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RELATIVE KINETIC ORDERING OF [1,3]-HYDROGEN MIGRATION, ANIONIC OXY-COPE REARRANGEMENT, AND BASE-ACCELERATED DEHYDRATION IN TERTIARY CYCLONONATRIENYL ALKOXIDES

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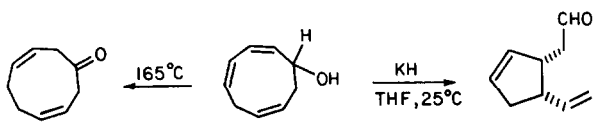
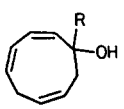
Summary: The reactivity exhibited by 1-methyl- and 1-ethyl-cis[3]-2,4,7-cyclononatrienol toward KH under various conditions has been examined.

Recent research activities have demonstrated that a highly ionized alkoxide substituent can substantially accelerate oxy-Cope rearrangements,[1] [1,5]-dienyl hydrogen shifts,[2] [1,3]-sigmatropic carbon migrations,[3] and [4+2] cycloreversions.[4] At least where oxy-Cope rearrangements are concerned, excellent stereochemical control can be achieved, and stereoselective syntheses based on this principle have been described for (±)-juvabione,[1] the primary prostaglandins,[2] various germacrane sesquiterpenes,[5] and (±)-coronafacic acid.[6] Pivotal to our earlier work with cis[3]-2,4,7-cyclononatrienol (1) was the finding that the predilection of the neutral system for thermal isomerization to 2 via [1,5]-hydrogen sigmatropy could be effectively overridden by conversion to the potassium alkoxide which rapidly gives only 3 at room temperature.

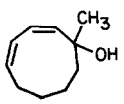


2 1 3

As a continuation of these studies, we have now examined the anionic behavior of the 1-methyl (4a) and 1-ethyl (4b) derivatives of 1 as well as that of the tertiary cyclononadienol 5. With the absence of a hydrogen atom geminal to the alkoxide substituent, new facets of oxy-anionic chemistry have been made apparent, and a relative kinetic ordering of mechanistic pathways established for these systems.



4a, R = CH_3
b, R = C_2H_5



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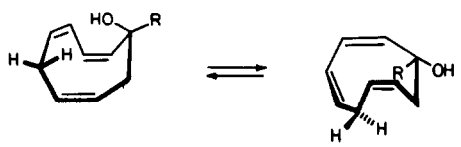
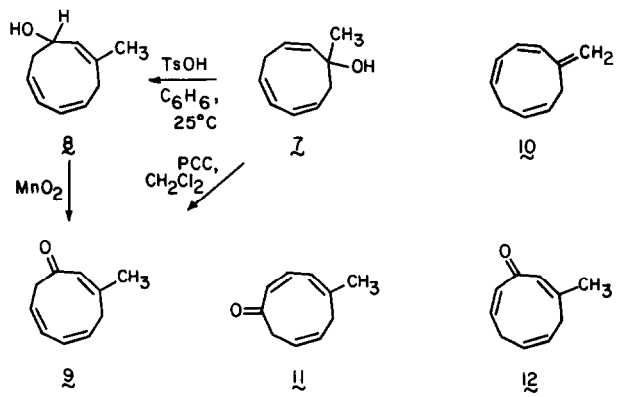
Manganese dioxide oxidation of 1 gave cis[3]-2,4,7-cyclononatrienone[7] which was converted to 4a and 5a[8] by reaction with the appropriate alkyllithium reagent. On the basis of the well

established dynamic behavior of cis[3]-1,3,6-cyclononatrienes,[9] it was anticipated that interconversion between crown conformations 6 and 6′ would occur rapidly above 0°C. In other words, conformational biases were considered unimportant a priori.



6 6′

When 4a was treated at -25°C with an excess of potassium hydride in dry tetrahydrofuran containing 18-crown-6 (1.2 equiv), clean conversion to an isomeric alcohol (7)[10] was complete within 3 hr.[11] The intact nature of a nine-membered ring in 7 was established by catalytic hydrogenation to 1-methylcyclononanol. In contrast to 4a which experiences dehydration to give 10[12] in the presence of p-toluenesulfonic acid (C_6H_6, 25°C), 7 undergoes conversion to a third cyclononatrienol (8) under identical conditions. Authentication of the structural assignments to 7 and 8 was achieved by oxidation. Thus, activated manganese dioxide acted on 8 to give 9[13] which expectedly[14] was the product of pyridinium chlorochromate (PCC) oxidation of 7. Of related interest is the PCC oxidation of 4a which gave a mixture of 11 (62%)[15] and 12 (38%).[16] The three cyclononatrienones could easily be distinguished on the basis of their ^{1}H NMR and UV spectra. The ethyl derivative 4b behaved comparably. The driving force underlying the conver-



8 7 10

9 11 12

sion of 4a to 7 would appear to be the higher level of conjugative interaction available to the 1,3-diene subunit in the latter (λ_{max} 235 nm) relative to the starting cyclononatrienol (shoulde at 220 nm).

When crown ether was omitted, 3 hr at 0°C was required for 4a-O^-K^+ to be totally isomerized (Table I). Importantly, these conditions led to production of 7 (47% isolated) and an insepa-

13a, R = CH_3 14a, R = CH_3

b, R = C_2H_5 b, R = C_2H_5

Table I. Rearrangement Behavior of 1-Methyl-cis^3-2,4,7-cyclononatrienol Derivatives.

Compd	Solv (additives)	T, °C	Time, hrs	[3,3]-C/[1,3]-H
4a-OH	C_6D_6	205	2	100:0
4a-O^-Na^+	THF	66	3	~90:10[a]
4a-O^-K^+	THF	0	3	~30:70[a]
4a-O^-K^+	THF (1.1 equiv 18-crown-6)	-25	<2	0:100
4a-O^-K^+	THF (3 equiv $Na^+\bar{C}H_2SOCH_3$)	0	1	0:100
4a-OCH_3	THF (2 equiv KOC_2H_5)	0	3	0:100[b]
4a-OCH_3	THF (2 equiv KOC_2H_5; 2 equiv 18-crown-6)	-25	2	0:100[c]

[a]These values are somewhat inaccurate owing to competing Cope rearrangement of 7-O^-K^+ under the reaction conditions. [b]< 10% conversion realized. [c]~90% conversion realized.

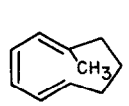
rable mixture of 13a and 14a (17% isolated). With sodium hydride in refluxing tetrahydrofuran the percentage of dienyl ketones rose to ca 90%. Isomerically pure samples of 13a and 14a were obtained by thermal rearrangement of neutral 4a (205°C, 2 hr, 85%) and 7 (205°, 3 hr, 86%), respectively. These observations establish that the fraction of rearrangement which passes through the oxy-Cope pathway increases in both the a and b series as the donor properties of the oxygen atom are decreased ($K^+ \rightarrow Na^+ \rightarrow H$) and the rate of isomerization falls off (Table I). Accordingly, the list of competing reactions which may be subject to acceleration via anionic substituents is further expanded.

To enable a comparative assessment of intra- versus intermolecular oxyanionic influences to be made, the methyl ether of 4a was prepared. Exposure of this methoxycyclononatriene to 2 equiv of potassium ethoxide in THF for 3 hr resulted in less than 10% conversion to 7-OCH_3. Although the efficiency of this [1,3]-hydrogen shift could be enhanced by the addition of 18-crown-6 (2 hr at -25°C; ca 90% conversion), neither set of conditions led to loss of starting material with the rapidity (qualitative studies only) observed in the case of 4a-O^-K^+.

When attention was directed to 5, the dienol was also noted to be somewhat more sluggish than 4a in its anionic response. For example, with potassium hydride in tetrahydrofuran it was necessary to heat the reaction mixture at the reflux temperature for ca 7 hr to achieve the consumption of 5. The action of sodium hydride in refluxing tetrahydrofuran for 24 hr had no effect. In the first experiment, a major product identified as 16 resulted (65%).[17] This structural assignment rests upon its conversion to Diels-Alder adduct 17 whose spectral features are unequivocal.[18] The formation of 16 is thought to arise by disrotatory cyclization of cyclononatriene 15, this intermediate materializing as a consequence of base-promoted dehydration of 5.

The present results demonstrate that anionic oxy-Cope rearrangement within the tertiary cis^3-2,4,7-cyclononatrienyl alkoxides becomes progressively less favored relative to [1,3]-hydrogen shift as charge separation is enhanced. Such systems find it more kinetically

feasible to undergo intramolecular abstraction of a doubly allylic ring proton when the basicity



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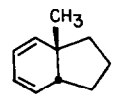

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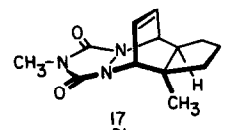

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of the alkoxide anion becomes sufficiently heightened by charge separation. In the conjugate base of 5, the comparable transannular proton is less acidic, and more forcing conditions are necessary to induce its abstraction. Clearly, these higher temperatures are also more conducive to promoting dehydration, a phenomenon not encountered with 5. Although the scope of our effort has been limited for the present to medium-ring compounds, at least two important points emerge: (a) conversion of structurally embellished 1,5-dien-3-ols to their alkoxides need not result uniquely in enhancement of the rate of oxy-Cope rearrangement; other reaction pathways may also become accelerated, and to a higher level; (b) in such circumstances, the Na^+ salt may exhibit chemistry different from that of the K^+ alkoxide, and investigation of both species is warranted.[19]

References and Notes

(1) (a) Evans, D. A.; Nelson, J. V. J. Am. Chem. Soc. 1980, 102, 774 and pertinent references cited therein; (b) Evans, D. A.; Baillargeon, D. J.; Nelson, J. V. ibid. 1978, 100, 2242. (2) Paquette, L. A.; Crouse, G. D.; Sharma, A. K. J. Am. Chem. Soc. 1980, 102, 3972. (3) (a) Thies, R. W.; Seitz, E. P. J. Chem. Soc. Chem. Commun. 1976, 816; (b) Wilson, S. R.; Mao, D. T. ibid. 1978, 479; Tetrahedron Lett. 1977, 2559; (c) Thies, R. W.; Seitz, E. P. J. Org. Chem. 1978, 43, 1050; (d) Wilson, S. R.; Misra, R. N. ibid. 1978, 43, 4903; (e) Thies, R. W.; Meshgini, M.; Chiarello, R. H.; Seitz, E. P. ibid. 1980, 45, 185. (4) Papies, O.; Grimme, W. Tetrahedron Lett. 1980, 2799. (5) Still, W. C. J. Am. Chem. Soc. 1977, 99, 4186. (6) Jung, M. E.; Hudspeth, J. P. J. Am. Chem. Soc. 1980, 102, 2463. (7) ^{1}H NMR ($CDCl_3$, δ) 6.6-5.5 (series of m, 6H), 3.32 (d, J = 5 Hz, 2H), and 2.76 (t, J = 6 Hz, 2H); $\lambda_{max}^{95\%\ EtOH}$ 277 nm (ε 3400). (8) 4a: ^{1}H NMR ($CDCl_3$, δ) 6.1-5.2 (series of m, 6H), 3.0-2.3 (series of m, 5H), and 1.38 (s, 3H); $\lambda_{max}^{95\%\ EtOH}$ 220 sh nm (ε 3500). 4b: ^{1}H NMR ($CDCl_3$, δ) 6.1-5.2 (series of m, 6H), 3.0-2.2 (series of m, 4H), 1.65 (q, J = 7 Hz, 2H), and 0.98 (t, J = 7 Hz, 3H); $\lambda_{max}^{95\%\ EtOH}$ 220 sh nm (ε 3000). (9) Paquette, L. A.; Ley, S. V.; Traynor, S. G.; Martin, J. T.; Geckle, J. M. J. Am. Chem. Soc. 1976, 98, 8162. (10) Mp 55-56°C; ^{1}H NMR ($CDCl_3$, δ) 6.0-5.1 (series of m, 6H), 2.87 (t with additional coupling, J = 6 Hz, 2H), 2.48 (dd, J = 8 and 1 Hz, 2H), 1.8 (s, 1H), and 1.45 (s, 3H); $\lambda_{max}^{95\%\ EtOH}$ 235 nm (ε 5100). (11) When the reaction mixture was processed with deuterium oxide, no deuterium incorporation on carbon was seen. (12) ^{1}H NMR ($CDCl_3$, δ) 6.35 (d, J = 12 Hz, 1H), 6.0-5.2 (series of m, 5H), 5.15 (s, 1H), 4.75 (s, 1H), 3.1 (d, J = 7 Hz, 2H), and 2.9 (t, J = 6 Hz, 2H). (13) ^{1}H NMR ($CDCl_3$, δ) 6.05-5.6 (series of m, 5H), 3.2 (d, J = 8 Hz, 2H), 2.85 (d, J = 6 Hz, 2H), and 1.88 (s, 3H); $\lambda_{max}^{95\%\ EtOH}$ 277 nm (ε 7100). (14) Dauben, W. G.; Michno, D. M. J. Org. Chem. 1977, 42, 682. (15) ^{1}H NMR ($CDCl_3$, δ) 6.6-5.7 (series of m, 5H), 3.3 (d, J = 6 Hz, 2H), 2.8 (d, J = 6 Hz, 2H), and 1.88 (s, 3H); $\lambda_{max}^{95\%\ EtOH}$ 286 nm (ε 5400). (16) ^{1}H NMR ($CDCl_3$, δ) 6.3-5.6 (series of m, 5H), 3.3-2.9 (m, 4H), and 1.88 (s, 3H); $\lambda_{max}^{95\%\ EtOH}$ 250 nm (ε 8900). (17) ^{1}H NMR ($CDCl_3$, δ) 5.9-5.25 (m, 4H), 2.62 (m, 1H), 2.3-1.2 (series of m, 6H), and 1.0 (s, 3H). (18) Mp 104-106°C; ^{1}H NMR ($CDCl_3$, δ) 6.3 (m, 2H), 4.72 (m, 1H), 4.53 (dd, J = 3 and 1 Hz, 1H), 3.0 (s, 3H), 2.3-0.95 (series of m, 7H), and 1.28 (s, 3H)
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