J. Org. Chem. 1984, 49, 187–189 187

Structure Elucidation Using Signal Intensity Effects in Carbon-13 Nuclear Magnetic Resonance

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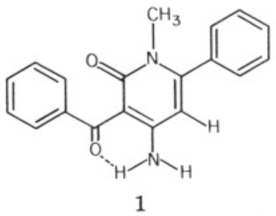
Received July 5, 1983

Our laboratory has been involved in developing NMR methods for structure identification that yield a distinction between potential candidates by simple inspection of the NMR spectrum. Of particular interest are experiments aimed at the perturbation of carbon-13 NMR signal intensities in a predictive manner.

Routine carbon-13 NMR analysis of structural problems mainly involves the collection of various spectra in order to obtain chemical-shift and signal-multiplicity information. Signal intensity, while a parameter that is always obtained, is usually neglected in analysis except for the evaluation of symmetry or determination of nonprotonated carbon centers. Since most carbon-13 NMR spectra are obtained in the fully proton-decoupled or gated modes,[1] signal intensity is primarily dependent upon the carbon relaxation rates and the nuclear Overhauser effect (NOE). Of course, the effects of RF filter, digitization, decoupler power, and efficiency should always be kept in mind as potential sources of unexpected differences in signal intensity.[2]

For small- and intermediate-sized molecules the NOE experienced for nonprotonated carbons is usually less than the maximum value. Since the NOE is strongly dependent upon $\sum_i r^{-6}(\mathrm{CH}_i)$,[3] the signal intensity observed for nonprotonated carbons can be exploited for structure evaluation. Under conditions where complete relaxation is allowed to occur, the signal intensity for these carbons is greatly affected by the number of nearest neighbor protons.[4] On the basis of this notion, there are two ways to effect changes in nonprotonated carbon signal intensities selectively: (1) by affecting the number of neighboring protons by some chemical method[5,6] and (2) by enhancing the intensity by an instrumental technique.

A useful chemical method of assisting both nonprotonated carbon shift assignment and structure determination is selective deuteration. It has been shown that deuteration can result in a substantial decrease of signal intensities for resonances of nearby nonprotonated carbons.[5] In certain instances resonance intensities resulting from carbonyl groups and other nonprotonated centers can be affected by exchange deuteration of hydrogen-bound protons.[7,8] In enamino–ketone type systems such as 1, exchange deuteration causes a decrease in the signal intensity of nearby centers as shown in Figure 1. In fact, under these conditions the resonances from C_1 and C_2 are seen to completely disappear, while the C_3 resonance is substantially reduced. This diminution of signal intensity is a result of the decrease in NOE to these carbon centers.



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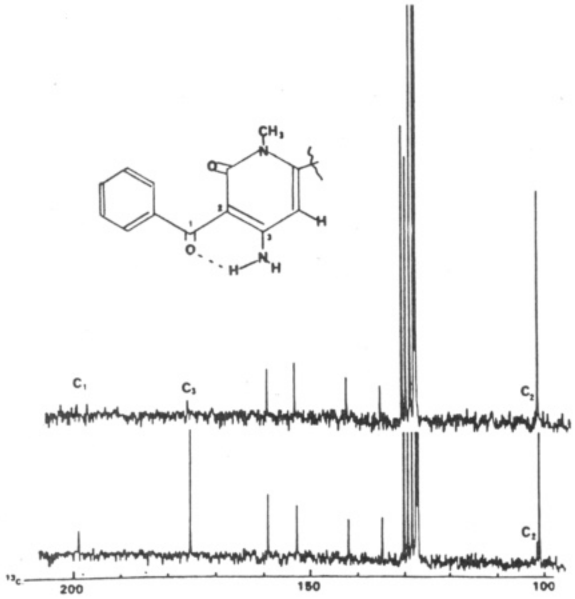
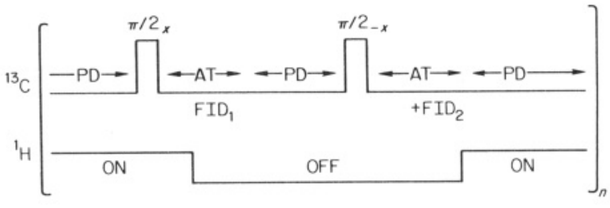


Figure 1. Proton-decoupled carbon-13 spectrum for 1 in MeOH (bottom) and MeOD (top).

Scheme I



An experiment that is complementary to the deuteration results can be envisioned whereby a signal enhancement is observed.[9] This experiment would require that the carbon center of interest be nonprotonated and have its NOE partially or completely dominated by nearby protons. When this situation pertains, saturation of the proton signal should result in a selective NOE to the nonprotonated center. The pulse sequence used to perform such an experiment is shown in Scheme I.

Selective decoupling is performed prior to the first 90° pulse and is turned off during the accumulation of FID_1. The second 90° pulse is applied 180° out of phase with the first, and the two FID's are added. This has the overall effect of subtracting FID_2 from FID_1, leaving only the residual NOE obtained. By necessity an even number of scans must be obtained. Random instrumental changes

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[†] Sandoz Inc.
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[7] M. J. Shapiro and A. D. Kahle, *Org. Magn. Reson.*, **12**, 235 (1979).

[8] G. M. Coppola, R. Damon, A. D. Kahle, and M. J. Shapiro, *J. Org. Chem.*, **46**, 1221 (1981).

[9] (a) J. J. Ford, W. A. Gibbons, and N. Niccolai, *J. Magn. Reson.*, **47**, 522 (1982); (b) M. A. Khaled and C. L. Watkins, *J. Am. Chem. Soc.*, **105**, 3363 (1983).

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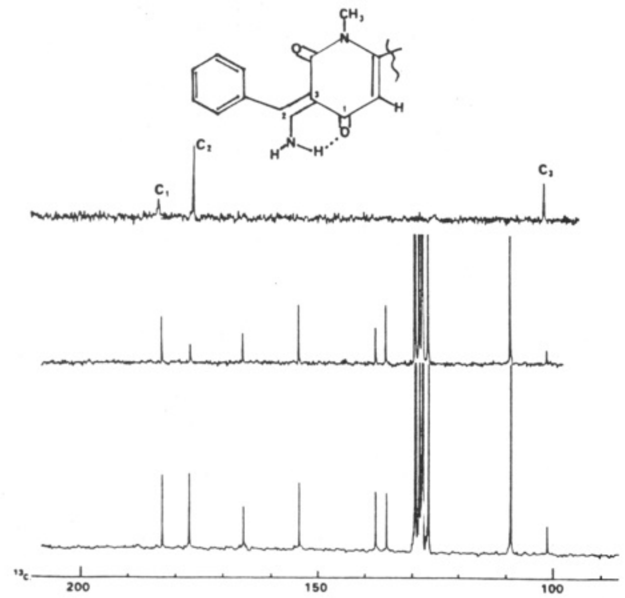
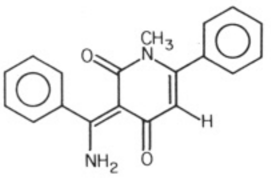


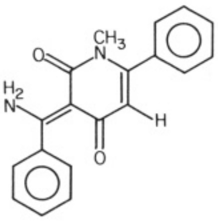
Figure 2. Proton-decoupled carbon-13 spectrum for **2** in MeOH (bottom), MeOD (center), and the difference heteronuclear NOE spectrum (top). ^{1}H irradiation at the frequency for the lowest field NH proton.

are averaged out by this type of sequence. In practice, eight dummy pulses are performed prior to collecting the first FID.

The method of difference heteronuclear NOE was applied to the question of whether **2** exists in the *E* or *Z* form.



2a



2b

The results of the NOE experiment, as well as those for the deuterium-exchange technique, are compared in Figure 2. Since we can readily distinguish the two different types of carbonyl groups from chemical-shift considerations, the amido carbonyl resonance δ 166 being to higher field than the enone carbonyl resonance δ 182, it is quite clear from the difference NOE that **2a** properly describes the structure of this molecule. A large NOE is observed for C_1, while none is found for the amido carbonyl. It is also evident from Figure 2 that the deuterium-exchange experiment results in the same conclusion with the C_1, C_2, and C_3 resonances showing decreased signal intensities.

An extension of the difference heteronuclear NOE to non-hydrogen-bond systems was applied to the problem of distinguishing the products formed by the transformation shown in Scheme II. Since all of the carbon-13 NMR assignments have been previously described,[10] the determination of structure relies simply on the observation of the appropriate resonances in the carbon-13 spectrum. For **3**, the difference NOE upon irradiation of the *tert*-butyl resonance should give rise to resonances at δ 167.3 and 117.8, while in **4** peaks at δ 178.2 and 115.0 are expected.

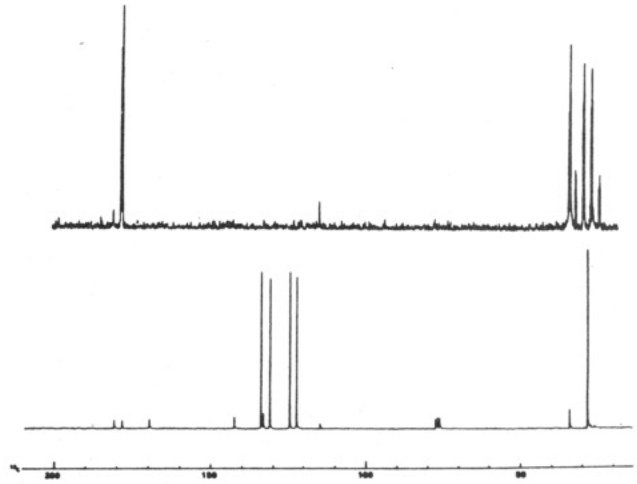


Figure 3. Proton-decoupled carbon spectrum (bottom) and difference heteronuclear spectrum (top) for **3**. ^{1}H irradiation at the *tert*-butyl group frequency.

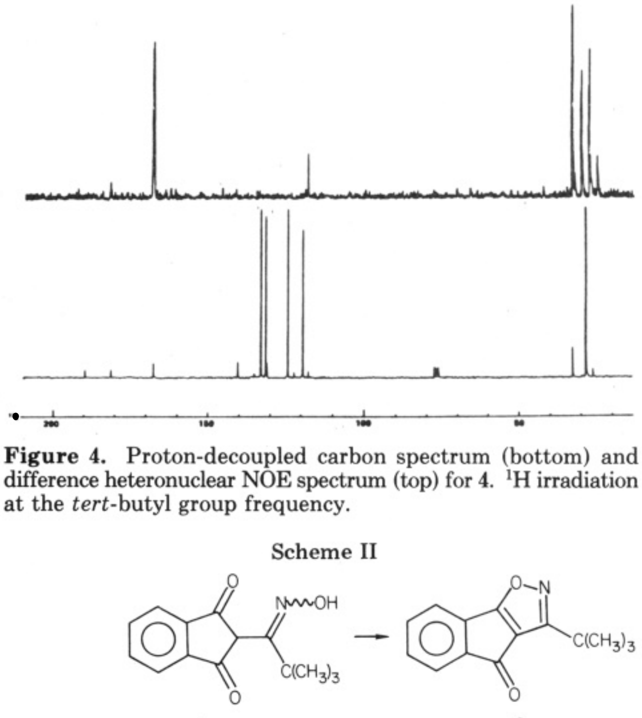
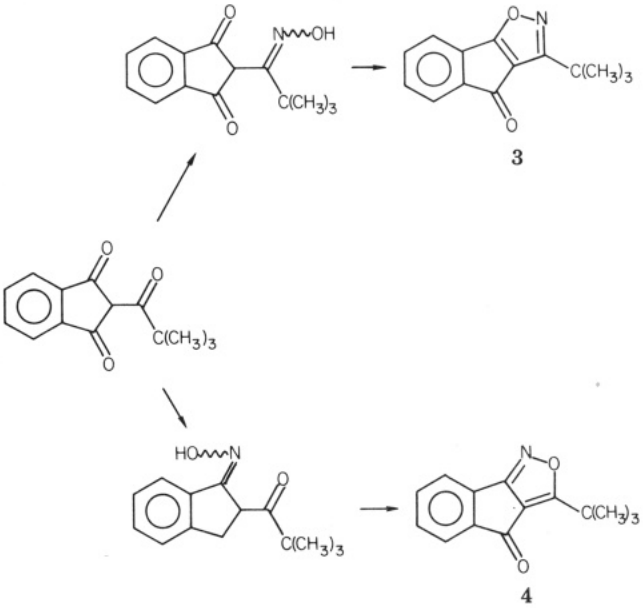


Figure 4. Proton-decoupled carbon spectrum (bottom) and difference heteronuclear NOE spectrum (top) for **4**. ^{1}H irradiation at the *tert*-butyl group frequency.

Scheme II



Shown in Figures 3 and 4 are the proton-decoupled spectra and difference heteronuclear NOE results for **3** and **4**, respectively. Assignment of structures based on these data is straightforward.

In summary, two methods of structure elucidation have been presented. Both are based upon signal intensities observed for nonprotonated carbon centers. In the in-

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stance of systems containing hydrogen bonds, the experiments are complementary. The heteronuclear difference NOE experiment should work well in all cases, except where severe spectral crowding in the ^{1}H NMR makes selective irradiation difficult.

Experimental Section

Compounds 1 and 2 have been previously reported.[7] The synthesis of compounds 3 and 4 have been described elsewhere.[10] All spectra were obtained on a JEOL FX-200 spectrometer in a 5-mm C/H probe. The experiments on 1 and 2 were obtained on CH_3OH (deuterioacetone lock) and CD_3OD samples. 2K scans were collected by using 16K double-precision accumulation. The NOE difference spectrum for 2 was obtained in deuteriochloroform solution. The spectra were transformed with a 2.5-Hz line broadening. The proton-decoupled and heteronuclear NOE experiments on 3 and 4 were obtained with use of deuteriochloroform as solvent and lock. The NOE difference spectra required overnight accumulation and were collected with a pulse delay of 5 s.

Acknowledgment. We thank Dr. J. Nadelson (Sandoz) for the use of his compounds and Dr. C. A. Evans (JEOL) for helpful discussions. T.L.L. acknowledges the Robert A. Welch Foundation Grant E-711 for partial support of this research.

Registry No. 2a, 87829-34-3; 3, 82501-33-5; 4, 82501-28-8.

Convenient Preparation of Sterically Hindered Selones

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Received June 14, 1983

Selenoketones (selones) 2 are very important intermediates in the preparation of a variety of extremely sterically hindered molecules.[1] They have interesting photochemical properties[2] and also have proved to be very efficient spin traps for a large number of common free radicals.[3] Unfortunately, further investigations of the properties and reactivities of selones have been severely limited by difficulties in the preparation of these molecules.

The most widely used method for the preparation of selones involves pyrolysis of a phosphoranylidenehydrazone (phosphazine) 1 in the presence of excess selenium, affording the selone, nitrogen, and triphenylphosphine selenide.[4] While these reactions can be optimized to afford the selones in typical yields of 66–85%, the yields are markedly affected by the age and purity of the selenium powder. The purity of the phosphazine is also important. Crystallization of the moisture-sensitive phosphazines is often difficult, lowering overall yields, and small amounts of hydrazone contaminants lead to significant reduction of the initially formed selones to unstable selenols. Finally, and perhaps most importantly, the temperature and rate of heating seem to be critical in the pyrolysis reaction. The pyrolysis of phosphazines without selenium affords diazo compounds in good to excellent yield;[4,5] if the rate of heating in the selone preparation is too rapid the selone initially formed can react with the in situ generated diazo compound to afford an olefin in a twofold extrusion reaction, significantly lowering selone yields (Scheme I). Recently an alternative method for the preparation of selenofenchone utilizing bis(tricyclohexyltin) selenide (3)–boron trichloride has been reported.[6] Unfortunately this method uses relatively large amounts of the selenium reagent and appears to be useful only for the preparation of small quantitites of selones.

Scheme I

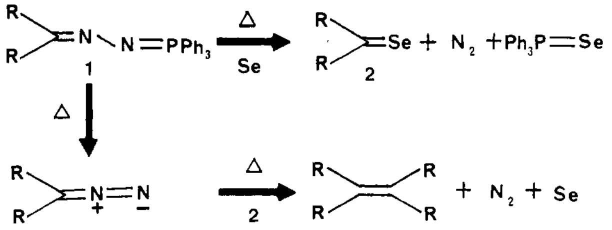
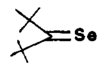
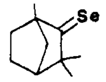
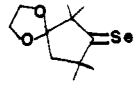
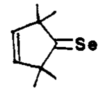
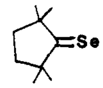
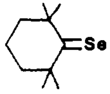
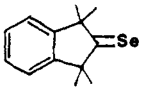
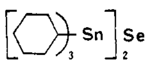
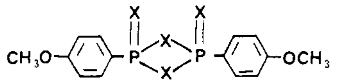


Table I[a]

Product Selone	Se_2Cl_2	Se_2Br_2	c
 7	45%	65%	29% (ref 4)
 8	40%	76% (50%)[b]	25% (ref 4)
 9	66%	80% (61%)[b]	48%
 10	—	70%	53% (ref 1a)
 11	—	68%	54%
 12	37%	73%	40%
 13	53%	80% (74%)[b]	75% (ref 1b)

[a] Isolated yield of pure product. [b] Diisopropylethylamine used in place of triethylamine. [c] Overall yield of selone from hydrazone via triphenylphosphoranylidenehydrazone.


3


4a, X = Se
4b, X = S

In our investigations of selone reactivity, we required multigram quantities of these compounds. One potential method for preparing selones in quantity would involve the use of the selenium analogue 4a of the dimer of (p-methoxyphenyl)thioxophosphine sulfide (4b), which is widely used as a thionating reagent.[7] Unfortunately the

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