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(20) Zeller, E. A.; Sarkar, S. *J. Biol. Chem.* **1962**, *237*, 2333.
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(22) NOTE ADDED IN PROOF. From the Swain equation, the 0.73 mol of ^3H released from *N*-[1-^{3}H]cyclopropylbenzylamine/mol of enzyme inactivated corresponds to 1.00 mol of ^3H released when the primary tritium isotope effect at that concentration of inactivator is considered.

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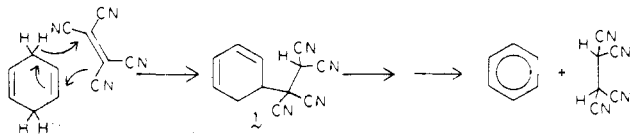
Aromatization of 1,4-Cyclohexadiene with Tetracyanoethylene: An Ene Reaction

Sir:

The aromatization of 1,4-dihydrobenzenes with tetracyanoethylene[1] (TCNE) is a very mild reaction that has seen occasional synthetic use.[2] It has been proposed that the reaction proceeds via hydride abstraction or electron-proton-electron transfer to yield a cyclohexadienyl cation[3] in analogy to quinone-mediated aromatizations, though the latter are themselves the subject of some mechanistic controversy.[4] Evidence is reported here that, at least for 1,4-cyclohexadiene (1,4-CHD) itself, the aromatization is actually initiated via an ene reaction with TCNE to give 5-(1,1,2,2-tetracyanoethyl)-1,3-cyclohexadiene (**1**). Intermediate **1** then decomposes,



perhaps by dissociation to cyclohexadienyl cation and tetracyanoethyl anion and thence to benzene and tetracyanoethane.[5]

In both tetrahydrofuran and acetonitrile-d_3 the disappearance of 1,4-CHD is a second-order reaction, first order in 1,4-CHD and first order in TCNE. The rate constants at 35.3 °C are 5.3×10^{-3} L M^{-1} min^{-1} and 6.4×10^{-2} L M^{-1} min^{-1}, respectively.[7] However, the appearance of benzene is much slower and does not give a good second-order plot. If the reaction is run in a sealed NMR tube, signals can be seen appearing in the region δ 5.8-6.6 in tandem initially with the disappearance of the 1,4-CHD signal (Figure 1a). These new signals reach a maximum and then gradually decrease with a corresponding increase in the benzene and tetracyanoethane signals (Figure 1b,c). Assuming that there are four vinyl hydrogens in the intermediate, the sum of the benzene, 1,4-CHD, and intermediate concentrations remains constant within experimental error throughout the reaction. Once the 1,4-CHD is >90% reacted, the conversion of the intermediate into benzene follows fairly good first-order kinetics with rate constants at 35.3 °C of 3.87×10^{-4} min^{-1} in THF and 1.62×10^{-3} min^{-1} in acetonitrile-d_3.[8] With the hypothesis in mind that the intermediate has structure **1**, a trapping experiment was attempted. Because TCNE is itself a very good dienophile and yet failed to react with the intermediate in Diels-Alder fashion, the more reactive *N*-phenyl triazolinedione (PTAD) was used. However, the reaction could not be run with the PTAD present initially because PTAD and 1,4-CHD themselves give an ene adduct very rapidly.[9] Therefore, a reaction run in an open NMR tube between TCNE and 1,4-CHD was allowed to proceed until most of the diene had reacted. The PTAD was

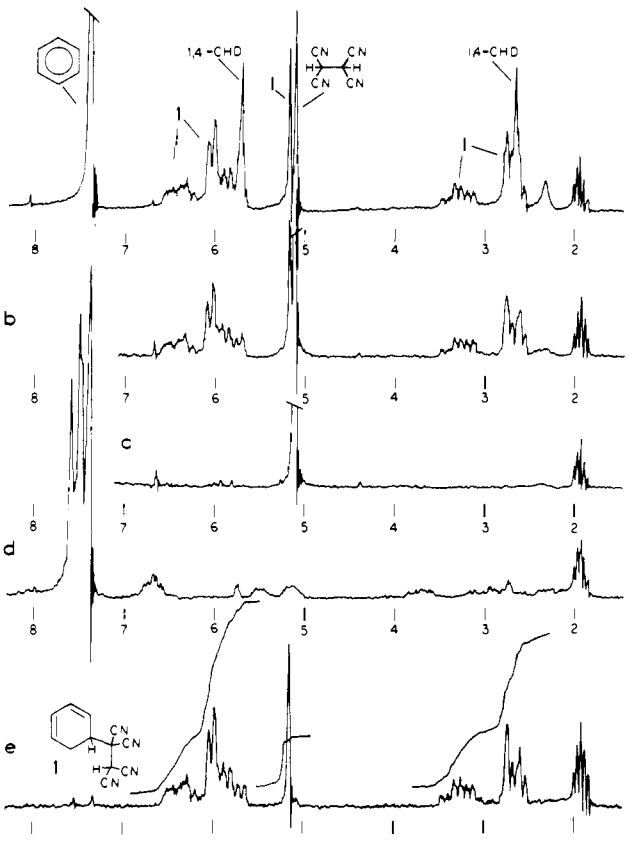


Figure 1. ^{1}H NMR spectra of (a) TCNE and 1,4-CHD after 25 min at 35 °C; (b) the same mixture after 4 h; (c) the same mixture after 24 h; (d) the same mixture after 4 h after addition of PTAD; (e) the isolated compound **1**. All spectra were in CD_3CN (residual protium in the solvent at δ 1.95) with Me_4Si internal standard. The large benzene signal in (b) and (c) has been omitted for the sake of clarity of the other spectra.

then introduced. The red color of the trapping agent faded in seconds and the spectrum of Figure 1d was observed. Although most of the signals are consistent with those expected for a Diels-Alder adduct of **1** and PTAD, the loss of both the singlets (δ 5.05 and 5.09) for the hydrogens α to the cyano groups in **1** and tetracyanoethane as well as the formation of 4-phenylurazole (isolated) indicated that more than mere trapping by a Diels-Alder reaction was occurring.[11] Because the trapping experiment produced a rather complex mixture and the trapped adduct was also of limited stability, a pure product could not be isolated. The resulting uncertainty in the precise structure of the trapped adduct (beyond reasonably strong assurance of its origin in a Diels-Alder reaction) led to an attempt to isolate the intermediate **1** itself. A solution of 300 mg of 1,4-CHD in acetonitrile was cooled to −20 °C and then added to 240 mg of freshly sublimed TCNE. The mixture was stored under N_2 at −12 °C for 24 h. Without warming, all volatiles were then pumped away at 0.03 mm of Hg. The oily residue was triturated with fresh cold acetonitrile, pumped again, triturated with CCl_4, and pumped dry a third time, all without warming above −10 °C, to yield an off-white solid. This was briefly stirred with a few milliliters of ethanol-free $CHCl_3$ at room temperature, the insoluble TCNE and tetracyanoethane were filtered off, and the filtrate was immediately evaporated (no heating) to give white crystals of **1** in 36% yield (based on initial TCNE) with NMR spectrum as shown in Figure 1e.[12] These crystals are only modestly stable. A sample stored for a week at −12 °C turned pink and showed ~5% conversion into benzene and tetracyanoethane. When dissolved in acetonitrile-d_3, **1** yielded benzene and tetracyanoethane quantitatively with, as expected, a slightly greater rate ($k = 1.86 \times 10^{-3}$ min^{-1} at 35.3 °C) than observed for the first-order

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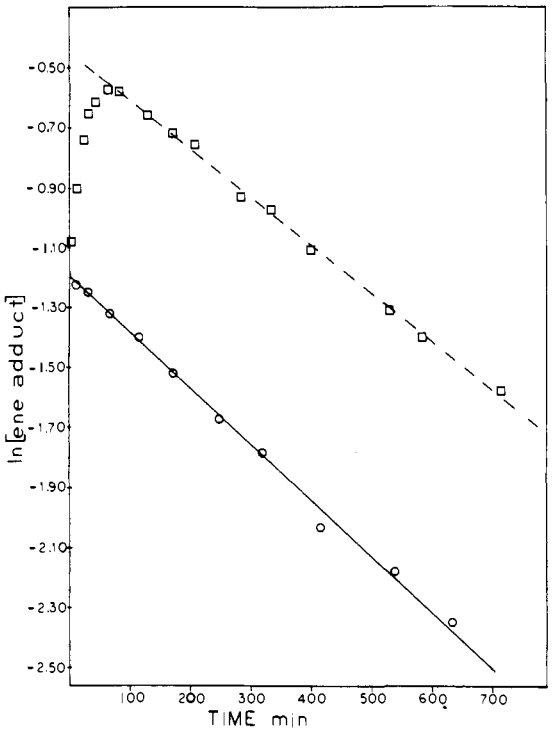

Figure 2. Plots of time vs. concentration of **1** in CD_3CN: (□) reaction starting with TCNE and 1,4-CHD; (○) reaction starting with preformed **1**; (- - -) least-squares line for points after 80 min; (—) least-squares line for all points with preformed **3**.

late stage of the direct TCNE reaction (Figure 2).

As to the further mechanistic details of the formation and decomposition of **1**, it should be noted that there is a modest color change upon mixing the TCNE and 1,4-CHD (to a light orange) presumably from a charge-transfer complex being formed. The tenfold increase in the rate constant for formation of **1** on going from THF to CD_3CN might be considered support for a rather more polar transition state than usual in the ene reaction,[13] though, if the charge-transfer complex is a true intermediate formed with a small but strongly solvent-dependent equilibrium constant, the same kinetic effect would result. The merely fourfold increase in the decomposition rate of **1** would seem small if the reaction proceeds through dissociation to cyclohexadienyl cation, but a preliminary run in a 65:35 acetone–water mixture showed a further large rate increase (more than another tenfold.)

Other 1,4-cyclohexadienes are being examined to see if the ene mechanism is a general one for TCNE-mediated aromatization. Also to be investigated is whether this mechanism extends to any of the quinone-mediated reactions. It has been noted that dichlorodicyanobenzoquinone is comparable with TCNE is its dienophilicity[4a] so that comparable activity as an enophile would be expected.[13,14] Furthermore, all of the experimental evidence cited in support of other mechanisms, such as the preference for axial hydrogen removal[4a-c] and isotope and steric effects,[4c-e] is also quite consistent with a concerted ene mechanism.[15] It should be noted that, in virtually all of the studies of these quinone and TCNE dehydrogenations, rates have been measured by following the decline in UV absorbance of the oxidant. Since that method precluded detection of nonabsorbing intermediates and since disappearance of the oxidant can no longer be assumed to occur as the rate-determining step of the reaction, earlier mechanistic conclusions should probably be reexamined.

References and Notes

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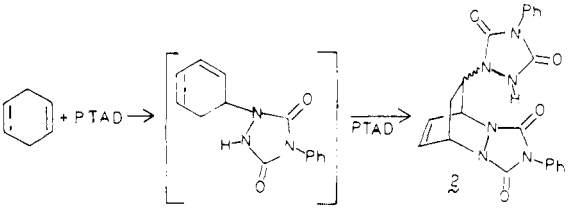
(5) A similar sequence was reported recently for the slow SO_2-mediated aromatization of 1,4-cyclohexadiene.[6]
(6) D. Masilamani and M. M. Rogic, *Tetrahedron Lett.*, 3785 (**1978**).
(7) Least-squares coefficients $r^2 = \geq 0.98$ for both solvents.
(8) Least-squares coefficients $r^2 = 0.98$ in THF and >0.99 in CD_3CN.
(9) This ene adduct could not be isolated because it in turn reacted rapidly with more PTAD to yield the 2:1 adduct of structure **2**.[10]



(10) White powder: mp 250–251 °C; NMR (CD_3CN) δ 7.5 (m, 11 H), 6.6 (m, 2 H), 5.1 (m, 3 H), 2.6 (m, 1 H), 2.0 (m, 1 H); IR (pellet) 3450, 3100, 1690, 1400 cm^{-1}; Anal. ($C_{22}H_{18}N_6O_4$) C, H, N.
(11) In a separate experiment it was found that tetracyanoethane alone with PTAD in acetonitrile yielded TCNE and 4-phenylurazole.
(12) **1**: white powder: mp 87.5–88 °C with almost immediate resolidification and second mp 170 °C with blackening; IR (pellet) 3040, 2900, 2230, 1630, 1405 cm^{-1}. Absent are significant peaks for TCNE (e.g., 1355 and 800 cm^{-1}) and for tetracyanoethane (e.g., 1190 and 900 cm^{-1}).
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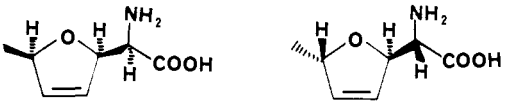
Total Synthesis and Revised Structural Assignment of (+)-Furanomycin

Sir:

The antibiotic (+)-furanomycin was isolated by Katagiri and co-workers from a culture filtrate of *Streptomyces threomyceticus*. The structure of (+)-furanomycin was determined by spectroscopic and degradative techniques to be (+)-$\alpha(R)$-amino(2,5-dihydro-5(R)-methyl)furan-2(R)-acetic acid (**1**) but the configurations at the asymmetric centers have



1 2a

not been confirmed either by X-ray studies or by a stereospecific synthesis.[1] The deceptively simple structure of **1** stands in contrast to the difficulties attached to its synthesis. A long and laborious route to **1**, involving 16 steps and an overall yield of <0.02% was reported in 1975.[2] As a result of our continuing studies on the synthesis of natural products by chirality transfer from carbohydrates, we sought to prepare furanomycin and its configurational isomers. In this communication we describe the asymmetric synthesis of 5(S),2(R),α(S)-furanomycin (**2a**) and its isomer (**2b**) with the opposite configuration at the amino acid functionality.[3] Unexpectedly, 5(S),2(R),α(S)-furanomycin was found to be identical with the natural (+)-furanomycin in every respect (360-MHz NMR, IR, optical rotation, melting point, mixture melting point, TLC, etc.).[4]

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