

**Figure 1.** Comparison of extended RISM and simulation<sup>4</sup> for reaction free energy surface (eq 5) at 25 °C. Gas-phase potential (---); solvent contribution, MC (-.-); RISM (▲); total free energy, simulation (—), RISM (●).

are qualitatively reliable.<sup>12</sup> The Lennard-Jones and charge parameters as a function of the reaction coordinate from Chandrasekhar et al. were used for the chlorine sites. The CH<sub>3</sub> moiety was simplified here as a single "atomic" site with Lennard-Jones parameters from TIPS methanol<sup>13</sup> and total charge equal to that in the all atom CH<sub>3</sub> representation.<sup>8</sup> As in previous calculations, a necessary repulsive term was added to the H-O and H-Cl potentials to avoid catastrophic overlap of the corresponding site charges in the calculations. An equally spaced  $\lambda$  grid of  $\Delta\lambda = 0.1$  was found adequate for the calculation of the relative quantity in eq 5.

Our values calculated at representative points, along with the gas-phase potential and Monte Carlo results, are shown in Figure 1, at 25 °C. It is clear that the new results follow the Monte Carlo simulation rather well and manifest a dramatic solvent effect on the reaction surface. The RISM theory yields a barrier height of 31 kcal/mol, slightly larger than the Monte Carlo and apparent experimental results of 26.3 and 26.6 kcal/mol, respectively. Also in accord with the Monte Carlo results, the ion-dipole potential minimum is substantially flattened by the solvent, with the potential becoming slightly repulsive further along the reaction coordinate.

The present comparative calculation has several sources for discrepancy. The approximate RISM theory successfully describes the short-range liquid structure, but the theory improperly describes the long-range order of polar liquids.<sup>2,14</sup> However, the largest part of this long-range error should be constant throughout the reaction, since the reaction system has a fixed net charge, and this part will cancel in the calculation of the potential of mean force. Also, we treat the methyl species as a single site while the Monte Carlo methyl potential included the hydrogens explicitly. Since most of the free energy changes are due to the transfer of charge from one chlorine to the other, this latter effect should be small. Further, in the Monte Carlo calculation, the TIP4P water potential was used,<sup>15</sup> while we use the simpler three-site TIPS form.

The charging method presented here presently requires only a small fraction of the computational time of the Monte Carlo simulation.<sup>8</sup> Further, the charging free energies do not invoke any pair additivity assumptions regarding the multipoint solute potential of mean force<sup>9</sup> and have been shown to allow reasonably accurate calculation of free energy differences. These results

encourage further application of the method to various chemical reactions as well as to conformational equilibria.

**Acknowledgment.** We thank Professor J. T. Hynes for stimulating our interest in this problem and Professor W. Jorgensen for providing details of his work prior to publication. Support of this research by grant from the Robert A. Welch Foundation is gratefully acknowledged. P.J.R. is an Alfred P. Sloan Fellow and the recipient of an NSF Presidential Young Investigator Award and NIH Research Career Development Award (CA00899) from the National Cancer Institute, DHHS.

Registry No. Cl<sup>-</sup>, 16887-00-6; CH<sub>3</sub>Cl, 74-87-3.

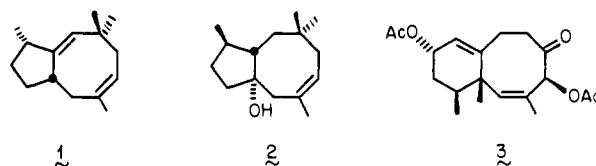
### Claisen Rearrangement of 6-Alkenyl-2-methylenetetrahydropyrans. A New Approach to Annulated 4-Cyclooctenones and a Stereospecific Synthesis of Precapnelladiene

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Received June 11, 1984

In recent years, several bicyclic marine natural products have been discovered that incorporate uncommon fused eight-membered rings in their structure. Precapnelladiene (1),<sup>1</sup> dactylo (2),<sup>2</sup> the closely related poitediol,<sup>3</sup> and neolemanyl acetate (3),<sup>4</sup> are ex-



emplary of this family of sesquiterpenes. Hydrocarbon 1, the presumed precursor to the tricyclic capnellenes and capnellens, likely serves as a key biosynthetic intermediate in the soft coral *Capnella imbricata*.

As part of a larger program directed toward the synthesis of mesocyclic<sup>5</sup> systems of this type,<sup>6</sup> we have investigated the feasibility of applying aliphatic Claisen rearrangement strategy<sup>7</sup> to the construction of these unusual molecular frameworks. The earlier studies by Büchi (4 → 5),<sup>8</sup> Danishefsky (6 → 7),<sup>9</sup> and Rhoads (8 → 9)<sup>10</sup> hold some relevance to the present report.<sup>11</sup>

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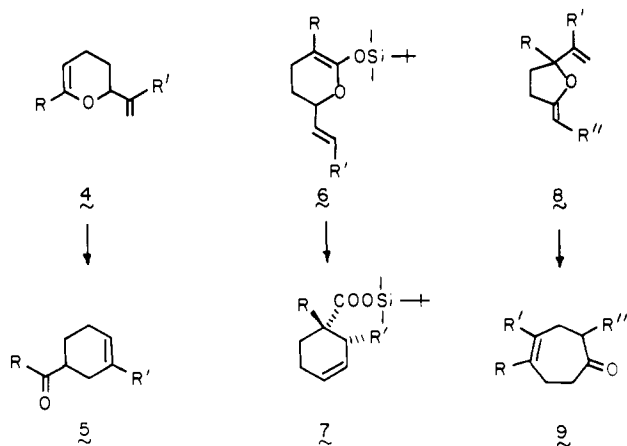
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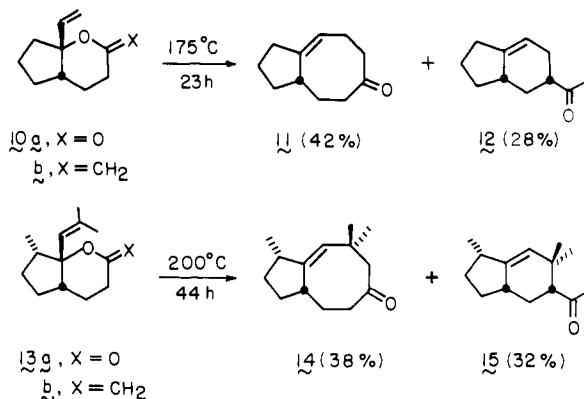
Of more immediate importance are the several thermodynamic and spectral studies that reveal 2-methylenetetrahydropyrans to be highly unstable relative to their endocyclic isomers, quite unlike **8**.<sup>12,13</sup> Consequently, it was a major concern that **10b**, **13b**, and their congeners might behave differently than **8** and isomerize to dihydropyrans prior to thermal rearrangement.

The synthetic route employed for preparation of model substrate **10b** involved addition of vinylmagnesium bromide to 2-(2-carbomethoxyethyl)cyclopentanone and treatment of the lactone with Tebbe reagent<sup>14</sup> (92%) (Scheme I). Upon heating toluene solutions of **10b** in KOH-coated soft glass tubes, a mixture rich in **11** was obtained.<sup>15</sup> The relative stereochemistry in **13** was initially set by thermal ene cyclization of 3-(3-butenyl)cyclopentanone.<sup>16</sup> Subsequent Baeyer–Villiger oxidation, ring opening with catalytic quantities of methoxide ion in methanol, oxidation with buffered PCC, and addition of (2-methyl-1-propenyl)lithium proceeded efficiently and without loss of stereochemistry to provide **13a**. Following methylation and thermolysis as before, **14** and **15** were produced in closely comparable amounts. This initial phase of the investigation did not involve any serious attempts at yield optimization.

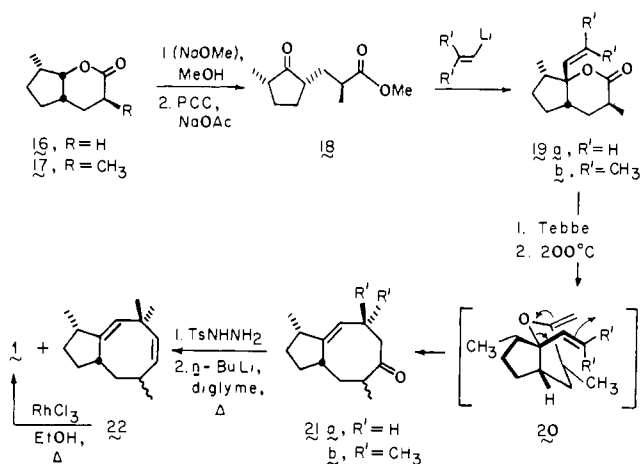
Several features of the competitive [1,3]-hydrogen migration are deserving of comment. The mechanism of this process is not known, and the possibility of catalysis by residual Ti- or Al-containing byproducts from the Tebbe reaction is real. Dredging models of **13b** show the  $\alpha$  (endo) proton of its allylic methylene group to be relatively inaccessible for steric reasons. Major reactivity differences arising from steric crowding have been previously noted in the transition-metal catalysis of allyl ether isomerization to vinyl ethers.<sup>17</sup> A stereocontrolled solution of the above complication therefore suggested itself.

Methylation of **16** afforded **17** stereospecifically (87%) (Scheme II). The latter could be converted into **18** (71%) without disruption of its three stereogenic centers. Through standard condensation with lithium reagents, **19a** (62%) and **19b** (65%) were obtained. Replacing the carbonyl oxygen by CH<sub>2</sub> and thermal rearrangement were smoothly effected (87–91% overall) in both

## Scheme I



## Scheme II



cases. The high yields are in keeping with location of the interactive groups on the open convex face of the substrate molecules (cf. **20**).<sup>18</sup> Especially interesting was the *exclusive* formation of cyclooctenone products **21a** and **21b** with preservation of the stereochemical integrity of two centers.<sup>19</sup> Epimerization occurs at the third because of enolate formation under the strongly basic thermolysis conditions. Noteworthy, the latter reaction simultaneously incorporates in **21b** the relative chirality and complete framework of **1**, a properly positioned double bond, and a neighboring *gem*-dimethyl-substituted quaternary carbon atom.

Finally, **21b** was converted to its tosylhydrazone (96%), decomposition of which was performed under carbenoid conditions<sup>20</sup> (*n*-BuLi, diglyme, reflux). The mixture of **1** (32%) and **22** (62%) proved chromatographically separable on silica gel impregnated with 2% silver nitrate. The infrared, <sup>1</sup>H NMR, and mass spectra of synthetic **1** proved identical with those furnished by Professor Djerassi.<sup>1,21</sup> Thus, the first total synthesis of precapnelladiene has been achieved in 10 steps from 8 $\alpha$ -methylbicyclo[3.3.0]octan-2-one with an overall yield of 8.1%. Allowance for the independent rhodium trichloride promoted isomerization<sup>22</sup> of **22** to

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(19) The possibility cannot be discounted at this time that *exo*-*endo* olefin isomerization also occurs during pyrolysis of the vinyl ethers derived from **19** and is reversible but that Claisen rearrangement via the endocyclic enol ether is retarded kinetically.

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(21) Relevantly, the olefinic out-of-plane deformation for **1** appears at 849 cm<sup>-1</sup> and not at 899 cm<sup>-1</sup> as originally reported (typographical error). Also, epiprecapnelladiene possesses spectral properties distinctively different from those of **1**: Birch, A. M.; Pattenden, G. *J. Chem. Soc., Perkin Trans. 1* **1983**, 1913.

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1 increases the efficiency of the sequence to 20%.

**Acknowledgment.** This research was supported by Public Health Service Grant GM 30827. Additional resources were provided by a grant from the Eli Lilly Co. We also thank Dr. Richard Valpey for a generous gift of starting material.

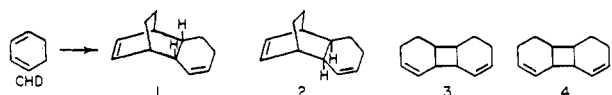
## Radical Cation and Triplex Diels-Alder Reactions of 1,3-Cyclohexadiene

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Dimerization of 1,3-cyclohexadiene (CHD) can be accomplished under a wide range of reaction conditions. Thermolysis at 200 °C gives the [4 + 2] Diels-Alder dimers as a mixture of endo and exo isomers **1** and **2**.<sup>1,2</sup> Triplet sensitization gives [2 + 2] dimers as a mixture of syn and anti configurations, **3** and **4**, as well as some of the exo [4 + 2] adduct **2**.<sup>2</sup> Schutte and

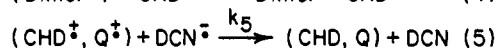
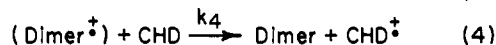
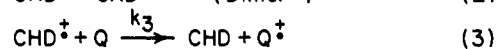
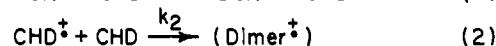


Freeman,<sup>3</sup> and later Hammond and co-workers,<sup>4</sup> studied the  $\gamma$ -radiation-induced dimerization and found that two processes were operating simultaneously. The first of these proceeds through triplet CHD (CHD\*<sup>3</sup>). The second is a chain reaction that features the combination of cyclohexadiene radical cation (CHD\*<sup>•</sup>) with neutral CHD. More recently, Bauld and his students<sup>5</sup> have reported that the oxidizing salt tris(*p*-bromophenyl)aminium hexachlorostibate ( $E_{\text{red}} = +0.762 \text{ V}$ )<sup>6</sup> initiates a radical cation chain dimerization of CHD, and some related dienes, that is in essence identical with the radiation-induced reaction. Jones<sup>7</sup> and later Bauld<sup>8</sup> found that these dimerizations can be initiated by singlet excited states of electron poor sensitizers.<sup>9</sup>

Herein we report the results of an investigation of the photochemical dimerization of CHD. The results implicate two distinct mechanisms. One of these operates in nonpolar solvent and appears to proceed through a triplex. The other sequence occurs in polar solvent and involves formation of CHD\*<sup>•</sup>. Our findings provide a test for the role of CHD\*<sup>•</sup> in the dimerizations initiated by the aminium salt.<sup>5</sup>

Oxidation of CHD to the radical cation is central to several routes suggested to lead to its dimerization. The cyclic voltammogram observed for this oxidation in acetonitrile is irreversible. The peak potential depends on the sweep rate and at 25 V/s occurs at 1.33 V.<sup>6b</sup>

### Scheme I



In concert with expectation from the Weller equation,<sup>10</sup> CHD quenches the fluorescence of 1,4-dicyanophthalene (DCN) in either benzene or acetonitrile solution at approximately the diffusion-limited rate ( $k_q\tau = 86$  and  $148 \text{ M}^{-1}$ , respectively). CHD dimers are formed by this reaction in both solvents.

Irradiation of DCN ( $1.0 \times 10^{-3} \text{ M}$ ) in a degassed acetonitrile solution containing 0.26 M CHD gives both [4 + 2] dimers **1** and **2** (ca. 6:1) and [2 + 2] dimers **3** and **4**.<sup>11</sup> The [4 + 2] adducts comprise more than 80% of the dimer mixture at 5% conversion. The ratio of **1** to **2** and of [4 + 2] to [2 + 2] dimers does not change significantly when the concentration of CHD is increased to 2.1 M. However, the quantum yield for formation of the dimers is increased approximately threefold by this change. Even at the lowest diene concentration, greater than 97% of the singlet-excited DCN (DCN\*<sup>1</sup>) is quenched by CHD.

Analysis of this reaction by laser flash photolysis clearly reveals the formation of radical ion intermediates.<sup>12</sup> Irradiation of an acetonitrile solution of DCN ( $1.0 \times 10^{-3} \text{ M}$ ) and CHD (0.58 M) with the output of a nitrogen laser (337 nm, 15 ns, 7 mJ) generates dicyanophthalene radical anion (DCN\*<sup>-</sup>).<sup>13</sup> The yield of DCN\*<sup>-</sup> does not change significantly when the concentration of CHD is increased to 2.1 M.

The formation of endo [4 + 2] dimer **1** can be quenched selectively by addition of 1,3,5-trimethoxybenzene (TMB) ( $E_{\text{ox}} = 1.16 \text{ V}^{14,6b}$ ). The Stern-Volmer slope depends on the CHD concentration and is  $260 \text{ M}^{-1}$  when CHD is 0.21 M and  $100 \text{ M}^{-1}$  when CHD is 0.42 M. In contrast, formation of the [2 + 2] dimer **4** is only slightly affected by TMB. When 4,4'-dimethoxybiphenyl ( $E_{\text{ox}} = 0.91 \text{ V}^{15,6b}$ ) is the quencher analogous results are obtained, but indene ( $E_{\text{ox}} = 1.35 \text{ V}^{16,6b}$ ) does not significantly inhibit dimer formation.

These findings all point to a mechanism for dimerization of CHD in acetonitrile that is essentially identical with that suggested to occur on  $\gamma$ -irradiation.<sup>3,4</sup> The CHD\*<sup>3</sup> formed from ion annihilation leads primarily to the [2 + 2] adducts, and a radical cation chain reaction, shown in Scheme I, yields mostly the endo [4 + 2] dimer. The selective quenchers (Q) intercept CHD\*<sup>•</sup> and inhibit formation of **1** when their oxidation potential is below that of CHD. With the reasonable assumptions that the exothermic oxidations of CHD by the dimer radical cation (dimer\*<sup>•</sup>) and of Q by CHD\*<sup>•</sup> occur at the diffusion limit and are irreversible, then the application of eq 6 to the quenching data (constant [Q]), vary

$$\frac{\phi}{\phi^{\circ} - \phi} = \frac{k_5[\text{DCN}^{\bullet-}]}{k_3[\text{Q}]} + \frac{k_2[\text{CHD}]}{k_3[\text{Q}]} \quad (6)$$

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