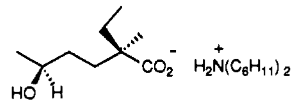
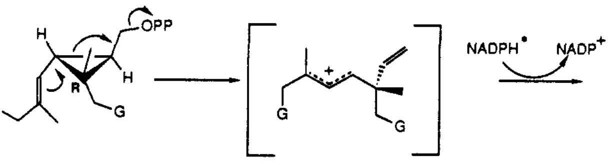
ether **13**. Removal of the silyl group and carbomethoxylation of the resulting pentyne **14** gave **15**. This ester was hydrogenated to the saturated derivative **16**, from which the tetrahydropyranyl ether was removed by methanolysis and the crude hydroxy ester **17** lactonized to (5*S*)-**18**.[8] Methylation[9] of **18** gave **8** and **19** (3:2, respectively), which were separated by gas–liquid chromatography and identified by comparison of their ^{1}H NMR spectra with published data.[10] Alkylation of the mixture of **8** and **19** with ethyl iodide gave the 2*R*,5*S* and 2*S*,5*S* lactones **9** and **20** (3:1) which were separated by HPLC (μ-Porasil) (Scheme III). The major diastereomer **9** was found to correspond with the lactone obtained from botryococcene and was shown to be trans by an X-ray crystal structure of the dicyclohexylamine salt, **21**, of the derived hydroxy acid.[11]



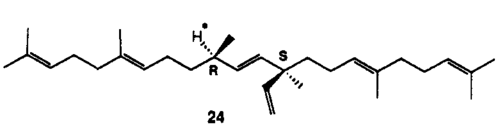
21

A parallel series of transformations from (*R*)-(+)-propylene oxide[12] provided the enantiomers of **7–9**. The absolute configurations of the lactones obtained from botryococcene were then determined from the ^{1}H NMR spectra (400 MHz) of 1:1 mixtures of natural and synthetic lactones in the presence of tris[3-[(heptafluoropropyl)hydroxymethylene]-(+)-camphorato]europium(III) [Eu(hfc)$_3$].[13] Progressive induced shifts of the methyl signals were observed with increasing Eu(hfc)$_3$ concentration for unmatched lactones.

The absolute configuration of botryococcene has important biogenetic implications. Taken with the incorporation studies of Casadevall[14] and Wolf,[15] our results show that the four nonmevalonoid methyl substituents are installed sequentially at the *si* face of the trisubstituted double bonds of the intact triterpenoid precursor. Further, the 10*S*,13*R* configuration of **1** is consistent with a biosynthesis via (*R*,*R*,*R*)-presqualene pyrophosphate (**22**) but deviates from the pathway to squalene in the subsequent collapse of **22** to **23**. This variant, which has precedent in the chemistry of monoterpenes containing an "irregular" linkage of isoprene units,[16] would be terminated by delivery of a hydrogen atom (presumably from NADPH) to C-13 from the *si* face of the allylic system.



22 G = geranyl **23**



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Acknowledgment. We are indebted to Dr. J. R. Maxwell, University of Bristol, for a sample of botryococcene and to Dr. D. A. Keszler and Scott Hein for the structure determination of **21**. Acknowledgement is made to the donors of the Petroleum Research Fund, administered by the American Chemical Society, for the support of this research. Funds for the purchase of a Bruker AM 400 NMR spectrometer were provided by the National Science Foundation (CHE-8216190) and the M. J. Murdock Charitable Trust.

Supplementary Material Available: Spectral data for compounds **1–21** (7 pages). Ordering information is given on any current masthead page.

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Facile Cyclization of the Valeronitrile Group Bound to a Nickel Macrocycle

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Received February 27, 1986

The formation of cyclic alkyl products in reactions of transition-metal complexes with linear cyclizable alkyl halides has been considered reliable evidence for the involvement of free radicals in these reactions.[1-9] The underlying assumption that the products were determined exclusively by the competition between radical cyclization and capture by the metal seems to have been correct in the work reported. On the other hand, several literature reports provide undeniable evidence of cyclizations/rearrangements of carbanions[10,11] and organometallic complexes in aprotic solvents.[12-19] Thus the formation of cyclic products from linear cyclizable precursors does not constitute sufficient evidence for the involvement of free radicals in a reaction.[20]

Scheme I

$$\mathrm{Ni(tmc)^{+} + RX \rightarrow Ni(tmc)^{2+} + R^{\bullet} + X^{-}} \tag{I-1}$$

$$\mathrm{Ni(tmc)^{+} + R^{\bullet} \rightarrow RNi(tmc)^{+}} \tag{I-2}$$

$$\mathrm{2Ni(tmc)^{+} + RX \rightarrow Ni(tmc)^{2+} + RNi(tmc)^{+} + X^{-}} \tag{I-3}$$

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(22) The complex is [(1*R*,4*R*,8*S*,11*S*)-1,4,8,11-tetramethyl-1,4,8,11-tetraazacyclotetradecane]nickel. Under the reaction conditions (pH ∼12) the nickel(II) complex is a mixture of aquo and hydroxo species [pK_a 11.93: Herron, N.; Moore, P. *Inorg. Chim. Acta* **1979**, *36*, 89]; for simplicity it is referred to as Ni(tmc)$^{2+}$ throughout.

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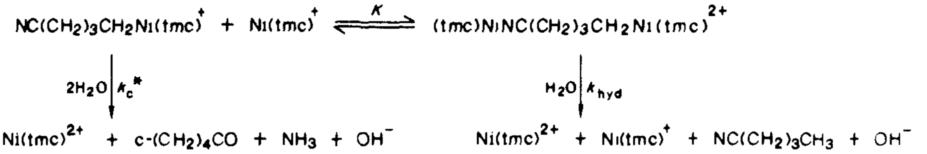
Scheme II



The reduction of $Br(CH_2)_4CN$ in alkaline, aqueous solution by the nickel(I) macrocycle[21,22] (*R,R,S,S*)-$Ni(tmc)^+$ yields the acyclic organonickel complex $NC(CH_2)_3CH_2Ni(tmc)^+$ (λ_{max} 394 nm, ϵ 2.0×10^3 M^{-1} cm^{-1}). This is as expected from the free radical process (Scheme I) established[21] for the reactions of $Ni(tmc)^+$ with alkyl halides, since this particular radical undergoes unimolecular cyclization more slowly ($k_c = 4 \times 10^3$ s^{-1})[2] than the rate at which it is captured by a second $Ni(tmc)^+$ ($k_2 = 10^7$–10^8 M^{-1} s^{-1}; [Ni(I)] $\sim 10^{-3}$ M). When 0.5–1 M H_3O^+ is added immediately to the freshly prepared complex, it rapidly hydrolyzes to the acyclic product $CH_3(CH_2)_3CN$.

If, on the other hand, the acyclic organonickel complex is allowed to stand in solution at pH 2–12, then cyclopentanone is the only organic product formed in ~100% yield.[23] These results and others cited below are taken as evidence that *after* the initial metal–carbon bond has formed, cyclization occurs in concert with hydrolysis (eq 1). To our knowledge, this is unprecedented in aqueous solution.

$$NC(CH_2)_3CH_2Ni(tmc)^+ + 2H_2O \xrightarrow{k_c^*} Ni(tmc)^{2+} + c\text{-}(CH_2)_4CO + NH_3 + OH^- \quad (1)$$

We cite the following results concerning the decomposition of $NC(CH_2)_3CH_2Ni(tmc)^+$: (1) The reaction follows first-order kinetics, with $k_c^* = 0.134 \pm 0.004$ s^{-1} at 25.0 °C, independent of the concentration of excess $Br(CH_2)_4CN$. (2) In solutions prepared by using an excess of $Ni(tmc)^+$, treated with $Co(en)_3^{3+}$ to oxidize the excess, the rate constant was the same, $k_c^* = 0.136 \pm 0.008$ s^{-1}. (3) The rate constant in solutions containing dilute perchloric acid, extrapolated to $[H^+] = 0$ to correct for the direct reaction with H_3O^+ ($k = 0.8$ M^{-1} s^{-1}), gave $k_c^* = 0.15 \pm 0.01$ s^{-1}. (4) The exclusive products in the three circumstances cited are $Ni(tmc)^{2+}$ and cyclopentanone. (5) Various tests were performed to check for the possibility that unimolecular homolysis[24] of the organonickel complex was occurring, but none gave positive results, and chemical analysis showed that no nickel(I) was produced during the decomposition.[25] (6) The decomposition rate constant decreases as $[Ni(tmc)^+]$ increases (see Figure 1), in a fashion that suggests rapid and reversible association between it and $NC(CH_2)_3CH_2Ni(tmc)^+$, probably through the cyano group. Cyclization within the binuclear complex is thus prevented and both organic products are obtained.

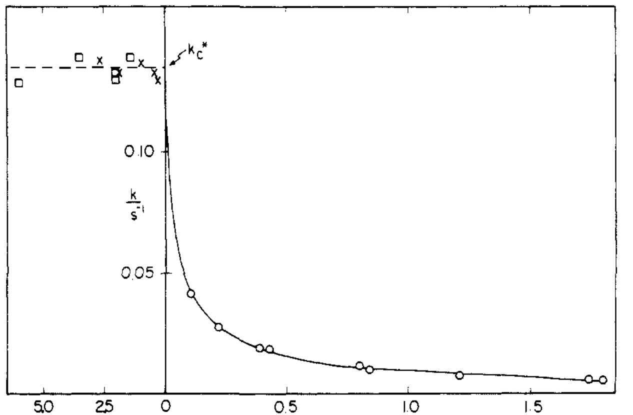
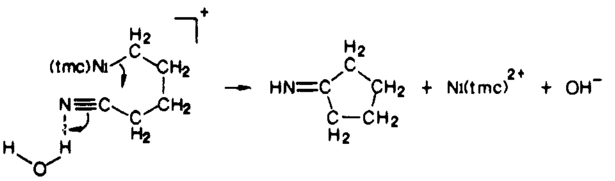


Figure 1. Dependence of the rate constant for the decomposition of $NC(CH_2)_3CH_2Ni(tmc)^+$ on large (6–10-fold) excess of $Ni(tmc)^+$ (right) and the presence of scavengers for $Ni(tmc)^+$ (left): $Co(en)_3^{3+}$ (squares) and $Br(CH_2)_4CN$ (crosses). Conditions: 25 °C, pH 12, $\mu \sim 0.03$ M.

Scheme II is consistent with the data and leads to the rate constant given by eq 2. A least-squares fit gives $k_c^* = 0.132 \pm 0.010$ s^{-1}, $K = (1.74 \pm 0.19) \times 10^4$ M^{-1}, and $k_{hyd} = (2.0 \pm 0.6) \times 10^{-3}$ s^{-1} at 25 °C and $\mu \sim 0.03$ M. The agreement between the best-fit value of k_c^* (0.132 s^{-1}) for experiments in the presence of different $[Ni(tmc)^+]$ and that measured in the absence of any Ni(I) (i.e., with RBr, $Co(en)_3^{3+}$, or H_3O^+ added, 0.135 s^{-1}) strongly supports the proposal. The large equilibrium constant for association of Ni(I) and this organonickel complex (eq 1) is unexpected in view of the great lability of the axial ligands in the d^9 Ni(I) complex, but similar complexation of the organonickel complex with one less CH_2 group (which, as expected, does not cyclize), corroborates the occurrence of an association step.

$$k = \frac{k_c^* + k_h K[Ni(tmc)^+]}{1 + K[Ni(tmc)^+]} \quad (2)$$

The values of the rate constants at 25 °C and activation parameters for the cyclizations of $NC(CH_2)_3CH_2Ni(tmc)^+$ ($k_c^* = 0.135$ s^{-1}, $\Delta H^\ddagger = 19.8 \pm 0.3$ kcal mol^{-1}, $\Delta S^\ddagger = 4.0 \pm 1.0$ cal mol^{-1} K^{-1}) and the free radical[26] ($k_c = 3.9 \times 10^3$ s^{-1}, $\Delta H^\ddagger = 8.0$ kcal mol^{-1}, $\Delta S^\ddagger = -15.2$ cal mol^{-1} K^{-1}) definitely show that these are two different processes. Indeed, the cyclizing entity in the nickel complex is probably best considered a nickel-bound *carbanion*. The main contributions to the activation enthalpy come from cyclization and the breaking of the Ni–C bond. The relatively high $\Delta S^\ddagger$ seems to indicate that cyclization occurs in concert with hydrolysis, eq 3, and not as an entirely intramolecular process with the transient formation of $(CH_2)_4CNNi(tmc)^+$.



(3)

Extensions of these investigations to $CH_2{=}CH(CH_2)_3CH_2Ni(tmc)^+$ (which also seems to cyclize) and to analogous isomeric organonickel complexes (*R,S,R,S*)-$RNi(tmc)^+$ promise to define further the mechanism of this most unusual transformation.

Acknowledgment. This work was supported by the U.S. Department of Energy, Office of Basic Energy Sciences, Chemical Sciences Division, under Contract W-7405-Eng-82. A.B. acknowledges the NATO support, Grant 559/83, and useful discussions with Dr. A. Petrou.

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(23) The organic products were analyzed gas chromatographically by use of a Hewlett-Packard 5790A instrument. The analyses were done isothermally at 167 °C on a Porapak Q column.

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