

Table I. Acid-Catalyzed Reactions of Nitriles with Benzene<sup>a</sup>

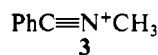
run	nitrile	acid <sup>c</sup>	-H <sub>0</sub> <sup>d</sup>	time, min	phenylated product
1	HCN <sup>b</sup>	23% TFSA-77% TFA	10.6	300	0
2	HCN <sup>b</sup>	55% TFSA-45% TFA	11.8	300	3
3	HCN <sup>b</sup>	80% TFSA-20% TFA	12.7	300	11
4	HCN <sup>b</sup>	TFSA	13.7	30	44
5	HCN <sup>b</sup>	99% TFSA-1% SbF <sub>5</sub>	16.8	30	65
6	HCN <sup>b</sup>	95% TFSA-5% SbF <sub>5</sub>	>18	5	92
7	(CH <sub>3</sub> ) <sub>3</sub> SiCN	55% TFSA-45% TFA	11.8	300	2
8	(CH <sub>3</sub> ) <sub>3</sub> SiCN	80% TFSA-20% TFA	12.7	30	17
9	(CH <sub>3</sub> ) <sub>3</sub> SiCN	TFSA	13.7	30	55
10	(CH <sub>3</sub> ) <sub>3</sub> SiCN	95% TFSA-5% SbF <sub>5</sub>	>18	5	99
11	PhCN	55% TFSA-45% TFA	11.8	300	11 <sup>e</sup>
12	PhCN	TFSA	13.7	120	14 <sup>f</sup>
13	PhCN	95% TFSA-5% SbF <sub>5</sub>	>18	30	54 <sup>g</sup>

<sup>a</sup>All the reactions were performed at 20 °C. <sup>b</sup>Sodium cyanide was used as a source of HCN. <sup>c</sup>Compositions of mixed acids are given in weight percentages. In all the reactions, a 450-fold molar excess of the acid was used. <sup>d</sup>Footnote 6. <sup>e</sup>Accompanied by a 15% yield of PhCN and 17% of 2,4,6-triphenyltriazine. <sup>f</sup>Accompanied by a 50% yield of PhCN. <sup>g</sup>Accompanied by a 29% yield of PhCN.

The reaction with benzene in the presence of the acid proceeded in a very similar way to the case of hydrogen cyanide. Here again, a strong acid is required, and the higher the acidity is, the better the result. Though attempts to find good conditions for the reaction of acetonitrile with benzene were unsuccessful, we could react benzonitrile with benzene. In the presence of a weak acid system, the yield of benzophenone obtained after hydrolysis of the product was very low, but in a medium of higher acidity, significant formation of benzophenone was attained (Table I).

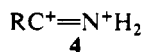
In all cases, very high acidity is required for the reaction. The Lewis acid functions so as to raise the acidity, but seems to have no special role, because the reaction definitely proceeds in neat TFSA. Since the basicity (pK<sub>BH</sub><sup>+</sup>) of nitriles is around -10 to -11 (-10.5 for benzonitrile and -10.12 for acetonitrile),<sup>7</sup> the nitriles in 23% TFSA-77% TFA are roughly half-protonated. In an acid system with H<sub>0</sub> < -12, monoprotonation should be almost complete. Nevertheless, further increase of the acidity is very favorable for the reactions, implying that additional protonation on the monoprotonated species **1** is required for the reactions.

In order to obtain further evidence for the participation of the second protonation, the reaction of *N*-methylbenzonitrilium triflate (**3**)<sup>8</sup> with benzene was analyzed. This ion reacts with activated



aromatics,<sup>8</sup> but does not react with benzene even in the presence of TFA. TFSA can catalyze the reaction, but only very slowly (20 h) and in low yield (3%). The stronger acid TFSA-SbF<sub>5</sub> (5%) was acidic enough to allow the reaction to proceed, and benzophenone (55%) was isolated. This definitely indicates that protonation is required for the reaction with benzene.

Thus, it is concluded that the reactive species, the dication **4**, is formed by protonation of *N*-protonated or *N*-alkylated nitriles in the highly acidic media. The stable nitrilium ion or a carbocation stabilized by an imino group is protonated to form a carbocation (**4**) destabilized by an iminium cation group. This activation of the carbocation makes the reaction proceed.



The electronic nature of the species has been fully analyzed by Schwarz et al.<sup>9</sup> According to the calculations for the diprotonated hydrogen cyanide H<sub>3</sub>CN<sup>2+</sup>, the *N,N*-diprotonated planar structure is preferable to the *C,N*-diprotonated one. The *N,N*-diprotonated species bears more positive charge on the carbon atom than does the latter. The dicationic species is more energetic

(7) Deno, N. C.; Gaugler, R. W.; Wisotsky, M. J. *J. Org. Chem.* **1966**, *31*, 1967. Olah, G. A.; Kiorsky, T. E. *J. Am. Chem. Soc.* **1968**, *90*, 4666.

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(9) Koch, W.; Heinrich, N.; Schwarz, H. *J. Am. Chem. Soc.* **1986**, *108*, 5400.

than the monocation and thus can react readily with benzene.

The present understanding of the Houben-Hoesch and Gattermann reactions can be extended to some Friedel-Crafts type reactions.<sup>10</sup> Since C-protonated carbon monoxide is isosteric with hydrogen cyanide, the Gattermann-Koch reaction is suspected to involve the diprotonated carbon monoxide<sup>11</sup> as the electrophile.

(10) Olah, G. A.; Prakash, S.; Lammertsma, K. *Res. Chem. Intermed.* **1989**, *12*, 141.

(11) Bouma, W. J.; Radom, L. *J. Am. Chem. Soc.* **1983**, *105*, 5484.

### Raman Spectrum of Matrix-Isolated Cyclobutadiene. Evidence for Environmental Hindrance to Heavy-Atom Tunneling?

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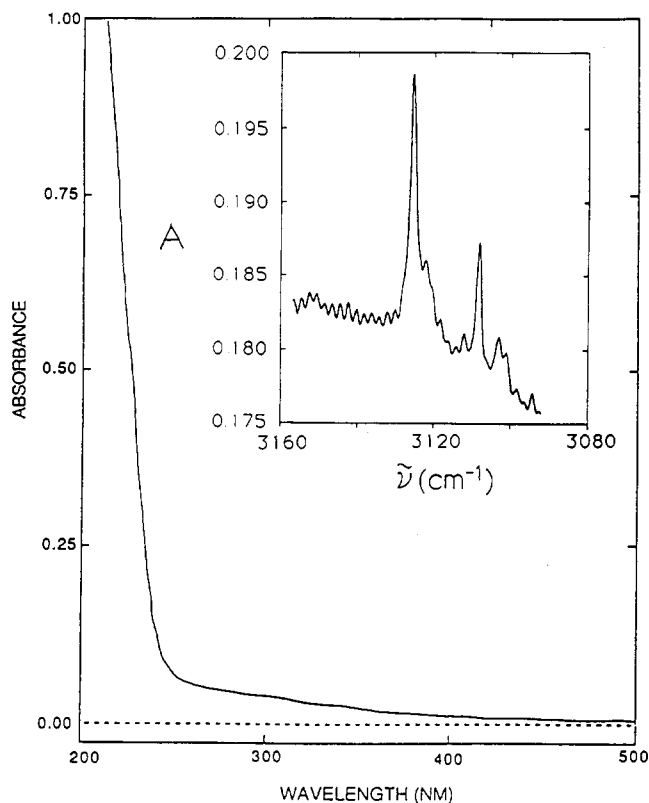
We have recorded the Raman spectrum of matrix-isolated cyclobutadiene (**1**)<sup>1</sup> as a function of temperature and find that it agrees much better with expectations for a rectangular species with a harmonic force field than those for a species tunneling at the previously computed<sup>2</sup> very rapid rates (~10<sup>11</sup> s<sup>-1</sup>) between two rectangular geometries.

Matrix-isolated cyclobutene-3,4-dicarboxylic anhydride (**2**) produces **1**, CO, and CO<sub>2</sub> upon 254-nm irradiation.<sup>3</sup> We have also detected the byproducts **3-5** by their IR spectra in Ar and Ne matrices. Simultaneous irradiation at 254 and 313 nm (Mineralight lamp UVGL25, with filter removed) destroys the byproducts and removes all UV absorption peaks above 230 nm while converting a minor fraction of **1** to acetylene. The use of a sapphire substrate permits simultaneous observation of the UV spectrum and the C-H stretching bands in the IR spectrum of

(1) For recent reviews, see: (a) Maier, G. *Angew. Chem., Int. Ed. Engl.* **1988**, *27*, 309. (b) Arnold, B.; Michl, J. In *Kinetics and Spectroscopy of Carbenes and Biradicals*; Platz, M. S., Ed.; Plenum: New York, NY, 1990; Chapter 1, p 1.

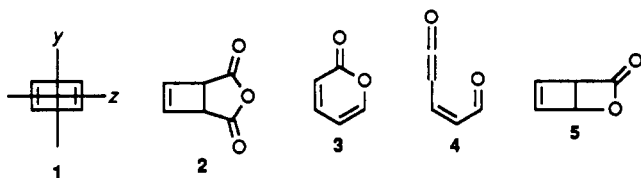
(2) (a) Carpenter, B. K. *J. Am. Chem. Soc.* **1983**, *105*, 1700. (b) Huang, M.-J.; Wolfsberg, M. *J. Am. Chem. Soc.* **1984**, *106*, 4039. (c) Dewar, M. J. S.; Merz, K. M., Jr.; Stewart, J. J. P. *J. Am. Chem. Soc.* **1984**, *106*, 4040. (d) Čárský, P.; Bartlett, R. J.; Fitzgerald, G.; Noga, J.; Spirko, V. *J. Chem. Phys.* **1988**, *89*, 3008. (e) Čárský, P.; Spirko, V.; Hess, B. A., Jr.; Schaad, L. J. *J. Chem. Phys.* **1990**, *92*, 6069. (f) Čárský, P.; Downing, J. W.; Michl, J. *Int. J. Quantum Chem.* In press.

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**Figure 1.** UV-visible and IR absorption of argon-matrix isolated cyclobutadiene (**1**) on a sapphire substrate.

**1** (Figure 1), demonstrating clearly that the reported<sup>4</sup> absorption peaks near 300 nm are due to byproducts, as has been claimed<sup>3</sup> and disputed.<sup>5</sup> However, a weak tail of cyclobutadiene absorption reaches into the visible region since continued irradiation with very intense visible light slowly converts it to acetylene.



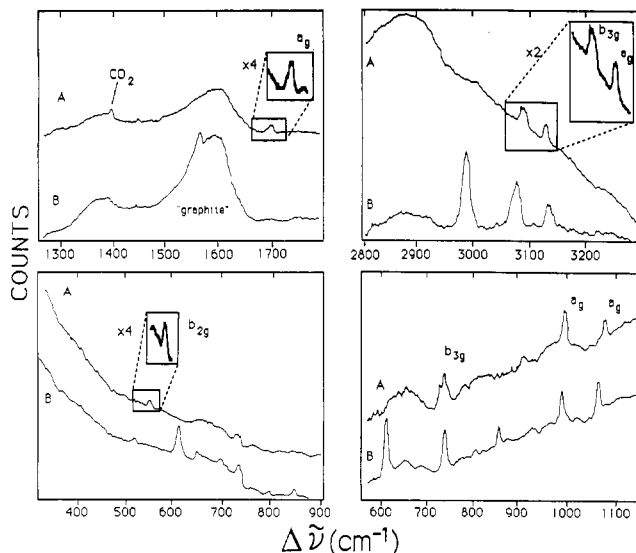
Neon (argon) matrix samples deposited at 4 K (30 K) on a silver substrate attached to an APD Cryogenics HC-4 MK1/HS4 Heliplex closed-cycle refrigerator under conditions established to guarantee the near absence of byproducts 3–5 were used to measure the Raman spectrum (Ar ion laser, 514.5 nm, 1.2 W in (10  $\mu\text{m}$ )<sup>2</sup>, Spex Triplemate spectrograph with EG&G PARC 1254 OMA detector). In addition to the known peaks of CO (2145  $\pm$  5  $\text{cm}^{-1}$ ), CO<sub>2</sub> (1340  $\pm$  5  $\text{cm}^{-1}$ ), and acetylene (3374 and 1974  $\pm$  5  $\text{cm}^{-1}$ ), it contains reproducible peaks at 531, 723, 989, 1059, 1678, 3093, and 3140  $\pm$  5  $\text{cm}^{-1}$  (Figure 2).

The spectrum can be compared with spectra calculated without and with tunneling explicitly included. The first calculation,<sup>2e,6</sup> at the 6-31G\* MP2 level, was for a rectangular equilibrium geometry using the harmonic approximation. The observed peaks can be assigned to a  $b_{2g}$  out-of-plane C—H bend calculated at 500  $\text{cm}^{-1}$ , mixed motions of  $b_{3g}$  (861  $\text{cm}^{-1}$ ),  $a_g$  (992  $\text{cm}^{-1}$ ), and  $a_g$  (1150  $\text{cm}^{-1}$ ) symmetries, an  $a_g$  C=C stretch (1604  $\text{cm}^{-1}$ ), and  $b_{3g}$  (3265  $\text{cm}^{-1}$ ) and  $a_g$  (3309  $\text{cm}^{-1}$ ) C—H stretches, respectively, in the  $D_{2h}$  symmetry group.

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**Figure 2.** Raman spectra of neon-matrix-isolated precursor **2** before (B) and after (A) irradiation at 254 and 313 nm. In the inserts, only the vertical scale is expanded.

The second calculation,<sup>2e</sup> at the GVB 4-31G level, used an anharmonic approximation in which tunneling between the two rectangular minima was considered explicitly in the three dimensions of the nuclear configuration space that correspond to  $a_g$  modes of the rectangle other than the C—H stretch, producing a 4.6- $\text{cm}^{-1}$  tunneling splitting of the ground vibrational state. The calculated transitions involving the excitation of  $a_g$  vibrations are doubled since they occur at different frequencies for the two components into which tunneling splits the ground vibrational state, with intensities dictated by the Boltzmann factors. The computed splitting of the “Kekulé” vibration at 1604  $\text{cm}^{-1}$  is substantial, 85  $\text{cm}^{-1}$ , and those predicted for the 992- and 1150- $\text{cm}^{-1}$  transitions are smaller, 20 and 3  $\text{cm}^{-1}$ , respectively.

This calculation has recently been repeated with a larger basis set.<sup>2f</sup> The new values for the splitting are 4.4  $\text{cm}^{-1}$  for the ground vibrational state, 71  $\text{cm}^{-1}$  for the Kekulé vibration, and 1 and 19  $\text{cm}^{-1}$ , respectively, for the 992- and 1150- $\text{cm}^{-1}$  vibrations.

The experimental spectrum clearly agrees much better with that calculated in the harmonic approximation, in which the effects of tunneling are neglected. In particular, only one peak appears in the C=C stretching region, and the maximum tunneling splitting of this spectroscopic transition that can be accommodated is about 10  $\text{cm}^{-1}$ . This suggests that the tunneling is much slower than calculated. Once results for a series of isotopically substituted derivatives of matrix-isolated **1** are available, it may be possible to perform a meaningful harmonic force field analysis, ignoring tunneling altogether.

Moreover, the Raman spectrum is temperature-independent throughout the accessible range,  $\sim$ 4 to  $\sim$ 6 K in neon and  $\sim$ 4 to  $\sim$ 25 K in argon, although for a 4.5- $\text{cm}^{-1}$  splitting of the lowest vibrational state the Boltzmann factors predict population ratios in the two sublevels to be 10:3 at 5 K, 10:5 at 10 K, and 10:7 at 20 K. This, too, is compatible with a ground-state tunneling splitting much smaller (or much bigger) than calculated.

On the basis of chemical trapping experiments,<sup>7</sup> matrix-isolation <sup>13</sup>C NMR,<sup>8</sup> and polarized IR<sup>8</sup> measurements, there is no doubt that the tunneling between the rectangular forms of matrix-isolated **1** occurs on a submillisecond scale. However, the present results demonstrate that the tunneling splitting is much smaller and the tunneling rate thus presumably much slower than expected from theory for an isolated molecule. Either the theory is far off the mark or the presence of the matrix environment, including the

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CO<sub>2</sub> and CO byproducts, has a dramatic hindering effect on the tunneling; for theoretical arguments for the plausibility of the latter, see ref 9.

**Acknowledgment.** Support from the National Science Foundation (Grants No. CHE 8796257 and CHE 8910759) and from the Welch Foundation (Grant No. F-751) is gratefully acknowledged.

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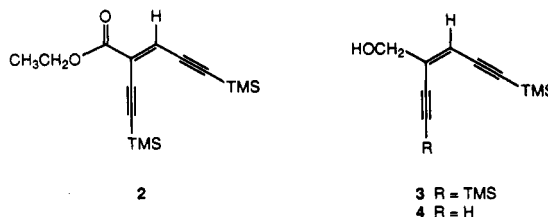
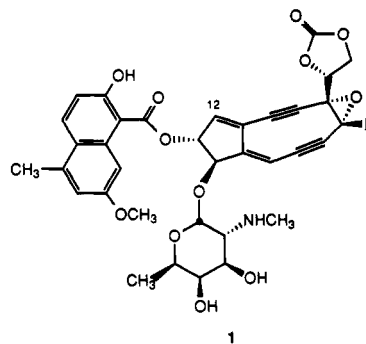
## Enantioselective Synthesis of the Epoxy Diyne Core of Neocarzinostatin Chromophore

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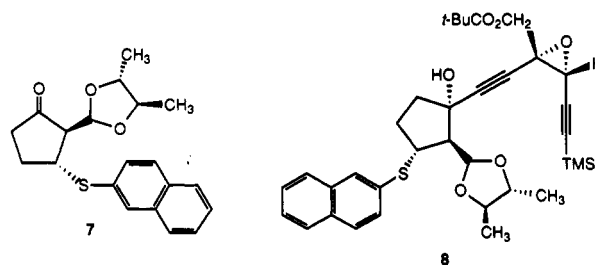
Contribution No. 8120, Arnold and Mabel Beckman Laboratories of Chemical Synthesis California Institute of Technology Pasadena, California 91125  
Received September 14, 1990

The chromophore component (**1**)<sup>1</sup> of the antitumor agent neocarzinostatin<sup>2</sup> exhibits potent cytotoxicity and DNA-cleaving activity.<sup>3</sup> DNA cleavage is believed to be initiated by an exceptionally facile nucleophilic addition of thiol to C12 of **1** followed by a rapid rearrangement reaction leading to the formation of a carbon-centered biradical.<sup>4</sup> The highly strained carbocyclic skeleton of **1** and unusual assembly of functional groups along its periphery, most notably the epoxy diyne subunit, are central to this reactivity. The epoxide ring plays a critical role in all known chemistry of **1**; epoxide opening has been clearly demonstrated to occur in thiol activation of **1**<sup>4</sup> and in the reaction of **1** with strong acids<sup>5</sup> and may underlie the extreme base sensitivity of **1** as well (*t*<sub>1/2</sub> ~ 30 s, pH 8, 0 °C).<sup>6</sup> These same features of structure and chemical instability distinguish **1** as a challenging target for synthesis. This communication describes a convergent and enantioselective synthesis of a highly functionalized epoxy diyne analogue of **1**.<sup>7</sup>

(*Z*)-Ethylene 2,3-dibromopropenoate and (trimethylsilyl)acetylene (2.75 equiv) are coupled in the presence of (Ph<sub>3</sub>P)<sub>2</sub>PdCl<sub>2</sub>, CuI, and triethylamine in tetrahydrofuran (THF) at 23 °C to afford the (*Z*)-enediynes **2** in 88% yield after flash column chromatography.<sup>8</sup> Reduction of **2** with diisobutylaluminum hydride in toluene then furnishes alcohol **3** (82%). The acetylenic groups of **3** are differentiated by selective desilylation with a reagent prepared by limited exposure (5 min at -20 °C) of sodium tri-



methoxyborohydride (1.25 equiv) to water (0.5 equiv) in THF (reaction at -20 °C for 2.5 h). Pure monodesilylated product **4** (60%) and recovered starting material **3** (20%) are obtained after flash column chromatography. Catalytic asymmetric epoxidation<sup>9</sup> of **4** ((-)-diethyl tartrate, CH<sub>2</sub>Cl<sub>2</sub>, -5 °C for 36 h) followed by in situ esterification with pivaloyl chloride produces *R,R* epoxy diyne **5** in 83% yield and 93% ee.<sup>10</sup>



(1) Isolation of **1**: (a) Napier, M. A.; Holmquist, B.; Strydom, D. J.; Goldberg, I. H. *Biochem. Biophys. Res. Commun.* **1979**, *89*, 635. (b) Koide, Y.; Ishii, F.; Hasuda, K.; Koyama, Y.; Edo, K.; Katamine, S.; Kitame, F.; Ishida, N. *J. Antibiot.* **1980**, *33*, 342. Chromophore structure: (c) Edo, K.; Mizugaki, M.; Koide, Y.; Seto, H.; Furihata, K.; Otake, N.; Ishida, N. *Tetrahedron Lett.* **1985**, *26*, 331. Carbohydrate stereochemistry: (d) Edo, K.; Akiyama, Y.; Saito, K.; Mizugaki, M.; Koide, Y.; Ishida, N. *J. Antibiot.* **1986**, *39*, 1615. Chromophore stereochemistry: (e) Myers, A. G.; Proteau, P. J.; Handel, T. M. *J. Am. Chem. Soc.* **1988**, *110*, 7212.

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(8) Myers, A. G.; Alauddin, M. M.; Fuhry, M. M.; Dragovich, P. S.; Finney, N. S.; Harrington, P. M. *Tetrahedron Lett.* **1989**, *30*, 6997 and references therein. All synthetic intermediates afforded satisfactory spectroscopic data including HRMS and/or combustion analytical data.

Cyclopentanone is formylated in high yield in a new procedure involving sequential treatment of a mechanically stirred solution of potassium *tert*-butoxide in THF (1.1 equiv, 1.3 M) at 0 °C with ethyl formate (3.9 equiv; CAUTION: gas evolution!) and a solution of cyclopentanone (1 equiv) in ethyl formate (9.5 equiv).<sup>11</sup> After stirring at 0 °C for 3 h and at 23 °C for 12 h, acidification (pH 1), and extractive isolation, 2-formylcyclopentanone is obtained as a solid in 87% yield (mp 78 °C, lit. mp<sup>11a</sup> 76-77 °C). Selenenylation of 2-formylcyclopentanone with

(9) Experiments with **4** and (*Z*)-enediynes lacking a free hydroxyl group have shown that the allylic alcohol is required for successful epoxidation, having only been achieved with the catalytic version of the Sharpless asymmetric epoxidation: Gao, Y.; Hanson, R. M.; Klunder, J. M.; Ko, S. Y.; Masamune, H.; Sharpless, K. B. *J. Am. Chem. Soc.* **1987**, *109*, 5765 and references therein.

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