The Role of Nucleophilic Solvents in the Acid-Catalyzed Cyclization of a Cross-Conjugated Cycloalkadienone

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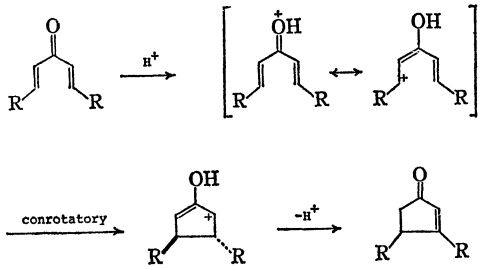
In acetic acid or methanol containing a trace amount of H_2SO_4, 2,8-cyclononadienone cyclizes readily to give bicyclic ketones; the mechanism including the role of the nucleophilic media is discussed.

The acid-catalyzed cyclization of cross-conjugated dienones to produce cyclopentenones is known as the Nazarov cyclization.[1] Woodward and coworkers analyzed the reaction with *di*-1-cyclohexenyl ketone and concluded the transformation as occurring through conrotatory ring closure of the protonated dienone–hydroxypentadienyl cation resonance hybrid (Scheme 1).[2] As might be expected, common and medium-sized cycloalkadienones in an oxygen-protonated form are thermally stable, because the symmetry-allowed electrocyclization is sterically prohibited by the presence of a methylene chain which links the β and β' carbons. This paper describes an example where a combination of an acid and certain nucleophiles can facilitate the so far restricted cyclization of a medium-sized cyclic dienone.



Scheme I.

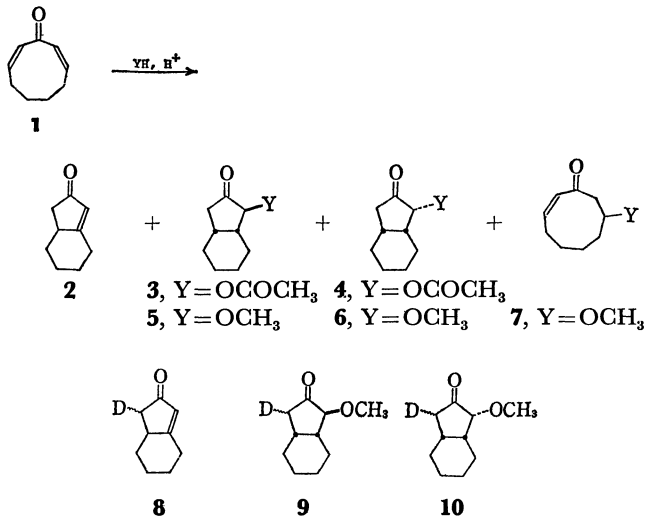
2,8-Cyclononadienone (**1**) in 97% H_2SO_4 or FSO_3H exists in a protonated form as indicated by spectral data (NMR and UV)[3,4] and remains unchanged for an extended period below room temperature. The dienone is also inert in acetic acid below 30 °C. Remarkably, however, when a drop of H_2SO_4 was added to an acetic acid solution of **1**, spontaneous reaction took place at room temperature yielding the bicyclic enone **2** (25%) and the epimeric acetoxy ketones **3** and **4** (40% combined yield).

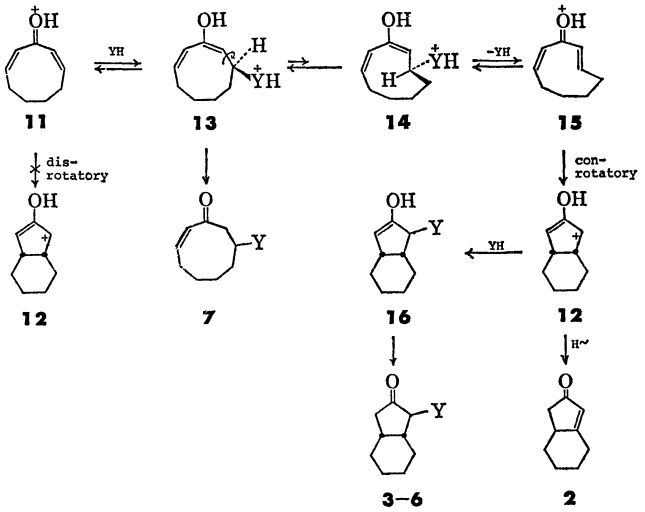
No reactions were observed when **1** was allowed to stand in methanol solution at room temperature. Again, rapid reaction was caused by the addition of a drop of H_2SO_4, and there was obtained a mixture of **2** (6%), the bicyclic methoxy ketones **5** and **6** (72%), and the monocyclic methoxy ketone **7** (7%). These products **2**—**7** were stable under the present reaction and workup conditions.

The reaction in methanol-*O*-*d* as solvent gave the deuterium-incorporated bicyclic products **8**—**10**. The mass spectral analysis showed that these consisted mainly (69—85%) of d_1 material and contained some d_0 and d_2 products. The NMR spectra indicated that the deuterium atoms are located specifically at position α to carbonyl group but randomly with respect to stereochemistry, the *exo* to *endo* ratio being approximately 1 : 1. Control experiments showed that **2** suffers protium-deuterium exchange to some extent under the present reaction conditions.

The observed reactions forming the bicyclic ketones are characteristic of the nine-membered dienone **1**. With seven-, eight-, and twelve-membered cross-conjugated dienones, only mixtures of monocyclic solvent-incorporated products were obtained.

Apparently the presence of both acidic and nucleophilic species is a necessary condition for promotion of the β,β' bond-forming reaction of **1**. Although

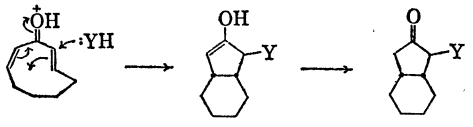




YH=CH_3COOH or CH_3OH

Scheme II.

there may be a variety of possible mechanisms conceivable, the most likely seems to be a pathway which involves solvent-assisted *cis-trans* isomerization of **1** in a key step as outlined in Scheme II. The protonated *cis, cis* dienone **11** cannot undergo unimolecular electrocyclizations; the disrotatory ring closure to the bicyclic hydroxyallyl cation **12** is symmetry-forbidden, while the alternative conrotatory cyclization to the *trans*-fused bicyclic system is unlikely due to the high strain energy involved in the transition state as indicated by molecular models. Reaction of **11** with the nucleophilic solvent YH at the electron-deficient β carbon produces the dienol adduct **13**.[5] Reketonization gives the monocyclic adduct **7**. If the conformational change, **13**→**14**, followed by elimination of YH occurs prior to ketonization, then the key intermediate, protonated *cis, trans* dienone **15**,[6] is formed, which in turn undergoes conrotatory ring closure to give **12**. Its proton reorganization affords the bicyclic enone **2**, while nucleophilic trapping with YH and subsequent ketonization produces the epimeric bicyclic solvent adducts **3**—**6**. Patterns of the deuterium incorporation observed for the reaction in methanol-*O-d* solvent are also consistent with the mechanism of Scheme II. The conformational change of type **13**→**14**, an essential process for the formation of the reactive *cis, trans* dienone, would be feasible only with the nine-membered dienone **1**; with the lower homologs, the form corresponding to **14** could hardly be accomodated in the conformational equilibrium. With twelve-membered dienones, the *cis-trans* isomerism in the protonated form also seems possible. Neither *cis, cis* nor *cis,trans* isomer, however, is strained enough to undergo the unimolecular electrocyclization to give bicyclic hydroxypentadienyl cations.



15 **16** **3—6**

Scheme III.

Photochemically generated *cis, trans*-2,8-cyclononadienone is known to undergo the cyclization in protic solvents with or without added Brönsted acids.[7] Under the present reaction conditions, **3**—**6** may also be derived *via* bimolecular reaction of **15** and YH as illustrated in Scheme III. An alternative mechanism involving direct, bimolecular reaction between the *cis,cis* dienone **11** and YH is unlikely to be operating, since it could not explain the profound ring-size effect on the reaction course.

Experimental

General. NMR spectra were taken in CCl_4 solution using a JEOLCO Model C-60 H instrument. IR spectra were obtained on a JASCO Model DS-402 G spectrometer. A Hitachi Model RMU-6C mass-spectrometer was used for mass spectral analysis. Gas-liquid partition chromatography (glpc) was done with a Yanagimoto Model G-8 chromatograph equipped with a 2-m column of 5% poly(ethylene glycol succinate) on Celite 545. Product ratio was determined using C_{12}—C_{16} hydrocarbons as internal standard. Thin-layer chromatography (tlc) was carried out on silica gel (E. Merck GF_{254} silica gel). 2,8-Cyclononadienone (**1**) was prepared by the method of Garbisch.[8]

Reaction of 2,8-Cyclononadienone (1) in Nucleophilic Solvents Containing H_2SO_4. A solution of **1** (492 mg, 3.64 mmol) in acetic acid (5 ml) containing one drop of 96% H_2SO_4 was stirred at room temperature for 20 min. The mixture was diluted with water, neutralized with sodium bicarbonate, and extracted with ether. The ethereal solution was washed with water, dried over $MgSO_4$, and concentrated *in vacuo* to give a crude oil (514 mg). Glpc analysis (150 °C) of the oil indicated the formation of bicyclo[4.3.0]non-6-en-8-one (**2**) (25% yield), *exo*-7-acetoxy-*cis*-bicyclo[4.3.0]nonan-8-one (**3**) and *endo*-7-acetoxy-*cis*-bicyclo[4.3.0]nonan-8-one (**4**) (5 : 2 ratio, 40% combined yield). Each compound was separated by preparative tlc (1 : 1 *n*-hexane–ether) and identified by comparison of the NMR and IR data with those of an authentic sample.[4,7]

Similarly, when a 10% methanol solution of **1** containing a trace amount of H_2SO_4 was allowed to stand for 20 min at room temperature, a mixture of the enone **2** and the methanol adducts was obtained. Glpc analysis (140 °C) of the crude product showed the formation of **2** (6%), *exo*-7-methoxy-*cis*-bicyclo[4.3.0]nonan-8-one (**5**) and *endo*-7-methoxy-*cis*-bicyclo[4.3.0]nonan-8-one (**6**) (5 : 2 ratio, 72%), and 8-methoxy-2-cyclononenone (**7**) (7%).[7] The identity of these compounds was established by comparison with authentic specimens.

Reaction of 1 in Methanol-O-d *Containing D_2SO_4.* The dienone **1** (129 mg, 0.96 mmol) was dissolved in methanol-*O-d* (1 ml, E. Merck, deuterium content >99%) containing a trace amount of 97% D_2SO_4 (E. Merck, deuterium content >99%). The resulting solution was stirred at room temperature for 20 min, diluted with dichloromethane (10 ml), and washed with water three times. The organic layer was dired by being passed through a short Na_2SO_4-silica gel column and concentrated *in vacuo* to leave a crude oil (156 mg), which contained the solvent adducts as the major components. In order to minimize loss of deuterium atom from the products, the reaction mixture was worked up as quick as possible. About 10 min were required for this work-up procedure. Preparative tlc with a 1 : 1 *n*-hexane–ether mixture (2 developments) afforded bicyclo-[4.3.0]non-6-en-8-one-9-*d* (**8**) (13 mg), *exo*-7-methoxy-*cis*-bicyclo[4.3.0]nonan-8-one-9-*d* (**9**) (73 mg), and *endo*-7-methoxy-*cis*-bicyclo[4.3.0]nonan-8-one-9-*d* (**10**) (56 mg). The deuterated derivative of **7** could not be isolated in a pure state. The structures were deduced from thier NMR spectra. The spectra taken in CCl_4 solution with the added $Eu(fod)_3$ shift reagent indicated that deuterium atom in these products was incorporated at the carbonyl α position, where the *exo* to *endo* ratio was approximately 1.0. The molecular ion peaks in the mass spectra appeared at *m/e* 137 for **8** and 169 for **9** and **10**. Comparison of the intensities with those of the neighboring peaks showed the extent of deuterium incorporation: **8** 15% d_0, 69% d_1, and 16% d_2; **9** 17% d_0, 82% d_1, and 1% d_2; **10** 13% d_0, 85% d_1, and 2% d_2. The enone **2** recovered after treatment with methanol-*O-d* containing D_2SO_4 at room temperature for 20 min contained deuterium atoms; 29% d_0, 54% d_1, and 17% d_2.

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