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Synthesis and Absolute Configuration of Enantiomerically Pure Vitamin K_3 2,3-Epoxide

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The 2,3-epoxide of vitamin K_3 (menadione, 1) has been prepared in enantiomerically pure form, and the absolute configuration has been deduced from the CD spectrum. The compound with the negative Cotton effect between 340 and 400 nm has the 2*R*,3*S* configuration.

The role of vitamin K in mammalian systems is far from clarified,[1] notwithstanding the discovery of these vitamins 40 years ago.[2] Vitamin K_3 epoxide (**2**) has been shown to have equal or higher[3] vitamin K activity than vitamin K_1 and has been implicated as a provitamin in the animal electron-transport system.[2] Recently it has been suggested that a vitamin K epoxide is involved in the carboxylase activity of vitamin K.[1]

Some time ago we reported[4] the synthesis of optically active vitamin K_3 epoxide (**2**) from vitamin K_3 (**1**)[5] using a chiral catalyst (**3**) in a phase-transfer system.

In view of the lack of information on the absolute configuration of chiral 1,4-naphthoquinone 2,3-epoxides in general and of vitamin K epoxides in particular, it seemed of importance to us to prepare vitamin K_3 2,3-epoxide in optically pure form and attempt to determine its absolute configuration. By use of the chiral phase-transfer reagent benzylquininium chloride (**3**) in catalytic amounts (see Experimental Section), optically active vitamin K_3 epoxide (**2**) could be obtained in consistent chemical yields of 65-70% and enantiomeric yields of 7-10%. With 30% hydrogen peroxide, aqueous sodium hydroxide, and toluene, the reaction appeared to proceed best between 35 and 45 °C. Crystallization of the crude epoxide from 90% alcohol followed by several crystallizations from absolute alcohol furnished beautiful colorless crystals: mp 95.5-96.5 °C; $[\alpha]_{578}^{21}$ 0°; $[\alpha]_{436}^{21}$ $-124 \pm 5°$. These rotations were not changed upon further purification. It is fortuitous that these crystallization attempts were carried out *prior* to our determination of the enantiomeric purity of the material (**2**) as obtained from the reaction since the low (7-10%) enantiomeric purity of the reaction product **2** might well have discouraged any but the most optimistic chemists from attempting purification by crystallization. Determination of the enantiomeric excess using the chiral shift reagent Eu(dcm)$_3$ confirmed that the initial product $[\alpha]_{430}^{21}$ $-12°$ had an enantiomeric purity of 10% and that the maximal specific rotation of vitamin K_3 epoxide (**2**) was $[\alpha]_{436}^{21}$ $-124 \pm 5°$ (*c* 0.25, acetone).

Chiroptical Properties and Absolute Configuration. The circular dichroism spectrum of (−)-**2** is reproduced in Figure 1. The Cotton effect at the longest wavelengths is moderately negative, shows pronounced fine structure with a spacing of approximately 1200 cm^{-1} characteristic for carbonyl $n \rightarrow \pi^*$ transitions, and corresponds to a weak absorption in the UV spectrum. In the latter the fine structure is not well resolved; its maxima are blue shifted by approximately 600 cm^{-1} with respect to those in the CD spectrum. Four other CD bands can be identified in the CD spectrum (Figure 1) part of which coincide with UV maxima, while part do not. We will concentrate in the following discussion on the Cotton effect around 370 nm, which we will treat in the same way as for other carbonyl compounds, namely, by means of qualitative MO arguments.[6-8]

The 10-π-electron system of **2** is isoelectronic with that of 1,2-divinylbenzene. The Walsh orbitals of the oxirane ring can only weakly interact with this wavelength system and are not considered as part of the chromophore. Under the approximation of a coplanar conjugated chromophore, this latter belongs to point group C_{2v}. The two highest occupied and the two lowest unoccupied π orbitals are schematically drawn in Figure 2 with their symmetry tables. The two combinations n^+ and n^- are not isoenergetic, n^- (b_2) lying somewhat higher than n^+ (a_1). This ordering follows from through-bond interaction with the σ skeleton of the nonaromatic ring. Calculations for similar systems gave analogous results.[9]

The first four $n \rightarrow \pi^*$ transitions lead to states of symmetry B_1 ($n^- \rightarrow \pi_6^*$), A_2 ($n^+ \rightarrow \pi_6^*$), A_2 ($n^- \rightarrow \pi_7^*$), and B_1 ($n^+ \rightarrow \pi_7^*$), respectively. Even after configurational interaction (CI) is allowed for, the CD band at longest wavelength should thus be mainly of $n^- \rightarrow \pi_6^*$ type. For-

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[1] J. W. Suttie, A. E. Larson, L. M. Canfield, and T. L. Carlisle, *Fed. Proc., Fed. Am. Soc. Exp. Biol.*, **37**, 2605 (1978).

[2] S. Ausbacher and E. Fernholtz, *J. Am. Chem. Soc.*, **61**, 1924 (1939). See also: E. A. Doisy, S. B. Binkley, and S. A. Thayer, *Chem. Rev.*, **28**, 477 (1941); S. Divald and M. M. Joullié in "Medical Chemistry", A. Burger, Ed., Wiley-Interscience, New York, 1969, p 102.

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[4] R. Helder, J. C. Hummelen, R. W. P. M. Laane, J. S. Wiering, and H. Wynberg, *Tetrahedron Lett.*, 1831 (1976). It is interesting to note that, to our knowledge, no one appears to have considered the possible chirality of vitamin K 2,3-epoxides even though their synthesis and study parallels those of vitamin K. Since successful resolution attempts with racemic 1,4-naphthoquinone 2,3-epoxides have not been reported, the asymmetrically catalyzed epoxidation appears to be the only in vitro route to the chiral epoxides. It would be of considerable interest to determine the chirality of vitamin K 2,3-epoxides isolated from vitamin K metabolism and, conversely, to study the vitamin K activity of optically active vitamin K 2,3-epoxides.

[5] 2-Methyl-1,4-naphthoquinone (**1**) has been known since 1925: V. Vesely and J. Knapp, *Recl. Trav. Chim. Pays-Bas*, **44**, 360 (1925); J. Madinaveita, *Rev. R. Acad. Cienc. Exactas, Fis. Nat. Madrid*, **31**, 617 (1934); *Chem. Abstr.*, **29**, 5438 (1935); L. F. Fieser, W. P. Campbell, E. M. Fry, and M. D. Gates, *J. Am. Chem. Soc.*, **61**, 3216 (1939).

[6] G. Snatzke, *Angew. Chem.*, **91**, 380 (1979); *Angew, Chem., Int. Ed. Engl.*, **18**, 363 (1979).

[7] G. Snatzke, *Pure Appl. Chem.*, **51**, 769 (1979).

[8] G. Snatzke in "Optical Activity and Chiral Discrimination", S. F. Mason, Ed., D. Reidel, Dordrecht, 1979, pp 25, 43.

[9] Cf. W. Hug, J. Kuhn, K. J. Seibold, H. Labhart, and G. Wagnière, *Helv. Chim. Acta*, **54**, 1451 (1971).

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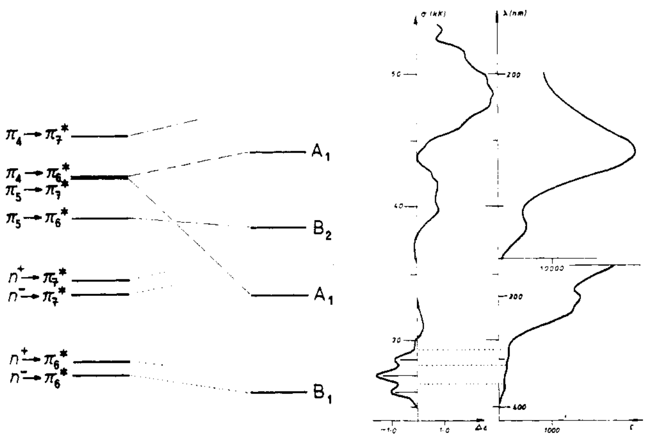

Figure 1. UV and CD spectra of (−)-**2** and possible assignment of some peaks. All four first $n\rightarrow\pi^*$ states are deliberately placed at lower energies than the first $\pi\rightarrow\pi^*$ state; only the first one ($n^-\rightarrow\pi_6^*$) can be associated unequivocally with the CD and UV absorptions around 360 nm. The assignment of the $\pi\rightarrow\pi^*$ bands is also tentative.

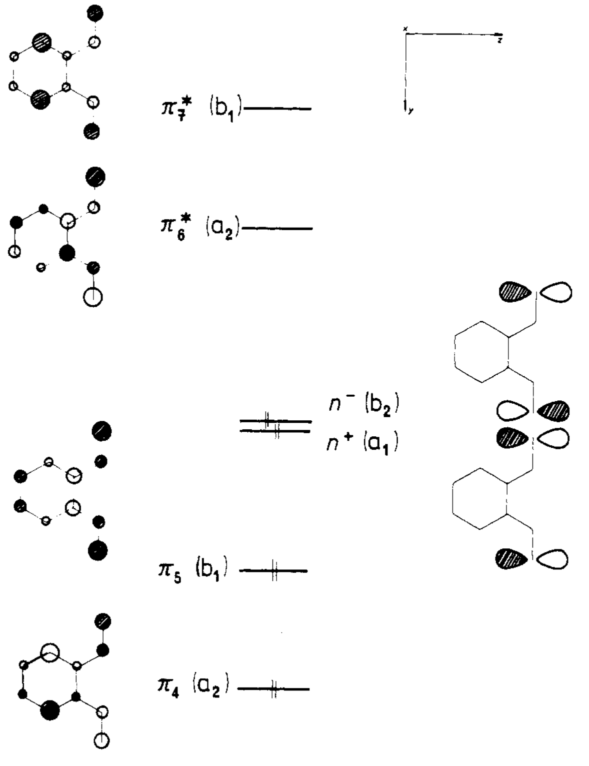

Figure 2. Schematic representation of the two highest occupied and the two lower virtual π orbitals of coplanar 1,2-divinylbenzene, isoelectronic with **2** (Hückel approximation), as well as the two nonbonding combinations n^+ and n^-. The spacing does not exactly correspond to orbital energies. The coordinate system used for the C_{2v} point group is indicated at the top.

mally an $A_1\rightarrow B_1$ transition is associated with an electric transition moment, μ_x, perpendicular to the plane of the molecule, and a magnetic transition moment, m_y, in this plane. The "multiplication recipe" for the pertinent orbitals[6-8] shows that this μ_x is negligably small because it originates from the (very weak) overlap between n^- and the π electrons of the benzene ring. On the other hand, m_y will be large and approximately equal to that of an $n\rightarrow\pi^*$ transition of a simple ketone. The magnitude of the g numbers ($g = \Delta\epsilon/\epsilon$) within the first Cotton effect is in full agreement with this. The blue shift of the UV peaks vs. the CD peaks will be very weak. Using a normal vibration of race a_2 or b_1 will enable this transition to steal (additional) electric transition moment from the $A_1\rightarrow B_1$ or the $A_1\rightarrow A_1$ transition, respectively, increasing by this $\vec{\mu}$ at somewhat higher energies, losing, on the other hand, magnetic transition moment. This can easily be read off the character table of point group C_{2v}. The functions μ^2 (UV spectrum) and $\mu m \cos(\vec{\mu}\cdot\vec{m})$ (CD spectrum) will thus have their maxima at different wavelengths.

Stronger configurational interaction (CI) could place a combination of the two possible $A_1\rightarrow A_2$ transitions at lower energies than the first $A_1\rightarrow B_1$ transition. It is electrically dipole forbidden and should have an m_z along the C_2 axis. The "multiplication receipe" shows, however, that this magnetic transition moment is very weak, and no pronounced Cotton effect is expected. The interaction of the two A_2 states is thus not very strong.

The first four $\pi\rightarrow\pi^*$ transitions are of symmetry B_2 ($\pi_5\rightarrow\pi_6^*$), A_1 ($\pi_5\rightarrow\pi_7^*$), A_1 ($\pi_4\rightarrow\pi_6^*$), and B_2 ($\pi_4\rightarrow\pi_7^*$), respectively. The two excited A_1 states are degenerate within the frame of the HMO approximation; the CI will split them, and interaction with higher lying A_1 states (e.g., doubly excited) will further bring down the lower lying combination. In the case of conjugated polyenes it has been argued[10] that this combination may be placed at even lower energy than the ($\pi\rightarrow\pi^*$) HOMO–LUMO transition. This is, however, not supported by the experimental spectra. From its position and its large ϵ value we assign the 261-nm band the $\pi_5\rightarrow\pi_6^*$ ($A_1\rightarrow B_2$) transition; the 302-nm band could either come from one of the other $n\rightarrow\pi^*$ transitions or from this aforementioned lower ($A_1\rightarrow A_1$) combination, for which a compensation of their individual (strong) electric transition moments is predicted, and, therefore, no large ϵ value should be found. No $\pi\rightarrow\sigma^*$, $\sigma\rightarrow\pi^*$, or $n\rightarrow\sigma^*$ bands are expected at such long wavelengths. The second high-energy combination of these two $A_1\rightarrow A_1$ transitions could then correspond to the strong 225-nm band.

Actually the nonaromatic ring of the molecule can adopt two boatlike conformations; in one of these the methyl group is nearly coplanar with the adjacent carbonyl group, whereas in the other conformation the respective torsion angle is approximately 45°. The chiral perturbation in the former conformer must be negligable, and only the latter will show stronger Cotton effects. Molecular models do not indicate an appreciable difference in energy between the two conformers, so the population of the second one should always be great enough to account for the measured CD.

The following discussion uses the approximate C_{2v} symmetry of a coplanar chromophore; actually, it is only of C_s symmetry, which, however, is also achiral. For the application of the qualitative MO theory the small deviation from coplanarity of the chromophoric system is of no paramount importance.

For circular dichroism to occur within the $n^-\rightarrow\pi_6^*$ ($A_1\rightarrow B_1$) band of **2** the missing electric transition moment in the y direction has to be stolen from another transition. This must be of $A_1\rightarrow B_2$ type, and the $\pi_5\rightarrow\pi_6^*$ transition is the energetically nearest candidate for this. Mixing of the two transitions or states is caused by chiral perturbation from the methyl group of **2**, as the epoxide ring is achirally arranged with respect to the chromophore. Both treatments (mixing of transitions and mixing of excited states) lead to the same result for the absolute configuration of (−)-**2**.

(a) Mixing of Transitions (Helicity Rule). The $n^-\rightarrow\pi_6^*$ transition gains a μ_y by admixture of a few percent

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[10] K. Schulten and M. Karplus, *Chem. Phys. Lett.*, **14**, 305 (1972).

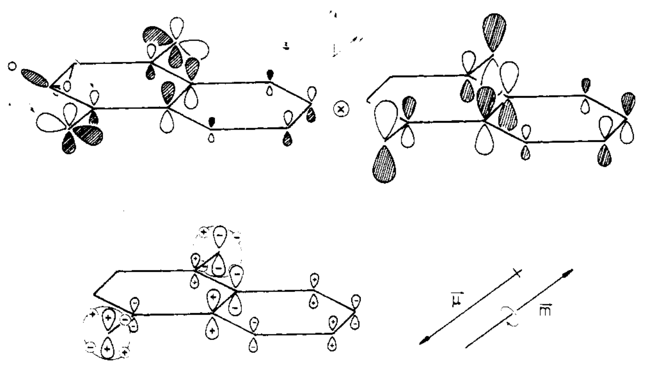

Figure 3. Chirality rule for longest wavelength CD band of **2**: top left, relative orbital phase signs for n⁻ and admixed π_5 as determined by negative overlap with the σ bond to the chiral perturber (methyl group); top right, π_6* MO (one of the two possibilities); bottom, representation of the signs of the product function $\psi_o \times \psi_e$ and direction of electric ($\vec{\mu}$) and magnetic ($\vec{m}$) transition moments. The antiparallel orientation of $\vec{\mu}$ and $\vec{m}$ leads to a negative CD. This treatment follows the general "recipe" given in ref 6.

of π_5 character to n⁻ by the chiral perturbation. As for twisted cycloalkanones,[6] this perturbation is represented by the nearest chiral σ bond, i.e., that to the methyl group of **2**. As the ordering should be (rising energy) σ, π_5, and n⁻, the σ character has to be mixed into n⁻ and π_5 with a negative sign. If the sign of the σ orbital lobe between the two C atoms is represented, e.g., by hatching, then negative overlap with both the nearest n⁻ and the p_x lobe leads to the relative phases given in Figure 3. Formal multiplication leads to the product function $\psi_o \times \psi_e$, also shown in Figure 3. It corresponds to an overall $\vec{\mu}$ in the negative *y* direction (coordinate system of Figure 3), whereas the charge rotation at the ends of the chromophoric system corresponds to a magnetic transition moment in the positive *y* direction. The CD for the given absolute configuration (2*R*,3*S*) will thus be negative.

(b) Mixing of States (Sector Rule). The n⁻→π_6* state is the first excited one (S_1), and the B_2 state (S_i) has definitely higher energy. Mixing gives a perturbed S_1 state, which corresponds to the energetically favored combination of S_1 and S_i (Figure 4). Both interactions, that with the multipole leading to μ_y and that with the (nearer) quadrupole associated with m_y, must therefore be either attractive or repulsive.[6] Placing a positive perturbing charge at the C atom of the methyl group of (2*R*,3*S*)-**2** determines the sign pattern within the quadrupole as shown in Figure 4, if attractive potentials are chosen. Attractive interaction with the nearest developing charge within the π system directs $\vec{\mu}$ along the $-y$ direction. The sign pattern of the quadrupole corresponds to the sign in the product function $\psi_o \times \psi_e$ of Figure 3, so $\vec{\mu}$ and $\vec{m}$ are again antiparallel. This second approach also leads, therefore, to a negative sign for the Cotton effect at the longest wavelengths for (2*R*,3*S*)-**2**.

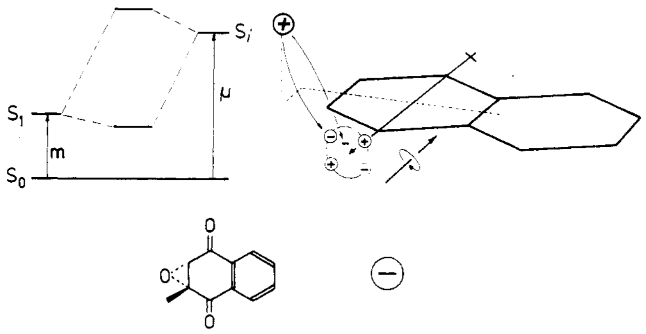

Figure 4. Sector rule for longest wavelength CD band of **2**: top left, interaction of S_1 (associated with m_y) and S_i (π_5→π_6*, associated with μ_x) by second-order perturbation; top right, induction of the signs of transient charges developed during the excitation by perturbation of a positive charge (C nucleus of methyl group). The correlation between the direction of $\vec{m}$ and the charge pattern within the quadrupoles around the carbonyl oxygen can be derived from Figure 3. A negative perturbing charge leads to the same result. The two transition moments are antiparallel; the CD is thus negative for the absolute configuration given at the bottom. For details cf. ref. 6.

Experimental Section

The epoxidation of 2-methyl-1,4-naphthoquinone (**1**) was carried out as follows. To a vigorously stirred solution of 0.5 g (2.9 mmol) of 2-methyl-1,4-naphthoquinone (**1**, mp 105–107 °C)[5] in 4 mL of toluene was added slowly a solution of 285 mg of sodium hydroxide in 2 mL of water and 2 mL of 30% hydrogen peroxide. To this two-phased system was added 25 mg of benzylquininium chloride.[11] The temperature of the reaction mixture was kept at 35–40 °C. At the lower temperature the reaction was complete in 2 h and at the higher in 25 min as indicated by the disappearance of the yellow color of **1**. The reaction was worked up by diluting the toluene layer with ether, washing the organic phase with water and saturated salt solution, and drying this over magnesium sulfate. The organic layer was passed through a short silica gel column with CH_2Cl_2. This treatment removed any last traces of catalyst. Evaporation of the eluate furnished 385 mg (70%) of colorless crystalline epoxyquinone **2**: $[\alpha]_{578}^{21}$ 0°; $[\alpha]_{436}^{21}$ −6.8° (*c* 0.4, $CHCl_3$). Runs on a larger scale (8.6 g) at slightly higher temperature (43 °C) furnished a lower chemical yield (46%) of epoxyquinone of somewhat higher enantiomeric purity ($[\alpha]_{436}^{21}$ −14° (*c* 0.5, acetone). Enantiomerically pure material was consistently obtained through repeated (four to ten times) careful recrystallization from alcohol. Pure (−)-2-methyl-1,4-naphthoquinone 2,3-epoxide was obtained as beautiful colorless needles: mp 95.5–96.5; $[\alpha]_{436}^{21}$ −124° (*c* 0.5, acetone); $[\alpha]_{578}^{21}$ 0°; NMR ($CDCl_3$, Me_4Si) δ 7.5–8.1 (m, 4 H), 3.86 (s, 1 H), 1.72 (s, 3 H); UV (isooctane) λ_{max} nm 374 sh (ϵ 52), 356 sh (151), 341 (180), 309 (1420), 302 (1570), 261 (5000), 225 (26 700); CD (isooctane) λ_{max} 382 nm ($\Delta\epsilon$ −1.05), 365 (−1.59), 350 (−0.92), 335 (−0.11), 324 (+0.21), 316 (+0.18), 251 (+0.81), 243 (+0.74), 239 (+0.74), 235 (+0.58), 224 sh (+0.3), 217 sh (+1.7), 211 (+2.84), 202 (+2.62), 194 sh (+1.8), 188 (+0.94). In acetonitrile the data were very similar.

Registry No. 1, 58-27-5; **2**, 61840-91-3.

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