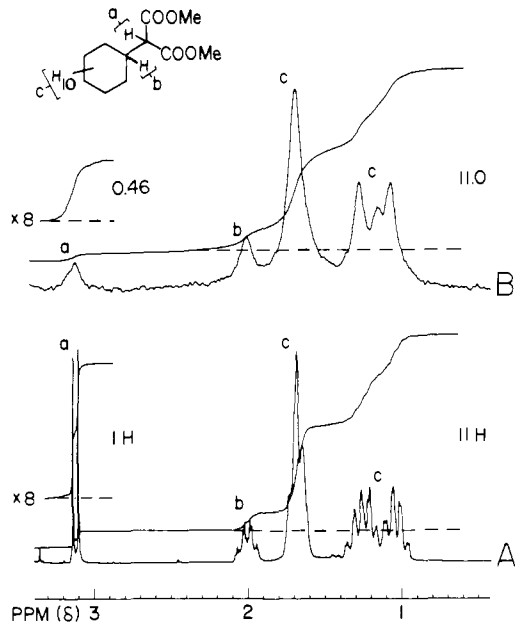

Figure 1. ^1H NMR (250 MHz) spectrum (A) and 38.4-MHz natural-abundance ^2H NMR spectrum (B) of dimethyl 2-cyclohexylmalonate produced by photolysis of dimethyl diazomalonate in excess cyclohexane.

Measurement of Deuterium Kinetic Isotope Effects in Organic Reactions by Natural-Abundance Deuterium NMR Spectroscopy

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Deuterium and tritium kinetic isotope effects have been widely used in the diagnosis of reaction mechanisms,[2] and the synthesis of isotopically labeled reactants has become a frequently necessary if often laborious task. However, deuterium is present in trace amounts (~0.015%)[3] in all ordinary hydrogen-containing compounds, and the advent of high-field NMR instrumentation now permits the relatively easy assessment of the amount of deuterium at specific molecular sites. The studies of Martin et al.[4a-c] and Grant et al.[4d] have shown that there can be dramatic variations in the deuterium distributions within identical compounds from different sources, which must reflect the differing chemical histories of these molecules. The high sensitivity of modern NMR spectrometers should permit the measurement of deuterium kinetic isotope effects using only deuterium at natural abundance as the isotopic label.

Consider the insertion of a carbene into a C–H bond of cyclohexane. Approximately 0.18% of the cyclohexane molecules will contain exactly one deuterium, very few will contain two or more (0.0003%), and the vast majority will contain none. The reaction of interest is the insertion of the carbene into monodeuteriocyclohexane, which involves intramolecular competition between different isotopic species at several chemically equivalent positions. The concentration of multiply labeled molecules is insignificant, and the undeuterated molecules will be invisible in the ^2H NMR. It is clear from the analysis of Melander and Saunders[5] that the ratio of the deuterium content of the product sites containing the hydrogens not transferred ($D_{retained}$) and that of the product sites containing the transferred hydrogen ($D_{transferred}$) will be constant throughout the course of the reaction and that the kinetic isotope effect for the C–H cleavage is given by

$$k_H/k_D = (D_{retained}/D_{transferred})[1/(n-1)] \quad (1)$$

where n is the number of chemically equivalent sites in the reactant.

The ^1H and ^2H NMR spectra[6] of dimethyl 2-cyclohexylmalonate prepared by photolysis of dimethyl diazomalonate[7] in the presence of excess cyclohexane[8] are illustrated in Figure 1. The deuterium resonances are readily assigned by comparison with the proton spectrum: the signals at δ 0.9–2.1 are due to the cyclohexyl group, while the peaks at δ 3.1 are those of transferred hydrogen. Comparison of the peak areas[9] in both spectra indicates that the rate of deuterium transfer has been roughly half as great as that of protium. Setting the integral of the retained cyclohexyl deuterium to 11.0 in arbitrary units, the integral of the transferred deuterium is 0.46. Cyclohexane has 12 chemically equivalent sites, so, from eq 1, $k_H/k_D = (11.0/0.46)[1/(12-1)] = 2.2$. Data from three separate experiments gave an average value for k_H/k_D of 2.1 ± 0.1. In a control experiment, dimethyl diazomalonate was photolyzed in the presence of 1:1 cyclohexane:cyclohexane-d_{12};

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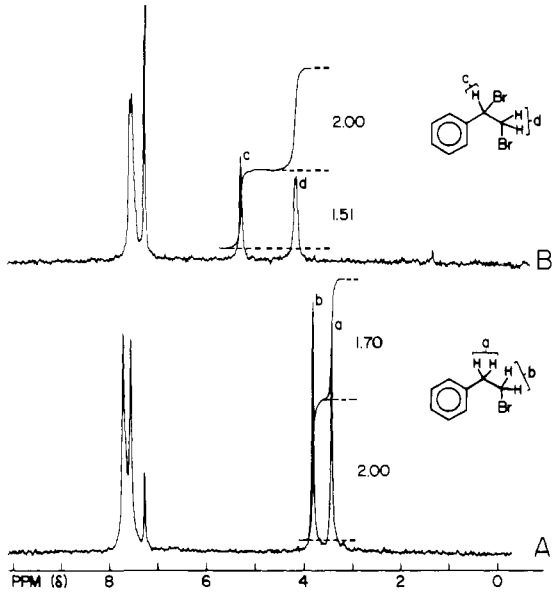

Figure 2. Natural-abundance 38.4-MHz ^2H NMR spectra of (2-bromoethyl)benzene (spectrum A) and styrene dibromide prepared by elimination and bromination of (2-bromoethyl)benzene (spectrum B). The peaks at δ 7.26 are due to chloroform.

analysis of the reaction mixture by GC-MS showed the ratio of protic and deuterated products to be 2.2, in good agreement with the ^2H NMR experiments.

In the preceding example the hydrogen from the broken C-H bond was retained in the product; more typically C-H cleavage results in loss of the hydrogen to the solvent, and in such cases the amount of transferred hydrogen must be obtained indirectly. We illustrate an appropriate method with a simple elimination reaction. The ^2H NMR spectra of (2-bromoethyl)benzene[10a] and the dibromide derivative[10b] of styrene generated by potassium *tert*-butoxide treatment of (2-bromoethyl)benzene[12] are displayed in Figure 2. The reaction was carried to completion, so the C-2 deuterium resonance may be employed as an integration standard in both spectra, and its integral is set to 2.00. Most of the C-1 deuterium has been retained in the course of this reaction: the starting material contains 1.70 units of deuterium at C-1, the product 1.51. The amount of transferred deuterium is given by the difference 1.70 - 1.51 = 0.19, and therefore k_H/k_D = (1.51/0.19)[1/(2 - 1)] = 7.9 ± 0.8, identical with the literature value of 7.9 ± 0.5 obtained for the elimination reaction of (2-bromo[1,1-$^2H_2$]ethyl)benzene under the same conditions.[12]

Natural-abundance ^2H NMR is a powerful method for the measurement of kinetic isotope effects in a wide variety of chemical reactions without recourse to synthesis of isotopically enriched reactants. However, the present analysis is applicable only when there can be intramolecular competition between hydrogen isotopes. This is true for a great many ordinary chemical reactions, but for enzymatic reactions the method is restricted to hydrogen removal from methyl groups or from substrates containing a proper rotation axis of symmetry.[13] In a future report we will describe our studies of kinetic isotope effects in biological transformations of methyl groups using natural-abundance ^2H NMR.

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Isolation and Structural Analyses of Two Conformers of the Eight-Membered Lactam on 1-Benzazocinone Derivatives

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In general, the conformational interconversions of medium- and large-membered cyclic compounds are so fast at room temperature[1] that it is very hard to isolate their conformers in two isomeric forms.[2]

Eight-membered lactams of 1-benzazocinone skeleton have been efficiently synthesized through the newly developed "*controlled crissocross annulation*"[3] as part of our synthetic approaches to mitomycins. These lactams have been found to consist of two conformers, and we report the first isolation and structural analyses of these conformers of benzazocinone derivatives at ordinary temperatures.

For the present work, compound **2** was obtained by the above-mentioned synthesis in one pot from **1** (Scheme I).[3]

When the keto group of **2** was protected by reaction with ethylene glycol at 80-90 °C, the resulting ketal **3** was found to consist of two stereoisomers, **3a** and **3b**, in the ratio of about 8:1, though it has only one asymmetric center in the molecule. Similar phenomena were also observed with other ketals (**4**, **5**). The isomers were separated at room temperature by conventional chromatography.[4] The most easily separable sulfonamides, **5a** and **5b** obtained in the ratio of 10.8:1, were chosen as the representative of the above ketals of detailed structural analysis. The interconversion between each **5a** and **5b** was investigated by comparison of the respective integrations of 6-methyl signals [**5a**, δ 0.68 (d); **5b**, δ 1.13 (d)] of ^{1}H NMR spectra at elevated temperatures. From the equilibrium ratio of the resulting mixture, the major isomer **5a** was proved to be the thermodynamically preferred one, since the spectrum of **5b** at 180 °C (Me_2SO-d_6) showed to isomerize mainly into **5a** in the ratio of 8.6:1 (**5a**:**5b**) while **5a** was slightly converted into **5b** (**5a**:**5b** = 10:1) at the same temperature.

From the ^{1}H NMR spectral data and NOE's of **5a**, the following important facts were revealed: two benzylic protons (11-H) had very different chemical shifts [δ 4.22 (d) and 5.62 (d)], caused by restricted rotation of the benzyl group; an NOE of 4% was observed only for the 6-Me signal on saturation of the 7-H signal.

The molecular structure of **5a** was finally established by X-ray crystal analysis as shown in Figure 1.

The aromatic proton (7-H) lies closer to 6-Me than to 6-H, which well explains the observed NOE's on **5a**. Also it is particularly noteworthy that both 6-H and 6-Me are close to the face of the benzene ring of the *N*-benzyl group. Thus, the above-described upfield shift of the 6-methyl signal can be ascribed to the shielding effects of this benzene ring.

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