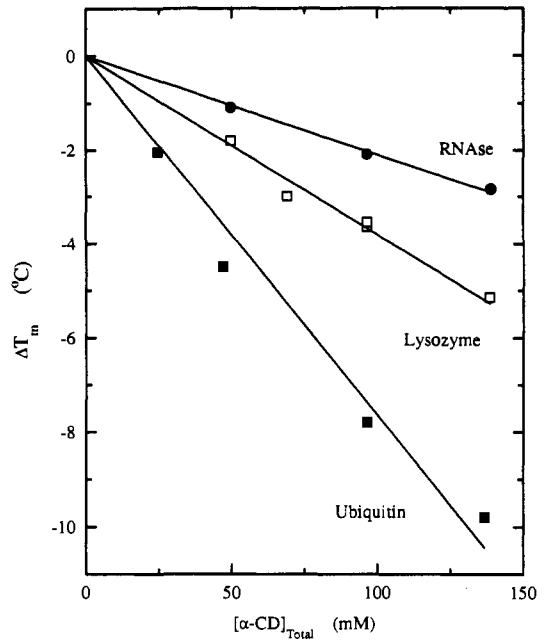

Figure 2. Decrease (ΔT_m) in transition temperatures with α-cyclodextrin concentration. Buffer conditions as in Figure 1. Transition temperatures (T_{m0}) and enthalpies (ΔH_{m0}) in the absence of α-CD were as follows: lysozyme, 67.7 °C, 114 kcal mol^{-1}; ribonuclease, 63.9 °C, 114 kcal mol^{-1}; ubiquitin, 69.2 °C, 59.3 kcal mol^{-1} (1 cal = 4.184 J).

account the effects reported here.

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Thermochemical Confirmation of the Mechanism of Action of Vitamin K

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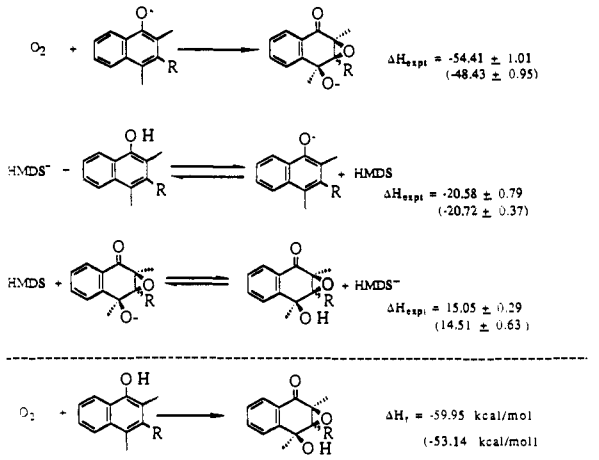
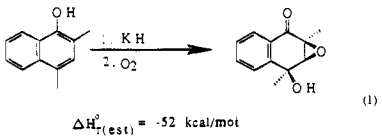
Vitamin K plays a key role in the complex cascade of steps on which the crucially important phenomenon of blood clotting depends.[1] Recently, two of us (P.D. and S.W.H.) proposed[2] a unique principle of base strength amplification to explain how the relatively weak naphthoxide anion ($pK_a \approx 10$) immediately available from vitamin K could be converted into a base strong enough ($pK_a \approx 27$) to effect carboxylation of glutamic acid to γ-carboxyglutamic acid in the presence of oxygen and carbon dioxide. The essence of the mechanism is the reaction of molecular oxygen with the biologically active hydroquinone form of vitamin K, vitamin KH_2. The oxidation leads to a powerfully basic α-epoxy tertiary alkoxide anion that is able to produce a carbanion at the γ-position of glutamate within the water-poor environment of the cell membrane or the hydrophobic interior of the carboxylase.

Dowd and Ham[2] used the oxygenation of an α-naphthol to a keto epoxy alcohol to construct a model system. The efficacy of the model was demonstrated by inducing a base-promoted Dieckmann ring closure of diethyl adipate simply by pumping oxygen into a solution of potassium 2,4-dimethylnaphthoxide in THF in the presence of 18-crown-6 polyether to sequester the potassium ion (eq 1).[2]

Scheme I[a]



[a] Bracketed numbers apply to the trimethyl compounds; R = H for the dimethyl series.



Stereochemical, structural, and labeling experiments are consistent with a strictly intramolecular oxygenation mechanism.[2,3] Thermochemical estimates for the reaction in eq 1 were made on the basis of reasonable interpolations from published heats of formation of intermediates and products required by the mechanism.[2] Specifically, the mechanism requires that the transformation in eq 1 be exothermic by about 52 kcal/mol and that the heat of deprotonation of the model epoxy alcohol should be approximately 10 kcal/mol less exothermic than its parent naphthol.

To test these proposals, the reaction in eq 1 was carried out in a Tronac 450 solution calorimeter at 25 °C using the dimethyl- and trimethylnaphthoxides shown in Scheme I. A 0.17 M solution of the 18-crown-6/potassium naphthoxide was prepared in THF, and successive increments of 99.8% oxygen (Matheson) were injected through a Teflon cannula from a 10-mL gas-tight syringe.[3] Reaction with oxygen was instantaneous and clean by NMR examination of products. In conformity with prediction,[2] the heats of reaction (ΔH_{ox}) for two complete runs of 11 measurement replicas were −54.41 ± 1.01 kcal/mol for oxygenation of the dimethylnaphthoxide and −48.43 ± 0.95 kcal/mol for the trimethylnaphthoxide. Since ion-pairing effects within the enzyme are unknown, it is interesting to note that $\Delta H_{ox} = -47.75 \pm 0.60$ kcal/mol for the former reaction in the absence of the crown ether.

Following the procedure of Arnett and Moe,[4] the heats of deprotonation (ΔH_{dep}) with lithium hexamethyldisilazide (LiHMDS) in THF at 25 °C for the epoxy alcohols and their naphthol precursors are as shown in Scheme I; each value is based on 12 replica measurements. Using 18-crown-6/KHMDS, $\Delta H_{dep} = -12.72 \pm 0.41$ kcal/mol for the trimethyl epoxy alcohol and $\Delta H_{dep} = -18.68 \pm 0.40$ kcal/mol for the 2,3,4-trimethylnaphthol were obtained. For comparison with a model tertiary alcohol, $\Delta H_{dep} = -13.41 \pm 0.21$ kcal/mol for dimethylbenzylcarbinol. An attempt was also made to compare the ΔH_{dep}'s of the alcohols with K^+DMSYL^- in DMSO.[5] However, the $DMSYL^-$ anion im-

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0002-7863/92/1514-9209$03.00/0

mediately attacked the epoxy compounds.

These data can be combined in the thermochemical cycle of Scheme I. From this the overall heats of reaction for the dimethyl and trimethyl series are -59.94 and -53.14 kcal/mol, respectively. The latter value is almost that predicted for reaction 1, but clearly substitution, solvation, and cationic effects make such good agreement partly fortuitous. In any case, the spontaneous oxygenation of the model generates more than enough energy to accomplish the base strength amplification required for the deprotonation reaction.

These data provide powerful support for the proposed mechanism of Dowd and Ham.[2] Not only is the unprecedented use of the biochemical reaction with oxygen demonstrated to be easily able to supply the large energetic demands of the base strength amplification mechanism, but the detailed thermochemical predictions which are specific to this proposal are also closely confirmed.

The mechanism of action of vitamin K represents a prime example of an energy transduction reaction in which the energy made available from oxidation is employed to effect acid-base chemistry.

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Hetero-Diels-Alder Addition of Sulfur Dioxide to 1,3-Dienes. Suprafaciality, Regioselectivity, and Stereoselectivity

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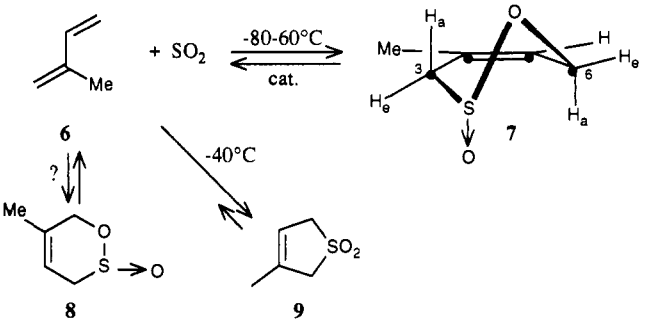
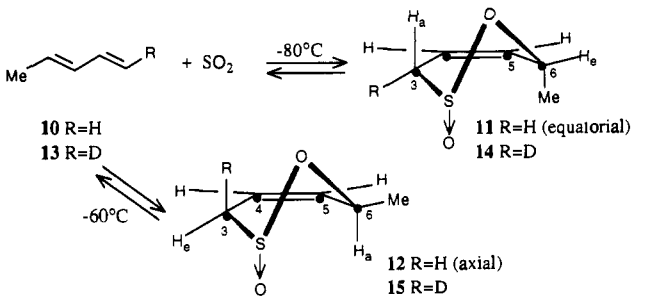
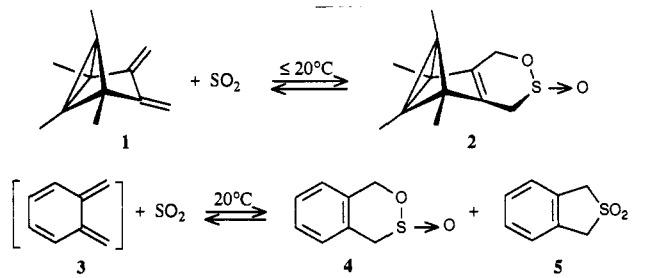
The cheletropic reaction ($_\omega 2_s + _\pi 4_s$)[1] of SO_2 with 1,3-dienes to give 2,5-dihydrothiophene 1,1-dioxides (sulfolenes) has been known since 1914.[2,3] Although selenium dioxide,[4] *N*-sulfenylamines[5] (RN=S=O), and sulfines (RR'C=S=O),[6,7] which have considerable structural analogy to SO_2, readily take part in hetero-Diels-Alder additions,[8] the [$_\pi 4_s + _\pi 2_s$]-cycloaddition of SO_2 to 1,3-dienes is a rare reaction which has been reported in only two cases. The first case involves the highly reactive diene **1**, which adds to SO_2 below 20 °C to give adduct **2** reversibly.[9] In the second case, *o*-quinodimethane (**3**) adds to SO_2, giving a 9:1 mixture of sultine **4** and sulfolene **5**.[10]

Scheme I



Scheme II





Previous attempts to generate 3,6-dihydro-1,2-oxathiin 2-oxides (sultines) derived from penta-1,3-diene and 1-phenylbutadiene via an indirect method suggested that monocyclic sultines undergo fast cycloreversions at 0 °C.[11] On lowering of the temperature, the entropy contribution to the free energy of the equilibrium 1,3-diene + SO_2 ⇄ sultine is expected to be reduced; thus the chances of observing a sultine in equilibrium with SO_2 and the corresponding diene should increase, provided the hetero-Diels-Alder addition is not too slow and can be made to occur faster than the concurrent and more exothermic cheletropic reaction diene + SO_2 → sulfolene. We report here that such conditions have been found for simple dienes such as isoprene (**6**) and (*E*)-piperylene (**10**). We shall also show that the hetero-Diels-Alder addition of SO_2 to (*E*,*E*)-1-deuteriopiperylene (**13**) is suprafacial for the diene and that it follows the Alder (endo) rule.[12]

When a 0.2 M solution of **6** in CD_2Cl_2/SO_2, 2/3 v/v, was allowed to stand for several hours between -80 and -60 °C (5-mm sealed NMR tube), no reaction was observed. However, upon addition of 0.5-1 equiv of CF_3COOH or $BF_3{\cdot}Et_2O$, the sultine **7** began to form. At -60 °C, the equilibrium **6** + SO_2 ⇄ **7** was reached in ca. 6 h and an equilibrium constant $K \cong 3 \times 10^{-2}$ mol^{-1} dm^3 was evaluated (toluene as internal reference). The regioi-

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