tography of the mixture on silica gel allowed the isolation of 5a in 60% yield, based on unrecovered starting material.

In order to form the tetrahydro and dihydropyran rings in phytuberin, diol 5b, which was prepared by hydrogenolysis of the benzyl groups in 5a, was reacted with 3.5 equiv of DIBAL-H (−40 °C, 1 h; 0 °C, 0.5 H), as described for the reduction of the related formylspropionate.2d Workup of the mixture with 2 N NaOH gave desacetylnphytuberin (1b), [α]24D +34.6° (c 0.1, EtOH), in 63% yield. This material exhibited identical spectral properties with those reported previously.3 Acetylation of 1b (Ac2O, Et3N, catalytic amount of 4-N,N-dimethylaminopyridine)4 gave 71% of (−)-phytuberin (1a), [α]24D +34.0° (c 0.25, EtOH), having IR and NMR spectral properties and TLC behavior identical with those of an authentic sample.6

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Received July 14, 1980

Extension of the Woodward–Hoffmann Rules to Heterocyclic Systems: Stereospecific Thermal Isomerization of 1-Azacyclobutene 1-Oxides

Sirs:

In a recent publication Snyder1 predicts, on the basis of calculated potential surfaces for isomerization of heterocyclenones, that 1-azacyclobutene will undergo ring opening in a conrotatory mode similar to cyclobutenes. This possible extension of the Woodward–Hoffmann rules to the isomerization of heterocyclenones has, to our knowledge, hitherto not been confirmed experimentally. A number of 2,3-dihydroazetes are known,2d and Cantrell3 and recently Harnisch and Szejtli4 have reported that several derivatives of these heterocycles are thermally unstable. Attempts to isolate the corresponding 2-aza-1,3-butaedienes were unsuccessful, probably because of rapid polymerization or hydrolysis if water is present.

We wish to report in this communication the stereospecific thermal isomerization of 2,3-dihydroazete 1-oxides together with the X-ray structure determination of one of the corresponding 2-aza-1,3-butaedienes. Recently we have obtained a number of 2,3-dihydroazetes from reactions of nitroalkenes 1-oxides with disubstituted nitrones,2e and 2-aza-1,3-butaedienes have been observed as intermediates in the thermal isomerization of two other 2,3-dihydroazetes were also identified with those of an authentic sample.9

8.41 (l), c = 8.41 (l), c = 11.74 (1), z = 4. Intensities were measured with Mo Kα radiation (λ = 0.7107 Å) on a single-crystal diffractometer in ω−φ scan mode (3° < φ < 20°). 1450 reflections were measured, of which 869 were significant (I > σ(I), counting statistics). The structure was solved by direct methods.12 Full-matrix least-squares refinement13 of positional and anisotropic parameters of the nonhydrogen atoms resulted in a final R factor of 5.5%. The structure of 2a14 is given in Figure 1.

The rate of the isomerization of 1a to 2a in chloroform was measured by 1H NMR spectroscopy at temperatures of 51.5, 61.1, and 71.5 °C. The rates were calculated from the decrease of the intensity of the singlet at 3.98 ppm corresponding to H-3 in 1a. The data fitted first-order kinetics, and from a plot of the rates vs. T−1, we obtained the activation parameters of the isomerization reaction (ΔH° = 27 ± 1 kcal mol−1 and ΔS° = 2 ± 3 eu). The rates of isomerization of two other 2,3-dihydroazete 1-oxides were also determined at 61.1 °C in chloroform (see Table 1). The isomerization of 1a to 2a was athermal process, and the rate was independent of temperature.


(8) Prolonged heating of 2a in chloroform at reflux caused polymerization; this accounts for the low isolated yield.

(9) In view of these results it is unlikely that 2H,1,2-oxaazete 2-oxides are the intermediates in the formation of nitrogen from 3-nitropheno[b]thiophene or 4-nitrothiophene and ynamines.10


(11) Due to steric interactions in the transition state, the formation of the E,E isomer is favored over the formation of the Z,Z isomer of 2a.


![Figure 1. ORTEP drawings of 1a and 2a.](image-url)

Table 1. Rate Constants for the Isomerizations of 1 to 2

<table>
<thead>
<tr>
<th>temp, °C</th>
<th>1a</th>
<th>1b</th>
<th>1c</th>
</tr>
</thead>
<tbody>
<tr>
<td>51.5</td>
<td>0.48 ± 0.01</td>
<td>51.5 ± 0.1</td>
<td>9.60 ± 0.3</td>
</tr>
<tr>
<td>61.1</td>
<td>1.50 ± 0.1</td>
<td>73 ± 3</td>
<td></td>
</tr>
<tr>
<td>71.9</td>
<td>5.71 ± 0.2</td>
<td>73 ± 3</td>
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</table>

Catalytically Active Models for the Active Site in Carbonic Anhydrase

Sir:

Carbonic anhydrase (CA) is a ubiquitous enzyme which catalyzes the interconversion of CO₂ and HCO₃⁻. Its active site consists of a Zn²⁺ ion bound pseudotetrahedrally to three histidine imidazoles and either a water molecule or OH⁻ ion.² The activity of CA is governed by the ionization of at least one group with a very low pK. Recently some model systems exhibiting CO₂ hydration have been reported,³ but as yet no catalytically active model which attempts to approximate the known Zn²⁺ binding site for CA has appeared. Herein we report preliminary results concerning two models for the active site of CA which show

(1) For recent reviews, see: Lindskog et al., Enzymes, 3rd Ed. 1971, 5, 587.

Acknowledgment. This investigation was supported by the Netherlands Foundation for Chemical Research (SON) with financial aid from the Netherlands Organization for Advancement of Pure Research (ZWO).

Supplementary Material Available: Tables of atomic positional and thermal parameters, interatomic distances and angles, and a list of observed and calculated structure factors (9 pages). Ordering information is given on any current masthead page.

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Received July 14, 1980

Table I. Rates of CO₂ Hydration Catalyzed by Complexes 1-Zn²⁺ and 2-Zn²⁺

<table>
<thead>
<tr>
<th>catalyst</th>
<th>pH</th>
<th>kcat b M⁻¹ s⁻¹</th>
<th>kcat/KM[^] M⁻¹ s⁻¹</th>
</tr>
</thead>
<tbody>
<tr>
<td>(imidazole)₂-Zn²⁺[^]</td>
<td>7.5</td>
<td>2.0</td>
<td></td>
</tr>
<tr>
<td>1-Zn²⁺</td>
<td>6.5</td>
<td>7.6 ± 0.5 x 10⁻¹²</td>
<td></td>
</tr>
<tr>
<td>1-Zn²⁺</td>
<td>7.5</td>
<td>2.4 ± 0.2 x 10⁻¹²</td>
<td></td>
</tr>
<tr>
<td>2a-Zn²⁺</td>
<td>7.5</td>
<td>7.5</td>
<td>d</td>
</tr>
<tr>
<td>2b-Zn²⁺</td>
<td>7.5</td>
<td>d</td>
<td></td>
</tr>
<tr>
<td>2-Zn²⁺</td>
<td>6.5</td>
<td>d</td>
<td></td>
</tr>
<tr>
<td>2-Zn²⁺</td>
<td>7.0</td>
<td>2.0 ± 0.4 x 10⁻¹²</td>
<td></td>
</tr>
<tr>
<td>human CAB[^]</td>
<td>1 x 10⁷</td>
<td></td>
<td></td>
</tr>
<tr>
<td>human CA[^]</td>
<td>8 x 10⁷</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

[^] Determined under pseudo-first-order conditions (with respect to CO₂) at 25 °C in 76% ethanol-H₂O according to procedures outlined in ref 6. Experiments with 2a-Zn²⁺ and 2b-Zn²⁺ for reasons of solubility were performed in H₂O. pH values are those directly read from electrode immersed in solution.
[^] kcat/KM = ([kcat/obsd] - [kcat/uncat]) / [cat], [cat] = 5 x 10⁻⁵ M. Reference 3a.
[^] d kobsd did not differ from that observed in the absence of catalyst.

Reference 4.

(5) In a less polar medium the pK is reduced to 5.8 (60% aqueous dioxane) pH's were determined directly from electrode readings in these media.
(7) This observation is tempered by the fact that the UV spectra of 1-Co²⁺ show the appearance of a well-defined 1:1 complex when [2e²⁺] / [Zn²⁺] = 1; no 2:1 complex is observed.³³ UV spectra of 2a and 2b in the presence of CoCl₂ show little if any evidence for 4-coordinate ligation.¹ On the other hand, the isopropyl phosphine 3e in the presence of CoCl₂ shows reversible formation of a tetrahedral species at increasing pH with bands appearing at 588 (285), 622 (450), 646 (516), 662 (501) nm (e).³⁶ The 2e-Co²⁺ spectra are highly anion dependent (Figure 1), reminiscent of the situation for the Co²⁺-enzyme.¹⁰ In the presence of ClO₄⁻ and NO₃⁻ the catalytic activity toward CO₂ hydration.

Ligand 1 in the presence of 1 equiv of Zn²⁺ shows reversible consumption of 1 equiv of OH⁻ with an apparent pK₆ of 6.5 in 76% ethanol-H₂O.² CO₂ hydration in the presence of 1-Zn²⁺ shows catalysis at pH 6.5 (Table I) which diminishes at pH >7 due to relative poor binding of Zn²⁺ by the N,N-diethylcarbamoyl group at C-4. Isotopic phosphine 3e which attempts to approximate the known Zn²⁺ binding site for CA has appeared. Herein we report preliminary results concerning two models for the active site of CA which show