

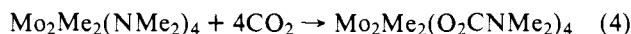
Figure 1. ^1H NMR spectrum of a mixture of anti and gauche $\text{Et}-(\text{Me}_2\text{N})_2\text{Mo}\equiv\text{Mo}(\text{NMe}_2)_2$ recorded in toluene- d_8 at -61°C and 270 MHz.

ligand and two resonances in the ratio of 3:2 for the OBU' groups.⁸ This is consistent with an ethane-like molecule $(\text{Bu}'\text{O})_2(\text{Et})\text{Mo}\equiv\text{Mo}(\text{OBU}')_3$ in which rotation about the $\text{Mo}\equiv\text{Mo}$ bond is rapid on the NMR time scale.⁹

$\text{Mo}_2\text{Et}_2(\text{NMe}_2)_4$ in toluene reacts rapidly with CO_2 (≥ 4 equiv) to give a pale yellow finely divided precipitate. This compound has not been structurally characterized but is considered to be $\text{Mo}_2(\text{O}_2\text{CNMe}_2)_4$ and to have the dimolybdenum tetraacetate structure $(\text{M}\equiv\text{M})^{10}$ on the following grounds: (i) analytical data,¹¹ (ii) infrared data,¹² and (iii) the appearance in the mass spectrum of a very strong ion corresponding to $\text{Mo}_2(\text{O}_2\text{CNMe}_2)_4^+$ (this is the ion of highest mass) and the doubly charged ion $\text{Mo}_2(\text{O}_2\text{CNMe}_2)_4^{2+}$. The compound is not appreciably soluble in hydrocarbon solvents, nor CD_2Cl_2 , but is sparingly soluble in pyridine.¹³

In a sealed NMR tube reaction $\text{Mo}_2\text{Et}_2(\text{NMe}_2)_4$ in toluene- d_8 was reacted with CO_2 (>4 equiv). The finely divided precipitate was centrifuged to the top of the tube and the ^1H NMR spectrum of the clear, virtually colorless solution was recorded. The only proton signals observed corresponded to ethylene and ethane which were in the integral ratio of 4:6, respectively.¹⁴ We conclude that the reaction between $\text{Mo}_2\text{Et}_2(\text{NMe}_2)_4$ and CO_2 proceeds stoichiometrically according to eq 1 and as such provides a model reaction for detailed studies of dinuclear reductive elimination.¹⁵ A simple intramolecular mechanism involving an initial β -hydride elimination, $\text{Et}-\text{Mo}\equiv\text{M}-\text{H} + \text{C}_2\text{H}_4$, followed by C-H reductive elimination across the $\text{Mo}\equiv\text{Mo}$ bond, $\text{Et}-\text{Mo}\equiv\text{Mo}-\text{H} \rightarrow \text{Et}-\text{H} + \text{Mo}\equiv\text{Mo}$, satisfies all our observations.

In contrast to the above we find that $\text{Mo}_2\text{Me}_2(\text{NMe}_2)_4$ reacts with CO_2 according to eq 4.



The compound $\text{Mo}_2\text{Me}_2(\text{O}_2\text{CNMe}_2)_4$ ¹⁶ is of sufficient thermal stability to allow the detection of the molecular ion $\text{Mo}_2\text{Me}_2(\text{O}_2\text{CNMe}_2)_4^+$ in the mass spectrometer. In the solid state and in solution $\text{Mo}_2\text{Me}_2(\text{O}_2\text{CNMe}_2)_4$ is believed to share the $\text{W}_2\text{Me}_2(\text{O}_2\text{CNEt}_2)_4$ structure¹⁷ which has a planar $\text{C}-\text{W}\equiv\text{W}-\text{C}$ unit with a $\text{C}-\text{W}-\text{W}$ angle equal to 106° .

Acknowledgments. We thank the Office of Naval Research for support of this work and Professor D. C. Bradley, Queen Mary College, London, who through the auspices of a NATO Grant kindly provided mass spectral results.

References and Notes

- (1) (a) G. Wilkinson, *Science*, **185**, 109 (1974); (b) P. J. Davidson, M. F. Lappert, and R. Pearce, *Acc. Chem. Res.*, **7**, 209 (1974); (c) R. R. Schrock and G.

- W. Parshall, *Chem. Rev.*, **76**, 243 (1976).
- (2) See, for example, the detailed studies of the thermal reaction $(\eta^5\text{-C}_5\text{H}_5)\text{-Fe}(\text{CO})(\text{PPh}_3)(\text{alkyl}) \rightarrow (\eta^5\text{-C}_5\text{H}_5)\text{Fe}(\text{CO})(\text{H})(\text{PPh}_3) + \text{olefin}$: D. L. Reger and E. C. Culbertson, *J. Am. Chem. Soc.*, **98**, 2789 (1976).
- (3) In M_2X_6 and $\text{M}_2\text{X}_6\text{-}\eta^n\text{Y}_n$ compounds (X, Y are uninegative monodentate ligands) the metals attain only 12-valence-shell electrons as a result of $\text{M}-\text{X}$ σ bonds and the $\text{M}-\text{M}$ triple bond. The metals are capable of increasing their coordination number and number of valence electrons by Lewis base association reactions; e.g., $\text{Mo}_2(\text{OSiMe}_3)_6 + 2\text{HNMe}_2 \rightleftharpoons \text{Mo}_2(\text{OSiMe}_3)_6(\text{HNMe}_2)_2$. M. H. Chisholm, F. A. Cotton, M. W. Extine, and W. W. Reichert, *J. Am. Chem. Soc.*, **100**, 153 (1978).
- (4) For reductive elimination in mononuclear chemistry, see C. A. Tolman, *Chem. Soc. Rev.*, **1**, 357 (1972).
- (5) M. Akiyama, M. H. Chisholm, F. A. Cotton, M. W. Extine, and C. A. Murillo, *Inorg. Chem.*, **16**, 320 (1977). Note all operations must be carried out in dry and oxygen-free solvents and atmosphere.
- (6) Found (calcd): C, 33.55 (33.79); H, 7.89 (8.04); N, 12.99 (13.15).
- (7) See the structural and dynamic behavior of the related compound $\text{W}_2\text{Me}_2(\text{NEt}_2)_4$: M. H. Chisholm, F. A. Cotton, M. W. Extine, M. Millar, and B. R. Stults, *Inorg. Chem.*, **15**, 2244 (1976).
- (8) Et group: $\delta(\text{CH}_2)$ 2.98, $\delta(\text{CH}_3)$ 1.78 ($J_{\text{HH}} = 7.9$ Hz). OBU' groups at -76°C : δ 1.60 and 1.56 in the integral ratio 3:2, respectively. Chemical shifts (δ) are given in parts per million downfield from Me_4Si .
- (9) Accidental magnetic degeneracy could account for the observed 3:2 spectrum (cf. predicted low-temperature limiting spectrum, 2:2:1).
- (10) For a recent review of compounds containing $\text{M}-\text{N}$ quadruple bonds, see F. A. Cotton, *Chem. Soc. Rev.*, **4**, 27 (1975). (b) The diethyl carbamate $\text{Cr}_2(\text{O}_2\text{CNEt}_2)_4(\text{HNt}_2)_2$ has recently been structurally characterized and shown to have a $\text{Cr}-\text{Cr}$ quadruple bond: M. H. Chisholm, F. A. Cotton, M. W. Extine, and D. C. Rideout, *Inorg. Chem.*, submitted for publication.
- (11) Found (calcd): C, 26.23 (26.48); H, 4.25 (4.44); N, 10.09 (10.29).
- (12) In particular the presence of a strong absorption at 1560 cm^{-1} assignable to $\nu(\text{NCO}_2)$ of a bridging bidentate carbamate ligand. See M. H. Chisholm and M. W. Extine, *J. Am. Chem. Soc.*, **99**, 782 (1977).
- (13) ^1H NMR data recorded at 100 MHz, 25°C in pyridine- d_5 : $\delta(\text{O}_2\text{CNMe}_2)$ 2.93 ppm relative to Me_4Si .
- (14) Found by weighing the traces 38–62. Any departure from the predicted ratio, 4:6, may be due to their differing solubilities or due to the inherent experimental error of weighing the cut traces.
- (15) Labeling studies are planned in order to investigate (i) the reversibility of β -hydrogen elimination and (ii) the intra- vs. intermolecular nature of the reaction.
- (16) Found (calcd): C, 29.50 (29.29); H, 5.14 (5.23); N, 9.65 (9.75).
- (17) M. H. Chisholm, F. A. Cotton, M. W. Extine, and B. R. Stults, *Inorg. Chem.*, **16**, 603 (1977).
- (18) Alfred P. Sloan Fellow, 1976–1978. Address correspondence to the Department of Chemistry, Indiana University, Bloomington, Ind. 47401.

Malcolm H. Chisholm*¹⁸

Deborah A. Haitko, Carlos A. Murillo

Department of Chemistry, Princeton University
Princeton, New Jersey 08540

Received June 6, 1978

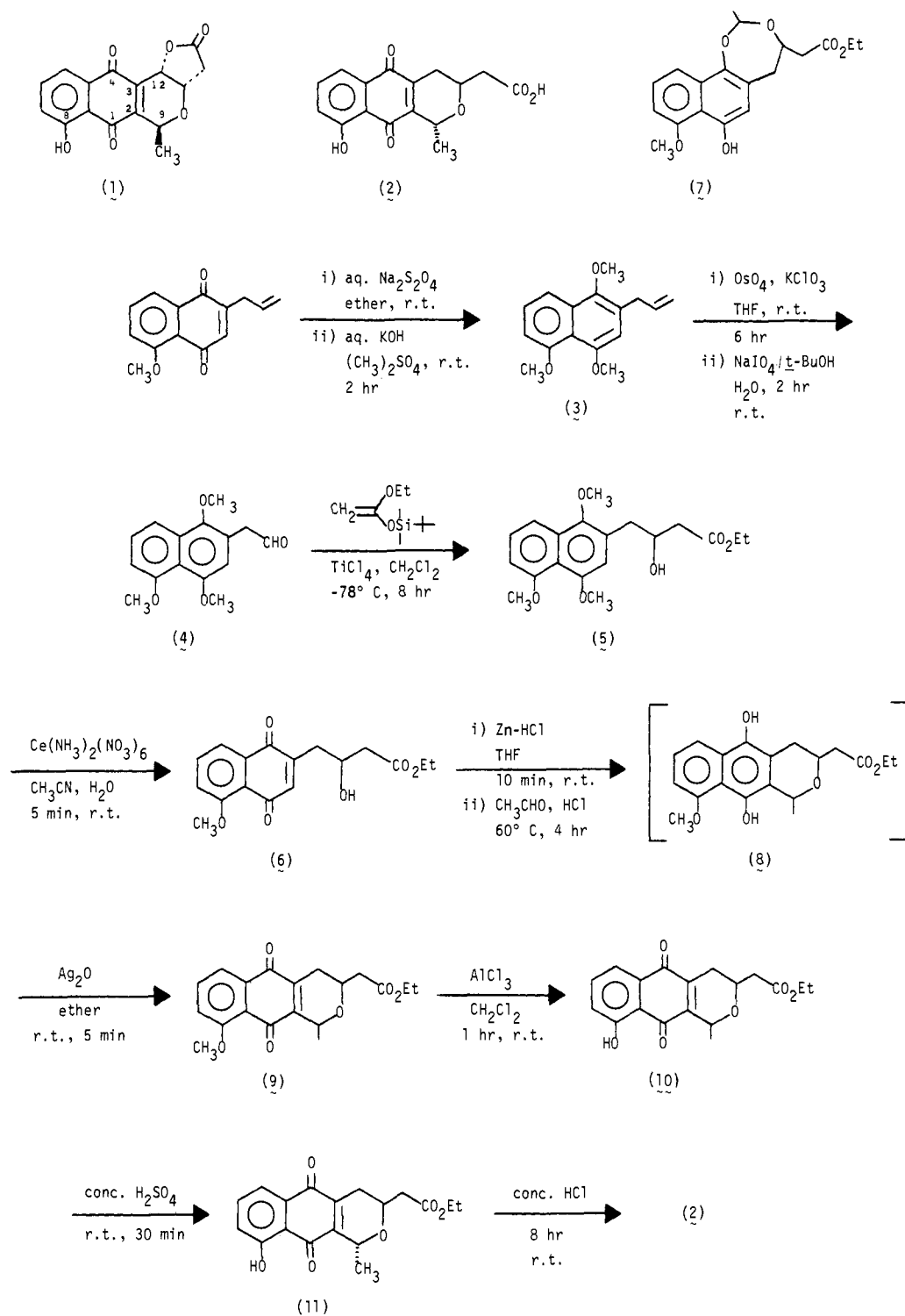
Stereoselective Total Synthesis of Racemic Kalafungin and Nanaomycin A

Sir:

Kalafungin (**1**)¹ and nanaomycins A (**2**)² and D (**1**)³ are members of the naphthoquinone class of antibiotics, which also includes frenolicin⁴ and griseusins A and B.⁵ These natural products are potent antimicrobial agents, and the nanaomycins, in particular, have been shown⁵ to be extremely active against mycoplasmas. In a recent publication,⁶ Moore pointed out that these compounds have potential antineoplastic activity, as bioreduction may transform them into biskalating agents functioning similarly to the currently useful drug, mitomycin.⁷ We wish to report the first total synthesis of kalafungin and of nanaomycins A and D.⁸

2-Allyl-5-methoxynaphthoquinone⁹ was reduced with sodium hydrosulfite and alkylated with dimethyl sulfate and potassium hydroxide giving 2-allyl-1,4,5-trimethoxynaphthalene (**3**) (mp $37.5\text{--}39^\circ\text{C}$)¹⁰ in 70% yield (Scheme I). Osmium tetroxide-potassium chlorate¹¹ converted the allyl derivative into the corresponding diol, which was readily cleaved by periodate to give the aldehyde (**4**) (mp $80.5\text{--}92^\circ\text{C}$)¹⁰ in 80% overall yield. Titanium tetrachloride catalyzed reaction¹² of ketene ethyl *tert*-butyldimethylsilyl acetal with aldehyde **4** provided the hydroxy ester **5** in 50% yield. Oxidation of the dimethyl ether of the quinol was accomplished using ceric

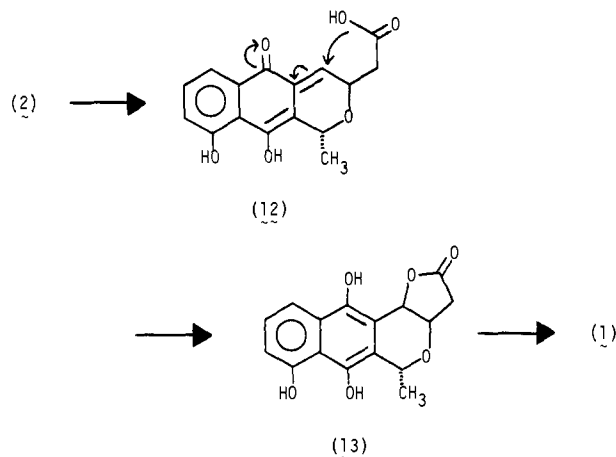
Scheme I



ammonium nitrate¹³ furnishing the quinone **6** (mp 119.5–120.5 °C)¹⁰ in 74% yield. Reduction of quinone **6** with zinc and hydrochloric acid gave the corresponding quinol, which, without purification, was treated with acetaldehyde and hydrochloric acid yielding an initial adduct. Based on NMR and mass spectral data,¹⁴ as well as the fact that silver oxide oxidation of the adduct gave the starting quinone **6**, we concluded that this substance was the acetal **7**. Further treatment with acetaldehyde and hydrochloric acid led to the tricyclic product **8**,^{8,9} which was oxidized quantitatively with silver oxide to the quinone **9** (mp 113–115 °C),¹⁰ obtainable in 51% overall yield from the starting hydroxy ester **6**. The cis stereochemistry for

the C₉ and C₁₁ substituents of compound **9** was assigned on the basis of NMR studies.¹⁵ Demethylation of the methyl ether **9** was achieved in 88% yield with aluminum chloride¹⁶ giving the phenolic product **10** (mp 93–94 °C).¹⁰ Concentrated sulfuric acid treatment caused epimerization at C₉ giving a 2:1 mixture¹⁷ of the trans and cis isomers **11** and **10**, respectively, from which the pure trans isomer **11** (mp 134 °C)¹⁰ was isolated by fractional recrystallization. By recycling of the mother liquor, **11** could be obtained in 70% yield from cis isomer **10**. Hydrolysis of the ethyl ester group was carried out in concentrated hydrochloric acid giving racemic nanaomycin A (**2**) (50%, mp 171–174 °C). Air oxidation of nanaomycin A has

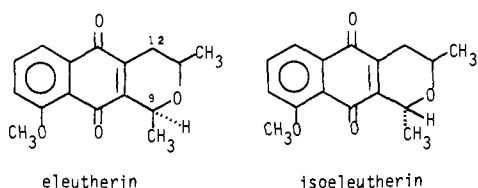
been reported to give nanaomycin D,³ and indeed, treatment of our synthetic nanaomycin A with air in methanolic solution gave a racemic mixture of kalafungin and nanaomycin D (**1**)³ (mp 135 °C dec). A plausible mechanism involves the quinone methide intermediate **12**⁶ in the oxidative process. Intramolecular conjugate addition of the carboxylic acid into the enone would then give the quinol lactone **13**, which could be readily oxidized to give the quinone.



The IR, NMR, mass, and UV spectra, as well as the TLC behavior of the synthetic nanaomycin A and kalafungin-nanaomycin D, were indistinguishable from those of the respective natural products.¹⁸

References and Notes

- M. E. Bergy, *J. Antibiot.*, **21**, 454 (1968); D. J. Duchamp, *Abstr. Am. Crystallogr.*, **82** (1968); H. Hoeksema and W. C. Krueger, *J. Antibiot.*, **29**, 704 (1976).
- S. Omura, H. Tanaka, Y. Koyama, R. Ōiwa, M. Katagiri, J. Awaya, T. Nagai, and T. Hata, *J. Antibiot.*, **27**, 363 (1974); H. Tanaka, Y. Koyama, J. Awaya, H. Marumo, R. Ōiwa, M. Katagiri, T. Nagai, and S. Omura, *ibid.*, **28**, 860 (1975); H. Tanaka, Y. Koyama, T. Nagai, H. Marumo and S. Omura, *ibid.*, **28**, 868 (1975).
- S. Omura, H. Tanaka, Y. Okada, and H. Marumo, *J. Chem. Soc., Chem. Commun.*, 320 (1976). Kalafungin and nanaomycin D are the enantiomers corresponding to structure 1.
- J. C. Van Meter, M. Dann, and N. Bohonos, "Antibacterial Agents Annual, 1960", Plenum Press, New York, N.Y., 1961, p 77; G. A. Ellestad, M. P. Kunstmann, H. A. Whaley, E. L. Patterson, *J. Am. Chem. Soc.*, **90**, 1325 (1968).
- N. Tsuji, M. Kobayashi, Y. Wakisaka, Y. Kawamura, M. Mayama, and K. Matsumoto, *J. Antibiot.*, **29**, 7 (1976); N. Tsuji, M. Kobayashi, Y. Terui, and K. Tori, *Tetrahedron*, **32**, 2207 (1976).
- H. W. Moore, *Science*, **197**, 527 (1977).
- M. Tomasz, C. M. Mercado, J. Olson, and N. Chatterjee, *Biochemistry*, **13**, 4878 (1974).
- As our efforts were drawing to a successful conclusion, a publication appeared describing the synthesis of 8-deoxy nanaomycin A: J. St. Pyrek, O. Achmatowicz, Jr., and A. Zamojski, *Tetrahedron*, **33**, 673 (1977).
- W. Eisenhuth and H. Schmid, *Helv. Chim. Acta*, **41**, 2021 (1958).
- NMR, IR, and mass spectra consistent with the assigned structure, as well as satisfactory C and H analyses, were obtained for this compound.
- G. Büchi, E. Demole, and A. F. Thomas, *J. Org. Chem.*, **38**, 123 (1973).
- K. Saigo, M. Osaki, and T. Mukaiyama, *Chem. Lett.*, 989 (1975).
- P. Jacob, III, P. S. Callery, A. T. Shulgin, and N. Castagnoli, Jr., *J. Org. Chem.*, **41**, 3627 (1976).
- The NMR spectrum of this unstable intermediate has a three-proton doublet centered around δ 1.60 ($J = 5.8$ Hz) coupled with a one-proton quartet at δ 4.78, and the mass spectrum shows a molecular ion peak at 346.
- The stereochemistry of natural nanaomycin A was assigned² by comparing its NMR spectrum with those of the eleutherin-isoeleutherin epimeric pair: D. W. Cameron, D. G. I. Kingston, N. Sheppard, and Lord Todd, *J. Chem. Soc.*, 98 (1964). In the natural nanaomycin A spectrum, the C₉ proton (δ 5.06, br q, $J_{9,12} < 1$ Hz) is similar to that of isoeleutherin, while the C₉ proton signal (δ 4.85, m, $J_{9,12} = 2$ Hz) in **9** is similar to that of eleutherin.



- A. S. Kende, Y.-G. Tsay, and J. E. Mills, *J. Am. Chem. Soc.*, **98**, 1967 (1976).
- The trans/cis ratio was estimated by NMR on the basis of the peak height ratio of the two sets of C₉ methyl doublets centered at δ 1.54 and at δ 1.55.
- We are grateful to Dr. Ōmura of the Kitasato Institute for providing us with an authentic sample of nanaomycin A and to Dr. Whitefield of The Upjohn Co. for an authentic sample of kalafungin. The authors thank Drs. M. Marx, J. A. Edwards, and J. G. Moffatt for critically reading the manuscript and for helpful discussion and encouragement throughout this project. We are also grateful to the Syntex Analytical Department for their expert help.

Tsung-tee Li,* Robert H. Ellison

Contribution No. 513

Institute of Organic Chemistry, Syntex Research
Palo Alto, California 94304

Received May 17, 1978

Transverse Relaxation of Multiple Quantum Coherence in Nuclear Magnetic Resonance as a Probe of Molecular Motion

Sir:

The development of pulse techniques for observations of zero and multiple quantum (MQ) coherences in NMR¹⁻³ has opened new perspectives for relaxation studies of multilevel spin systems. Though not directly observable, MQ coherences may be stimulated by appropriately tailored pulses.¹⁻⁵ Their time evolution is characterized by a decay similar in kind to the transverse (T_2) decay of normal 1Q magnetizations, but the decay rates are quantitatively different. In combination with conventional longitudinal and transverse relaxation measurements, the MQ decay rates therefore provide a powerful tool for detailed studies of relaxation pathways and molecular dynamics. In this communication, we demonstrate the utility of double quantum line widths for the determination of spectral densities of motion in two single deuteron systems, CDCl₃ and DC≡C—C≡N, partially ordered in a nematic solvent.

The use of two-dimensional Fourier transform techniques^{1,6,7} is essential for measurements of MQ decay rates in all but the very simplest^{3,4} spin systems. After an initial excitation, the MQ coherences are allowed to evolve for a time t_1 . The application of a "monitoring" pulse generates conventional (1Q) magnetizations with amplitudes which depend on the phases of the "invisible" coherences at $t = t_1$.^{1,4} The free induction decay, which develops during the subsequent period t_2 , yields the usual spectrum in a frequency domain F_2 . A series of such spectra obtained at regular increments of t_1 may be subjected to a second Fourier transformation with respect to t_1 . The modulation due to MQ coherences is thereby translated into resonance peaks in the frequency domain F_1 .

The NMR spectrum of a single partially ordered deuteron consists⁸ of two nondegenerate ($1 \rightarrow 0$ and $0 \rightarrow -1$) 1Q transitions at $\omega_0 \pm \omega_Q$. The double quantum (2Q) coherence of a simple three-level system may be readily excited⁴ by a "soft" pulse applied at an offset $\Delta\omega$ from the center ω_0 of the doublet. Provided that $\Delta\omega \ll \omega_1 \ll \omega_Q$, the largest 2Q coherence is obtained for a pulse width $t_{p1} = \pi\omega_Q/2\omega_1^2$.⁴ The monitoring pulse should ideally fulfill the condition $t_{p2} = \pi/2\omega_1$ with $\omega_1 \gg \omega_Q$. Alternatively, a weak ($\omega_1 \ll \omega_Q$) audiomodulated ($\omega_M \approx \omega_Q$) monitoring pulse may be used.⁹ Conditions for observation of the 2Q coherence for a single deuteron are not very stringent.⁴ Any effect of spurious excitation of transverse 1Q magnetization by the first pulse may be suppressed by use of phase alternation.^{5,10} Also, a monitoring pulse with $\omega_1 \approx \omega_Q$ was found to be adequate.

An example of a two-dimensional spectrum of a liquid crystalline solution of DCCCN is shown in Figure 1. A section (540 Hz = 110 points) of the folded, phase corrected, 1Q