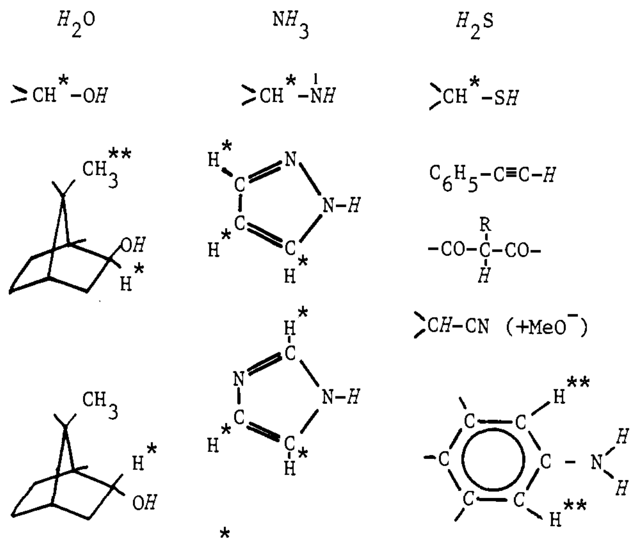
Chart I[a]

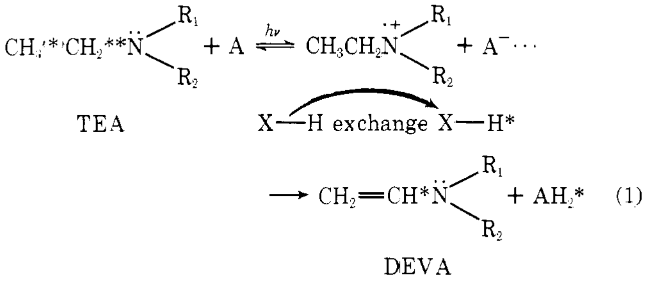


[a] H* = negative NOE (scalar coupling); H** = positive NOE (dipolar coupling); *H* = exchanging protons.

cations are *acidic* and exchange readily with the marked protons (-*H*) in the functional groups listed in Chart I.

Many reactions which generate aminium cations and their associated CIDNP have been outlined previously.[2,8a,11] These photoinduced electron-transfer reactions require polar solvents ($\epsilon > 20$) such as acetonitrile or dimethyl sulfoxide. The acceptors may be (a) aliphatic or aromatic nitriles,[11a] (b) aromatic hydrocarbons,[11b] or (c) ketones or quinones.[11c] Table I lists the sign (phase) of CIDNP observed in the α protons of the amines (-H**) and of the exchanging protons (-*H*), which is always opposite. Chart I correlates the CINOE observed in characteristic substrates.

The chemistry of the pump as well as the associated NMR and CIDNP lines should be compatible with the substrate. Some overlap of resonances is acceptable, such as resonance γ in Figure 1a′, which stems from the oxidation product diethylvinylamine (DEVA) derived from TEA (vide infra). The peaks α and β in Figure 1 are due to the ortho and para positions of biphenyl whose protons exchange with those of the aminium and of the substrates. The pump should also be highly reversible to assure a long duration of the CINOE. Nitriles and hydrocarbons were found to yield a higher reversibility than quinones or ketones. The irreversibility could be shown to be due to photoreduction of A to the dihydro form AH_2 and simultaneous oxidation (and possibly hydrolysis) of the amine to an eneamine, such as DEVA from TEA (eq 1). In support of the above scheme the CIDNP resonances of the eneamines and of AH_2 are observed. Furthermore, the polarization in the positions -*H*, -H*, and H** disappears upon deuteration of the α positions in the amines; cf. the difference between $CH_3CH_2CH_2N(CH_3)_2$ and $CH_3CH_2CD_2N(CD_3)_2$ in Table I. In presence of suitable bases (methoxide) even the solvent CD_2HCN displays CINOE because of the equilibrium $CH_3O^- + CD_3CN \rightleftharpoons CH_3OD + CD_2CN^-$ and subsequent exchange. Water can become strongly polarized, especially when occurring in small concentrations in aprotic solvents. This fact may be used to pump aqueous systems via a membrane together with a flow system.



$$CH_3{}^{*}CH_2{}^{**}\ddot{N}R_1R_2 + A \underset{}{\overset{h\nu}{\rightleftharpoons}} CH_3CH_2\overset{\cdot+}{N}R_1R_2 + A^{-}\cdots$$

TEA

$$X\text{—}H \xrightarrow{\text{exchange}} X\text{—}H^{*}$$

$$\longrightarrow CH_2{=}CH^{*}\ddot{N}R_1R_2 + AH_2^{*} \quad (1)$$

DEVA

The molecules investigated here (Chart I) are models for those of biochemical interest, such as sugars, nucleic acids, etc. There CINOE might well be quite selective. Especially attractive seems the possibility of pumping ^{15}N, where electronic pumps are inefficient because of the negative magnetic moment of ^{15}N and the associated negative enhancement, which causes an initial signal loss. CINOE could provide a superior alternative for positive ^{15}N signal enhancement. The above proton results seem encouraging.

References and Notes

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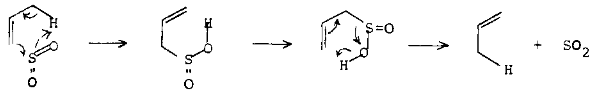
Annelation of 1,2-Cyclononadiene with Tetrachlorothiophene Dioxide. An Ene Reaction with Sulfur Dioxide

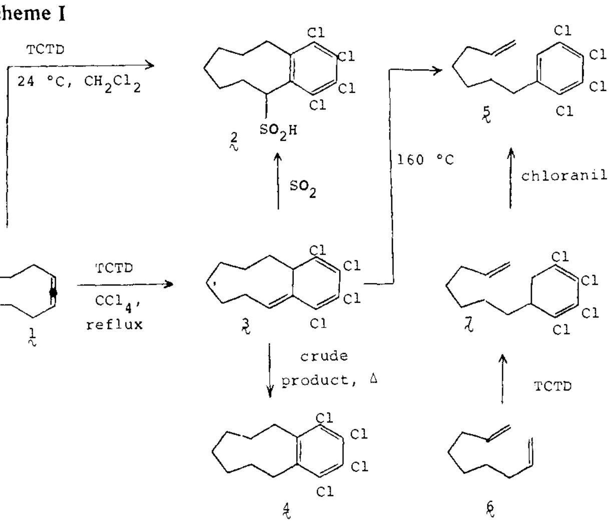
Sir:

Rogić and Masilamani[1] have proposed that the isomerization of olefins with sulfur dioxide involves an ene reaction to form an allylic sulfinic acid which undergoes 1,3 rearrangement, followed by a retro-ene reaction to give the isomerized olefin and sulfur dioxide. Direct evidence for the presence of the sulfinic acid is lacking. We report the isolation of a stable sulfinic acid in an ene reaction of an olefin with sulfur dioxide.



1,2-Cyclononadiene[2] (**1**) reacts with tetrachlorothiophene 1,1-dioxide (TCTD)[3] in dichloromethane at 24 °C to give the sulfinic acid **2** (mp 145–148 °C dec) in 79% isolated yield[4] (Scheme I). If the reaction is run in refluxing carbon tetrachloride, sulfur dioxide escapes from the reaction mixture and the triene **3** (mp 51–52 °C) and **2**, which is stable under these conditions, are isolated in 52 and 9% yields, respectively. When sulfur dioxide is passed into a solution of **3** in dichloromethane, an ene reaction occurs and the sulfinic acid **2** precipitates (76%

Scheme I



yield). Thus, the two steps by which **2** is formed at 24 °C are apparent.

The successful isolation of the sulfinic acid **2** from the ene reaction of **3** with sulfur dioxide is direct evidence that supports the initial step in the isomerization mechanism proposed by Rogić and Masilamani. The sulfinic acid is isolable in this case because the benzene ring does not participate in the rearrangement and retro-ene reactions characteristic of allylic sulfinic acids.[1b]

If a crude sample of **3** containing a small amount of **2** is distilled under vacuum, it undergoes an acid-catalyzed double-bond migration to the thermodynamically more stable benzocyclononene **4** (mp 110.5–111.7 °C). On the other hand, if pure **3** is heated at 160 °C, it undergoes an unusually facile, nearly quantitative retro-ene reaction to give **5** (mp 30.3–30.9 °C, bp 103 °C (3 mm)). The preference for a thermal [1, 5] shift over the symmetry forbidden [1, 3] sigmatropic shift in this system is evident. The number of known examples of this retro-ene reaction in all carbon systems is small, and they require temperatures in the range of 250–580 °C.[5] For example, *cis*-cyclononene itself is converted into 1,8-nonadiene to the extent of only 20% at 500 °C.[6] The more facile rearrangement in the present case can be attributed to the formation of the aromatic ring.

The preparation of **3**, uncomplicated by the presence of sulfur dioxide, also was carried out by heating 1,2-cyclononadiene with tetrachloro-α-pyrone[7] at 100 °C. The structure of **5** was corroborated by independent synthesis (Scheme I). 1,8-Nonadiene[8] (**6**) was monoannelated with TCTD at ~100 °C to give **7** (bp 131 °C (0.5 mm)) in 49% isolated yield. Compound **7** was aromatized to **5** by heating with chloranil at 160 °C.

Acknowledgment. We are indebted to F. A. Blissick for technical assistance and to E. W. Matthews for IR and UV spectral interpretations.

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^{113}Cd NMR of Metallothionein: Direct Evidence for the Existence of Polynuclear Metal Binding Sites

Sir:

The structural basis for the remarkable metal binding capacity of metallothionein (~6–7 g-atoms/mol, usually Zn^{2+} and Cd^{2+}) is of considerable interest owing to the recent postulated involvement of this protein in metal detoxification and/or metabolism.[1a,2] Metallothionein is a small protein (mol wt, ~6800) located in the kidney and liver of a wide variety of animal species, including man, and its synthesis can be induced by the administration of Cd^{2+}, Zn^{2+}, and other heavy metals.[3] The amino acid composition of the protein is very unusual in that there is a complete absence of histidine and aromatic amino acid residues while about 20 out of the total of 60 amino acids in the protein are cysteine residues.[1a,2c] All 20 cysteines have been shown to participate in metal ligation via mercaptide linkages.[1a,4] Since the ratio of cysteine/divalent metal ion in all metallothioneins is close to 3, it has been postulated that the metals in the protein exist as isolated, negatively charged trimercaptide complexes,[5] i.e., $[Me^{2+}(Cys^-)_3]^-$. In view of the known propensity of Cd^{2+} to form polynuclear complexes deriving from the ability of mercaptide sulfur atoms to act as bridges between two or three Cd^{2+} ions,[6] alternate structures involving oligomeric metal binding sites are equally likely to exist in metallothionein. In this paper, we report the observation of extensive ^{113}Cd–^{113}Cd spin coupling in the ^{113}Cd NMR spectrum of metallothionein II from rabbit liver. This result provides the first direct evidence for the existence of a polynuclear metal cluster arrangement in this protein.

Pure metallothionein II (one of the major isoproteins of metallothionein) was isolated[1a] from the livers of rabbits subjected to repeated injections of 96% enriched $^{113}CdCl_2$. Protein was concentrated for NMR to ~14 mM by ultrafiltration on a Diaflo UM-2 membrane. The metal content of the protein determined by atomic absorption and normalized to a total of 7 g-atoms of metal/mol of protein was 4.4 g-atoms of $^{113}Cd^{2+}$ and 2.6 g-atoms of Zn^{2+}/mol. The nonintegral metal content reflects the known heterogeneity of the native protein which is due to the presence of species containing different relative amounts of Zn^{2+} and Cd^{2+}.[3] ^{113}Cd spectra at 19.96 MHz were obtained on an extensively modified Bruker HFX-90 spectrometer and at 44.37 MHz on a Bruker CXP-200 spectrometer.

The ^{113}Cd NMR spectrum of metallothionein II in Figure 1A exhibits five resolved resonances centered at 604, 613, 623, 641, and 668 ppm downfield from 0.1 M $CdClO_4$. These chemical shift values are consistent with previous reports[7] and indicate that each Cd^{2+} ion in metallothionein is involved in extensive sulfur ligation. From the qualitative correlation between degree of deshielding and extent of sulfur ligation observed in a series of Cd^{2+}-alkylthiolate complexes,[8] it is likely that every Cd^{2+} ion in metallothionein is coordinated to at least three cysteine sulfur ligands. However, on the basis of available