48 h in 1,2,4-$Cl_3C_6H_3$; 1·$(CH_3)_2NCOCH_3$,[5] 165 °C for 24 h in 1,3,5-$(CH_3)_3C_6H_3$; 1·$(CH_3)_2NCHO$,[5] 165 °C for 12 h. In the 360-MHz ^1H NMR spectra, proton signals of incarcerated guests are far upfield of guests simply dissolved in $CDCl_3$: 1·$(CH_3)_2SO$, δ -1.02; 1·$(CH_3)_2NCOCH_3$, δ -2.30, -1.33, 1.05; 1·$(CH_3)_2NCHO$, δ -1.04, -0.21, and 4.14. Proton signals of the northern and southern hemispheres of the host are identical at 25 °C for **1**, for 1·$(CH_3)_2SO$, and for 1·$(CH_3)_2NCHO$, but different for 1·$(CH_3)_2NCOCH_3$. Thus end-to-end guest rotation relative to the host's north-south axis is inhibited only in 1·$(CH_3)_2NCOCH_3$.

Treating free **1** in appropriate solvents gave new hemicarceplexes, e.g.: 1·CH_3CN[3] (δ -2.42); 1·CS_2,[3] 1·pyridine[5] (heat required); 1·CH_2Br_2.[3] When treated with a 0.14 M solution of xenon in $CDCl_3$ at 25 °C, 1·Xe[5] formed, whose 1·^{129}Xe NMR signal was at -101 ppm (dissolved xenon, 0 ppm).[7] On silica gel -15% hexane/85% $CHCl_3$ (v/v), most complexes (and free **1**) had different R_f (TLC) values. These one-to-one complexes (^1H NMR proton counting and elemental analyses) were stable to laboratory manipulations at room temperature, but released their guests when subjected to FAB MS to give strong M + 1 signals for **1**.[7,8]

These results demonstrate that hemicarcerands can be designed and prepared whose portals show high structural recognition in guest entry, departure, and residence. We envision potential uses for hemicarceplexes: drug delivery systems; organ imaging; protection of bone from deposition of heavy metal salts useful in radiation therapy; light switches; information storage. We are examining these possibilities in many carceplexes.

(7) A k_{in} second-order rate constant for filling **1** (5 mM) with Xe (0.14 M) in $CDCl_3$ at 25 °C was estimated to be 0.055 min^{-1} M^{-1} (followed by ^1H NMR changes). A k_{out} first-order rate constant estimate in CD_2Cl_2 at 25 °C for 1·Xe + CD_2Cl_2 → 1·CD_2Cl_2 + Xe (followed by ^1H NMR changes) gave 2.5×10^{-4} min^{-1}. If we assume that k_{out} in CD_2Cl_2 ~ k_{out} in $CDCl_3$, K_e for 1 + Xe ⇄ 1·Xe is estimated to be ≈200 M^{-1}.

(8) The closest precedents to our hemicarcerands are the elegant *cryptophanes* of A. Collet (summarized in *Tetrahedron* **1987**, *43*, 5725-5759), who joined two cyclotriveratrylene-like modules with three ethylene bridges to give hollow molecules with three equivalent portals.

On the Mechanism of Action of Vitamin K. A New Nonenzymic Model

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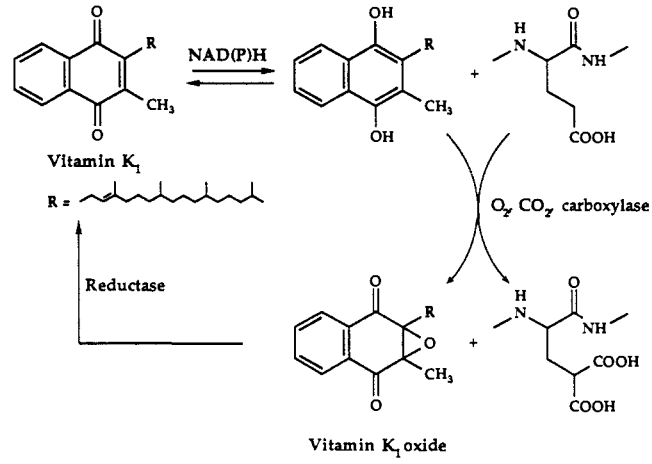
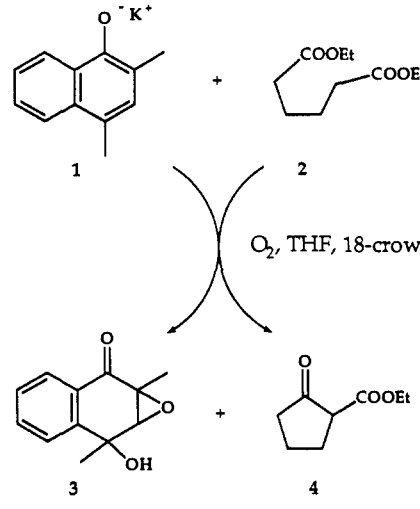
Vitamin K is essential for blood clotting.[1] It may also play a role in bone calcification[2] and have other broad functions in biological systems.[3] At the enzyme level, vitamin K is an obligatory cofactor promoting the posttranslational carboxylation[4] of selected glutamic acid residues in many of the proteins of the blood clotting cascade, including factor II (prothrombin), factor VII, factor IX, factor X, protein C, protein M, protein S, and protein Z, as well as the bone protein osteocalcin.[5]

The carboxylative conversion of glutamate to γ-carboxyglutamate requires the hydroquinone form of vitamin K (or vitamin K and NAD(P)H), oxygen, carbon dioxide, and a membrane-bound carboxylase[1] only recently isolated in pure form.[6] In the course of the carboxylation (Scheme I), vitamin K is converted to vitamin K oxide.[7] A second, reductase-catalyzed pathway returns vitamin K oxide to vitamin K for a new catalytic cycle.[8,9]

Scheme I



Scheme II



In coming to grips with the mechanism of action of vitamin K, it is important to establish whether the formation of vitamin K oxide is an integral part of the step that effects the carboxylation.[10] Through the recent efforts of Suttie and his collaborators,[11] it has been shown that the degree of carboxylation closely parallels the extent of formation of vitamin K oxide under diverse circumstances.[6]

Since the discovery of the vitamin K dependent carboxylation, a variety of mechanistic proposals have been advanced ranging from free-radical[12,13] to base-promoted pathways.[14-17] Missing

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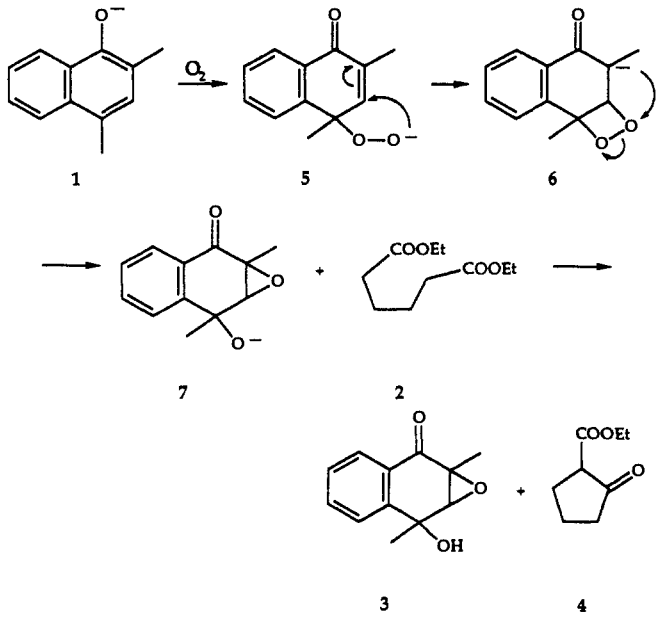
Scheme III

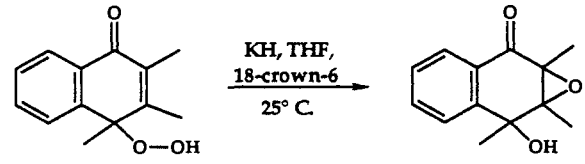


from the mechanistic picture is a working chemical model to show if, what, and how vitamin K oxide formation contributes to the condensation reaction.

We have discovered a new nonenzymic model which mimics the essential features of the vitamin K dependent condensation. Thus, when a THF solution of diethyl adipate (**2**) is treated at room temperature with potassium 2,4-dimethyl-1-naphthoxide (**1**) and 1.7 equiv of oxygen, bubbled in over a period of 3 h with a gas-tight syringe,[18] in the presence of 18-crown-6 (Scheme II), condensation (internal carboxylation) occurs to yield the 1-oxocyclopentane-2-carboxylate **4** (30–35%) and the keto epoxide **3** (50–60%).[19,20] When oxygen is excluded from the reaction, *no cyclization* of diethyl adipate (**2**) to ethyl 1-oxocyclopentane-2-carboxylate (**4**) occurs; less than 1% of **4** can readily be detected in the NMR spectrum of the total crude reaction product, and of course, none of the epoxide **3** is formed. Indeed, the oxygen-free control must be scrupulously carried out; otherwise, traces of cyclized product **4** are produced by small amounts of adventitious oxygen.

We suggest that the following sequence of events takes place (Scheme III). The naphthoxide **1** reacts *spontaneously* with oxygen, yielding the hydroperoxy anion **5**, which undergoes internal dioxetane formation to **6**. That step is followed by transformation of **6** to the epoxy alkoxide **7**,[21] which is a strong base and effects the condensation reaction of **2** to **4**. The naphthoxide **1** is not sufficiently basic to effect the condensation of **2** to **4**. Likewise, neither potassium *tert*-butylperoxide[16] nor potassium superoxide is sufficiently basic to effect the condensation of **2** to **4** under the reaction conditions used for the model in Scheme II.

To explore further the rearrangement of the hydroperoxy anion **5** to the oxide **7**, the stable hydroperoxide **8** was prepared by treatment of 2,3,4-trimethyl-1-naphthol with oxygen in chloroform.[22] When **8** is treated at room temperature with potassium hydride and 18-crown-6 in THF, rearrangement to the keto epoxide **9** occurs.



We propose that epoxidation is an *integral part of the vitamin K dependent carboxylation reaction*, driving the reaction by transforming the biologically accessible but weakly basic naphthoxide anion to the biologically remote but strongly basic alkoxide anion. The energy gained from converting the weak peroxide bond to the relatively strong carbon–oxygen bond of the epoxide is coupled to and bridges the energy gap between the weak naphthoxide and the strong alkoxide bases.

This is the first nonenzymic model mimicking the *carbon–carbon-bond-forming condensation reaction* dependent on vitamin K and leading to a keto epoxide. The model introduces *a novel basicity enhancement reaction* which may be the key to understanding how vitamin K functions and may have extensions to other chemical and biochemical transformations. Finally, this model suggests that *molecular oxygen is the initiating factor* in the vitamin K dependent carboxylation sequence.

Acknowledgment. This research was supported by the National Science Foundation. We thank Dr. Roger Hershline and Patricia Cottam for early experiments in this area, Professor Chien Ho for the use of his laboratory facilities, and Dr. S.-C. Choi for his assistance at a later stage of the research.

(16) Lawson and Suttie proposed that a hydroperoxide anion might be sufficiently basic to produce a carbanion intermediate: Lawson, A. E.; Suttie, J. W. *Proc. Natl. Acad. Sci. U.S.A.* **1978**, *75*, 5413. This conclusion has been contested by Olson et al.; Olson, R. E.; Hall, A. L.; Lee, F. C.; Kappel, W. K.; Meyer, R. G.; Bettger, W. J. In *Posttranslational Covalent Modification of Proteins*; Connor Johnson, B., Ed.; Academic Press: New York, 1983; pp 295–319. Hall, A. L.; Kloepper, R.; Zee-Chang, R. K.-Y.; Lee, F. C.; Olson, R. E. *Arch. Biochem. Biophys.* **1982**, *214*, 45.

(17) For an acetyl transfer reaction originating from a vitamin K hydroperoxide analogue, see: Wilson, R. M.; Tharp, G. *J. Am. Chem. Soc.* **1985**, *107*, 4100.

(18) It is important to limit the amount of oxygen and to add it slowly. Use of excess oxygen led to epoxy ketone **3** but yielded little or no cyclic product **4**.

(19) Yields are those of pure isolated products. All new substances exhibited satisfactory spectral properties.

(20) Diethyl pimelate was also successfully cyclized to 1-oxocyclohexane-2-carboxylate under the conditions of the transformation in Scheme II.

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The Allylic Epoxide Cyclization. A Method for the Control of Regiochemistry and Stereochemistry in Cyclohexane Systems

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We have developed a new method of vicinal stereocontrol, which we illustrate by the regio- and stereoselective transformations shown in eqs 1 and 2.

The reaction translates the stereochemistry of a simple trans epoxide into the stereocontrolled formation of three contiguous asymmetric centers, one of which is quaternary; it leads to products (cf. **2**, **4**, **5**) with well-differentiated functions which can easily be elaborated in various directions; and finally, it readily leads to homochiral products because of the availability of epoxides such as **7** (vide infra) in known absolute configuration.

The regio- and stereochemical results illustrated, for example, by **1** → **2** and **3** → **4** deserve comment.

The normal propensity observed in the intramolecular opening of an epoxide by a carbanion is for displacement to occur at the proximal end, with the resulting formation of the smaller carbocycle.[1] The desired formation of a cyclohexane rather than a cyclopentane ring could be achieved with trans-disubstituted

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