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 dihydrofuran 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, 1.0 h; 0 °C, 0.5 H), as described for the reduction of the related formylspirobutenolide.[3] Workup of the mixture with 2 N NaOH gave deacetylphytuberin (**1b**), $[\alpha]^{24}_D$ -34.6° (*c* 0.1, EtOH), in 63% yield. This material exhibited identical spectral properties with those reported previously.[2,3] Acetylation of **1b** (Ac_2O, Et_3N, catalytic amount of 4-*N*,*N*-dimethylaminopyridine[14]) gave 71% of (-)-phytuberin (**1a**), $[\alpha]^{24}_D$ -34.0 ° (*c* 0.25, EtOH), having IR and NMR spectral properties and TLC behavior identical with those of an authentic sample.[9]

(13) Since the best yield of the butenolide was obtained when 1 equiv of lithium dimethylcuprate was used, it is possible that the conjugate addition reaction was effected primarily via the mixed methylalkoxycuprate derived from reaction of lithium dimethylcuprate with the hydroxy group in **10**. For examples of conjugate additions using mixed alkylalkoxycuprates, see Posner, G. H.; Whitten, C. E.; Sterling, J. J. *J. Am. Chem. Soc.* **1973**, *95*, 7788.

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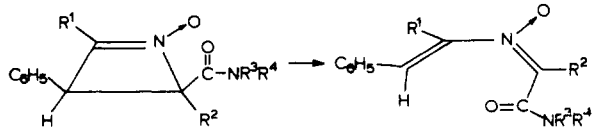
Extension of the Woodward-Hoffmann Rules to Heterocyclic Systems: Stereospecific Thermal Isomerization of 1-Azacyclobutene 1-Oxides

Sir:

In a recent publication Snyder[1] predicts, on the basis of calculated potential surfaces for isomerization of heteracyclobutenes, that 1-azacyclobutenes will undergo ring opening in a conrotatory mode similar to cyclobutenes. This possible extension of the Woodward-Hoffmann rules to the isomerization of heteracyclobutenes has, to our knowledge, hitherto not been confirmed experimentally. A number of 2,3-dihydroazetes are known,[2-6] and Cantrell[4] and recently Harnisch and Szeimies[5] have reported that several derivatives of these heterocycles are thermally unstable. Attempts to isolate the corresponding 2-aza-1,3-butadienes 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-butadiene 2-oxides. Recently we have obtained a number of 2,3-dihydroazete 1-oxides from reactions of nitroalkenes and 1-aminoacetylenes (ynamines). The structure of one of these four-membered cyclic nitrones, 2-(*N*,*N*-diethylcarbamoyl)-2,4-dimethyl-3-phenyl-2,3-dihydroazete 1-oxide (**1a**), has been de-



1 **2**

a $R^1=R^2=CH_3$, $R^3=R^4=CH_2CH_3$
b $R^1=CH_3$, $R^2=C_6H_5$, $R^3R^4=-(CH_2)_4-$
c $R^1=H$, $R^2=C_6H_5$, $R^3R^4=-(CH_2)_4-$

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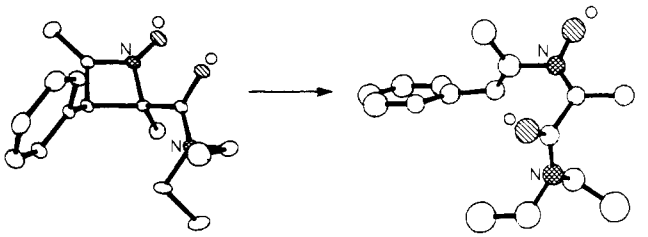

Figure 1. ORTEP drawings of **1a** and **2a**.

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

	10^5k, s		
temp, °C	1a	1b	1c
51.5	0.48 ± 0.01		
61.1	1.50 ± 0.1	9.60 ± 0.3	77 ± 3
71.9	5.71 ± 0.2		

termined by X-ray crystallography.[7] This revealed the stereochemistry of **1a** and showed that the two bulkiest substituents, the phenyl and the *N*,*N*-diethylcarbamoyl group, are on the same side of the almost flat four-membered ring. When a chloroform solution of this 2,3-dihydroazete 1-oxide was heated at reflux, isomerization to *N*-[1-(*N*,*N*-diethylcarbamoyl)-ethylidene]-1-phenyl-1-propen-2-amine *N*-oxide (**2a**) took place as indicated by ^1H NMR. After 20 h we isolated **2a** from the reaction mixture as a white crystalline solid (40%):[8,9] mp 117-120 °C; IR (KBr) $\nu_{C=C}$, $\nu_{C=O}$, and $\nu_{C=N}$ 1660, 1650, and 1630 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.98 and 1.23 (t, 6 H, $NCCH_3$), 2.32 (s, 6 H, $=C-CH_3$), 3.34 and 3.39 (q, 4 H, NCH_2-), 6.58 (s, 1 H, C=CH), 7.2-7.4 (m, 5 H, Ph); ^{13}C NMR ($CDCl_3$) δ 125.1 (=CH-), 142.0 and 143.1 (C=N and =CN), 164.1 (C=O). The structure of **2a** was determined by single-crystal X-ray analysis, and this unambiguously proved the *E*,*E* stereochemistry of **2a**.[11] This means that ring opening has taken place in a conrotatory mode in line with the isomerization of cyclobutenes.

Orthorhombic crystals of **2a** belong to space group $Pna2_1$ with a = 15.93 (1), b = 8.41 (1), c = 11.74 (1) Å, Z = 4. Intensities were measured with Mo Kα radiation (λ = 0.7107 Å) on a single-crystal diffractometer in ω-2θ scan mode ($3° < \theta < 20°$); 1450 reflections were measured, of which 869 were significant ($I > \sigma(I)$, counting statistics). The structure was solved by direct methods.[12] Full-matrix least-squares refinement[13] of positional and anisotropic parameters of the nonhydrogen atoms resulted in a final R_w factor of 5.5%. The structure of **2a**[14] 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 71.9 °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 ($\Delta H^{\ddagger}$ 27 ± 1 kcal mol^{-1} and $\Delta S^{\ddagger}$ - 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 I). The isom-

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(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 2*H*-1,2-oxazete 2-oxides are the intermediates in the formation of nitrones from 3-nitrobenzo[*b*]thiophene or 4-nitroisothiazole and ynamines.[10]
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(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**.
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erizations of both **1b** and **1c** are faster reactions than the conversion of **1a** to **2a**. These results demonstrate that substitution of a methyl group at C-4 in **1a** by a phenyl group (**1b**) and substitution of a methyl group at C-2 in **1b** by a proton (**1c**) both increase the rate of isomerization of the 1-azacyclobutene 1-oxides. These observations are consistent with the known effects of substitution at the various positions of cyclobutenes on the rate of isomerization.[15] Taking into account these known substituent effects on the rate of isomerization of cyclobutenes and assuming that the *N,N*-diethylcarbamoyl group at C-4 will decrease the activation energy by 1–2 kcal mol^{-1},[16] we have calculated a value of 28–29 kcal mol^{-1} for the activation energy of the isomerization of the unknown cyclobutene that corresponds with the 2,3-dihydroazete 1-oxide (**1a**). Therefore we conclude that substitution of an sp^2-hybridized carbon atom of a cyclobutene ring by an N–O group has only a small effect on the activation energy of the isomerization reaction. More important, this substitution does not change the stereochemical pathway of the reaction, which means that the Woodward–Hoffmann rules can be extended to electrocyclic reactions of 1-azacyclobutene 1-oxides.

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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Catalytically Active Models for the Active Site in Carbonic Anhydrase

Sir:

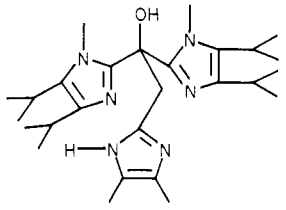
Carbonic anhydrase (CA) is a ubiquitous enzyme which catalyzes the interconversion of CO_2 and HCO_3^-. Its active site consists of a Zn^{2+} ion bound pseudotetrahedrally to three histidine imidazoles and either a water molecule or OH^- ion.[2] The activity of CA is governed by the ionization of at least one group with a pK_a around 7.[1] Recently some model systems exhibiting CO_2 hydration catalysis have been reported,[3] but as yet no catalytically active model which attempts to approximate the known Zn^{2+} binding site for CA has appeared. Herein we report preliminary results concerning two models for the active site of CA which show catalytic activity toward CO_2 hydration.

Table I. Rates of CO_2 Hydration Catalyzed by Complexes **1**-Zn^{2+} and **2**-Zn^{2+} [a]

catalyst	pH	k_{cat},[b] M^{-1} s^{-1}	k_{cat}/K_M, M^{-1} s^{-1}
$(imidazole)_2Zn^{2+}$ [c]	7.5	2.0	
1-Zn^{2+}	6.5	$7.6 \pm 0.5 \times 10^2$	
1-Zn^{2+}	7.5	$2.4 \pm 0.2 \times 10^2$	
2a-Zn^{2+}	7.5	*d*	
2b-Zn^{2+}	7.5	*d*	
2c-Zn^{2+}	6.5	*d*	
2c-Zn^{2+}	7.0	$2.0 \pm 0.4 \times 10^2$	
human CAB[e]			1×10^7
human CAC[e]			8×10^7

[a] Determined under pseudo-first-order conditions (with respect to CO_2) at 25 °C in 76% ethanol-H_2O according to procedures outlined in ref 6. Experiments with **2a**-Zn^{2+} and **2b**-Zn^{2+} for reasons of solubility were performed in H_2O. pH values are those directly read from electrode immersed in solution. [b] $k_{cat} = (k_{obsd} - k_{uncat})/[cat]$, $[cat] = 5 \times 10^{-4}$ M. [c] Reference 3a. [d] k_{obsd} did not differ from that observed in the absence of catalyst. [e] Khalifah, R. G. *J. Biol. Chem.* **1971**, *246*, 251, ref 6.

Ligand **1**[4] in the presence of 1 equiv of Zn^{2+} shows reversible



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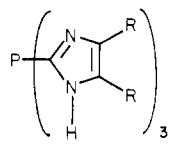

2a, R = H
b, R = CH_3
c, R = $CH(CH_3)_2$

consumption of 1 equiv of OH^- with an apparent pK_a of 6.5 in 76% ethanolic H_2O.[5] CO_2 hydration[6] in the presence of **1**-Zn^{2+} shows catalysis at pH 6.5 (Table I) which diminishes at pH >7 to a final k_{cat} of 240 ± 20 M^{-1} s^{-1} at pH 7.5. No catalysis by **1** is observed in the absence of Zn^{2+}. Although we do not have good evidence for the nature of the catalytically active species, UV spectra of **1**–Co^{2+} show the presence of what might be interpreted as tetrahedrally coordinated Co^{2+}.[7] The fact that the apparent catalysis is reduced at higher pH's indicates to us that the reversible titration is best explained by complex hydrolysis[4] leading to a less active species.

In order to circumvent this hydrolysis which we feel is probably due to relatively poor binding of Zn^{2+} by **1**,[4] we turned to phosphines **2a–c**[8] which appear from models to be reasonable tridentate ligands for the CA metal binding site. ^1H NMR spectra of **2c** in methanol-d_4–D_2O as a function of increasing $[Zn^{2+}]$ show the appearance of a well-defined 1:1 complex when $[\mathbf{2c}]/[Zn^{2+}] = 1$; no 2:1 complex is observed.[8b] UV spectra of **2a** and **2b** in the presence of $CoCl_2$ show little if any evidence for 4-coordinate ligation.[9] On the other hand, the isopropyl phopsphine **2c** in the presence of $CoCl_2$ shows reversible formation of a tetrahedral species at increasing pH with bands appearing at 588 (285), 622 (450), 646 (516), 662 (501) nm (ϵ).[9c] The **2c**–Co^{2+} spectra are highly anion dependent (Figure 1), reminiscent of the situation for the Co^{2+}–enzyme.[10] In the presence of ClO_4^- and NO_3^- the

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(7) This observation is tempered by the fact that the UV spectra of **1**–Co^{2+} are not completely reversible (reproducible) as a function of pH.

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