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Geometric Dependence to Long-Range Interaction of Fused Cyclopropane Rings in Tris-σ-homotropylium Cations

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Abstract: Solvolysis of *syn,anti,anti*-trishomocycloheptatrienyl 3,5-dinitrobenzoate (**10**-ODNB) in 80% aqueous acetone produces the starting alcohol **10** and its epimer (**12**) without disruption of the three cyclopropane rings. Comparable treatment of the anti,anti,anti derivative (**12**-ODNB) afforded the same two products in comparable ratios. Since methanolysis led to the corresponding methyl ethers, it is clear that *O*-alkyl cleavage in these examples does not result in structural isomerization. A quite different profile was observed with the *syn,anti,syn*- (**17**-ODNB) and *anti,anti,syn*-trishomocycloheptatrienyl 3,5-dinitrobenzoates (**19**-ODNB). In both instances, ring opening occurred exclusively to give *cis,cis,anti*-bicyclo[7.1.0]deca-4,7-dien-2-ol (**20**), *cis,cis,trans*-2,5,8-cyclodecatrien-1-ol (**22**), and their respective dinitrobenzoates. The rate constants and thermodynamic parameters for all four trishomocycloheptatriene isomers were also experimentally determined. Because of extensive internal return in the case of **10**-ODNB, a triangular kinetic scheme requiring computer iteration was set up and solved. The entire spectrum of kinetic studies shows the relative reactivity gap to be a factor of more than 10^2, with **10**-ODNB ionizing more rapidly than the remaining three, which show closely comparable rate profiles. Noteworthily, all four systems are significantly less reactive than other known biscyclopropylcarbinyl systems. The mechanistic schemes which can be delineated on the basis of these data and deuterium isotope labeling, particularly as they pertain to dihedral-angle relationships of leaving groups to neighboring cyclopropane rings and to possible σ trishomoaromaticity, are discussed.

Our investigations of the possible generation of trishomotropylium cations have so far focused predominantly on the "π approach" involving **1** as substrate.[1,2] Owing to existing geometric constraints in **2** which limit the dihedral angles attainable by the p orbitals of the allyl cation moiety and the pair of rearside π bonds, the olefinic centers appear incapable of entering into homoconjugative charge delocalization to produce **3**. It is not known whether there also exists an electronic

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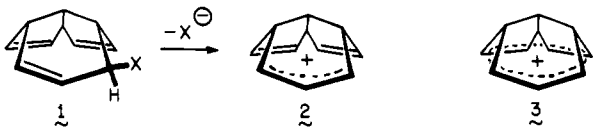


impedance to formation of this "anchored" trishomotropylium species (**3**).[3] Relevantly, earlier studies by several groups have shown that twofold interruption of the 6π7C tropylium topology does not seriously disrupt charge delocalization under the proper circumstances.[4-8]

These discoveries have stimulated evaluation by us of the complementary "σ approach" to various trishomotropylium cations. Particular interest is attached to the three pairs of epimeric substrates **4–6,** for they encompass the complete

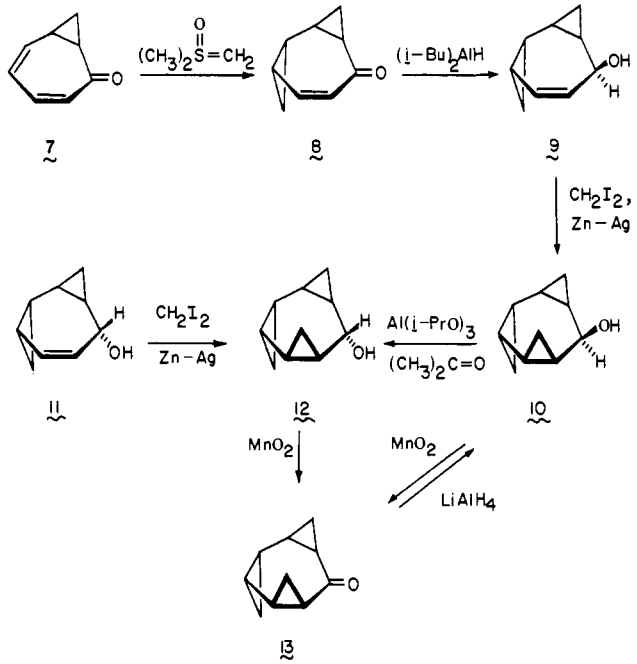
range of distinct geometric arrangements which can be adopted by the methylene groups, Through direct incorporation of stereochemical features into the carbocation precursors, a more exhaustive assessment of the stereoelectronic requirements for σ trishomoaromaticity[9] is made possible.

To the present, synthetic developments have permitted access to the four compounds defined by **4** and **5**. Derivatives of the all-syn framework **6** have disappointingly not yet yielded to ready synthesis. Nonetheless, the chemical behavior of **4** and **5** makes quite clear certain consequences of divergent "bent-bond" arrangements and leaving-group stereochemistries on the ability of three neighboring laterally fused cyclopropane rings, physically held in a cyclic array, to enter into mutual interaction,

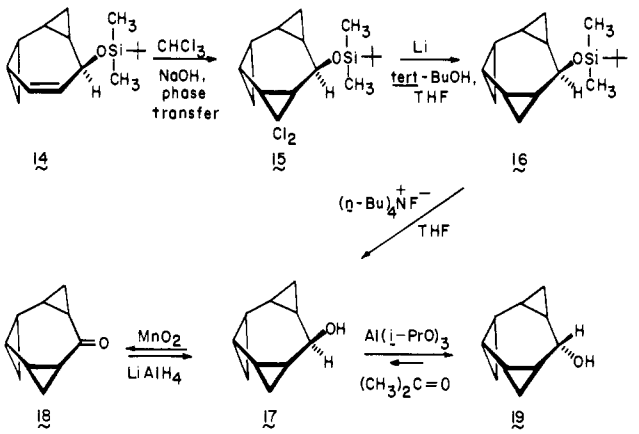
Results

Synthetic Considerations. Homotropone **7,** presently available in reasonably large quantities by chemical modification of 1,5-cyclooctadiene,[10] was converted to *anti*-2,4-bishomotropone (**8**) and *anti,anti*-2,4,6-trishomotropone (**13**) by suitable modification of the procedure originally developed by Kitahara and co-workers.[11] Reduction of **8** with diisobutylaluminum hydride produced in high yield a mixture of

Scheme I



Scheme II



two epimeric alcohols in a ratio of 18:1. The major isomer was purified by crystallization and identified as **9** on the basis of spectral comparisons with an authentic sample.[8c] Since **8** adopts a rigid conformation having its two cyclopropane rings projected equatorially, a strong kinetic preference for pseudoequatorial delivery of hydride is seen to be operative. Alcohol **9** did not readily undergo Simmons–Smith cyclopropanation (Scheme I). A multicomponent mixture was invariably obtained from which **10** could be isolated only by preparative-scale VPC. A solution to the availability of **10** was resolved when it was discovered that **13** was cleanly (in >95% purity) reduced to this alcohol with lithium aluminum hydride.

Structural assignment to **10** is founded upon ^1H and ^{13}C NMR spectral data and its chemical behavior. The >C*H*OH proton appears as a doublet of triplets (J = 9 and 4 Hz) at δ 4.33 in $CDCl_3$ solution. The proton-decoupled carbon spectrum features only six lines. Exposure of **10** to aluminum isopropoxide and a small quantity of acetone resulted in equilibration with almost complete conversion to **12**. This route to the equatorial alcohol was highly serviceable, especially since Simmons–Smith cyclopropanation of **11**[8c] was determined to give **12** only in low (38%) yield. The α-hydroxyl proton of **12** is seen as a highly shielded triplet (J = 8 Hz) at δ 2.43. As in the case of **10,** the ^{13}C NMR spectrum consists of six lines. Additionally, both alcohols could be readily oxidized to **13** with manganese dioxide.

Stereochemically pure **17** was obtained by initial conversion of **9** to its *tert*-butyldimethylsilyl ether, followed by dichlorocarbene addition under phase-transfer conditions, reductive dechlorination, and treatment with fluoride ion (Scheme II). As a consequence of the steric bulk of the silyl blocking group, a single isomer of trishomocycloheptatriene **15** was produced. That entry of the dichlorocarbene had occurred anti to the oxygen atom was confirmed by an examination of the ^{13}C NMR spectrum of **16,** which contains 14 peaks. The >C*H*OH proton of **17** is seen as a characteristic multiplet with a chemical shift of δ 4.42. Manganese dioxide oxidation of **17** afforded *anti,syn*-2,4,6-trishomotropone (**18**).

Reduction of this ketone with a variety of reagents did not proceed with stereoselectivity adequate for our synthetic purposes. With lithium aluminum hydride, for example, conversion to a 1:1 mixture of **17** and **19** was observed. Both sodium borohydride and diisobutylaluminum hydride gave rise to a somewhat higher preponderance of the undesired **17** (2:1 and 4.5:1, respectively). However, epimerization of **17** with aluminum isopropoxide in the predescribed manner returned a mixture highly enriched in **19** (80%). After conversion of this mixture to the 3,5-dinitrobenzoates and fractional recrystallization, quantities of **19**-ODNB of ca. 98% purity could be obtained. Saponification of this derivative gave essentially pure **19**. The α-hydroxyl proton of this isomer is seen as a broadened

Table I. Solvolysis Rate Calculation for **10**-ODNB in 80% Aqueous Acetone at 40.0 °C

Time, s	mL of 0.0100 N NaOH-H_2O	[HODNB], M	$[HODNB]_\infty - [HODNB]_t$, M	ln X^a	ln C^b
2500	0.115	0.001 15	0.010 81	0.101 10	0.072 65
4300	0.161	0.001 61	0.010 35	0.144 58	0.119 89
6100	0.188	0.001 88	0.010 08	0.171 02	0.163 07
7900	0.219	0.002 19	0.009 77	0.202 25	0.202 40
11500	0.272	0.002 72	0.009 24	0.258 03	0.270 36
15100	0.312	0.003 12	0.008 84	0.302 28	0.325 58
22300	0.400	0.004 00	0.007 96	0.407 14	0.405 29
∞	1.196	0.011 96			

[a] $X = [HODNB]_\infty/([HODNB]_\infty - [HODNB]_t)$. [b] Computer-derived values of $(k_1 + k_2 - k_3)/(k_2e^{-k_3t} + (k_1 - k_3)e^{-(k_1+k_2)t})$ having minimal total absolute error in relation to X.

Table II. Solvolysis Rate Calculation for **10**-ODNB in 80% Aqueous Acetone at 60.0 °C

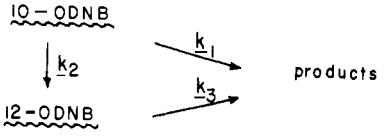
Time, s	mL of 0.0100 N NaOH-H_2O	[HODNB], M	$[HODNB]_\infty - [HODNB]_t$, M	ln X^a	ln C^b
500	0.228	0.002 28	0.010 18	0.202 10	0.163 06
1100	0.341	0.003 41	0.009 05	0.319 76	0.319 35
1700	0.356	0.003 56	0.008 90	0.336 47	0.437 08
2300	0.435	0.004 35	0.008 11	0.429 43	0.522 81
3860	0.560	0.005 60	0.006 86	0.596 82	0.644 91
4700	0.616	0.006 16	0.006 30	0.681 97	0.675 49
6500	0.724	0.007 24	0.005 22	0.870 03	0.706 19
∞	1.246	0.012 46			

[a] $X = [HODNB]_\infty/([HODNB]_\infty - [HODNB]_t)$. [b] Computer-derived values of $(k_1 + k_2 - k_3)/(k_2e^{-k_3t} + (k_1 - k_3)e^{-(k_1+k_2)t})$ having minimal total absolute error in relation to X.

doublet (J = 7 Hz) at δ 3.60; the upfield shift relative to its counterpart in **17** is, of course, a direct consequence of its axial projection into a region of the molecule where the shielding anisotropies of the three cyclopropane rings are exerting their effects. Additional supportive evidence for the assignments to **17** and **19** comes from their ten-line ^{13}C NMR spectra, which unquestionably reveal the lack of a symmetry element.

Each 3,5-dinitrobenzoate was obtained by conventional reaction with 3,5-dinitrobenzoyl chloride in dry pyridine.

Kinetic Studies. The rates of solvolysis of the four 3,5-dinitrobenzoates were determined in 80% aqueous acetone using a standard titrimetric procedure. The titrimetric rate constant for **10**-ODNB at 40 °C was observed to drift slowly downward from 4.00×10^{-5} to 1.53×10^{-5} s^{-1} through approximately 1 half-life. Hydrolysis of this compound at 60 °C for 4 h in the presence of 2,6-lutidine gave a mixture of **10**-ODNB (15%), **12**-ODNB (5%), **10** (28%), and **12** (52%). The operation of an internal return process was thereby revealed, Subsequently, the internal return product of this reaction (**12**-ODNB) was independently shown to solvolyze at a slower rate than **10**-ODNB. The gradual falling off of rate with time has been attributed to this causative factor. The general mechanistic profile followed by **10**-ODNB is therefore one which encompasses the triangular kinetic scheme shown below,[12,14] where k_1 and k_3 represent the first order rate constants for conversion of **10**-ODNB and **12**-ODNB, respectively, to alcohol products



and k_2 is the rate of epimerization of starting material. The sum of k_1 and k_2 comprises the rate constant k_t for total disappearance of **10**-ODNB.

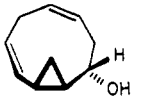
The best values of k_1, k_2, and k_3 were obtained by determining k_3 directly by experiment, estimating k_1 from a plot of the instantaneous rate constants vs. time and extrapolated to zero time,[12] and evaluating k_2 with the aid of an appropriate iterative computer program.[13c,15] Sample results are provided in Tables I and II. Very large uncertainties are apparent, but sufficient accuracy is considered present to make approximate comparison with the other three isomers.

On the other hand, the infinity titers for **17**-ODNB and **19**-ODNB were only 85–90% of the theoretical values after 20 and/or 40 half-lives. With application of the experimental infinity values, the titrimetric rate constants for these esters proved to be constant (correlation coefficient 0.993–0.999) through approximately 1.5 half-lives. The rate constants and thermodynamic parameters for all four substrates are collected in Table III.

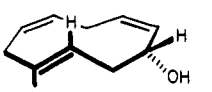
Product Determinations. After preparative-scale solvolysis of the 3,5-dinitrobenzoates in 80% aqueous acetone containing 2,6-lutidine for approximately 10 half-lives, the product mixtures were analyzed by VPC and the individual components were subsequently isolated by preparative thin layer chromatography. Identification of the products was achieved by suitable comparison of IR and ^1H NMR spectra.

As concerns **10**-ODNB and **12**-ODNB, the two major products were shown to be **10** and **12**. The relative ratios of these alcohols appear to be independent of the stereochemistry of the starting dinitrobenzoate (Table IV). Little tendency for skeletal rearrangement was noted.

In contrast, the solvolyses of **17**-ODNB and **19**-ODNB resulted exclusively in the isolation of rearranged alcohols and their corresponding 3,5-dinitrobenzoates (from internal return) (Table V). The alcohols were determined to be **20** and **21**.[16]



20



21

Additionally, **21** was obtained in good yield by acid-catalyzed isomerization of **17**. Saponification of the purified ester products afforded **20** and **21**, respectively; the structural interrelationships of all the products were thereby established. Fivefold TLC purification revealed that **19**-ODNB also gave

Table III. Rate Constants and Activation Parameters Obtained from Solvolysis of **10**-, **12**-, **17**-, and **19**-ODNBs

compd	rate constant designation	T, °C	$k \times 10^6$, s^{-1}	ΔH, kcal/mol (60 °C)	$\Delta S^{\ddagger}$, eu (60 °C)	k_{rel} (60 °C)
10-ODNB	k_i	40.0	69.4	23.5	−2.1	280
		50.0	477			
		60.0	703			
	k_1	40.0	26.5	26.2	2.3	
			30.7			
		50.0	160			
			160			
		60.0	350			
			357			
	k_2	40.0	37.1	21.9	−8.3	
			44.5			
		50.0	317			
			317			
		60.0	350			
			350			
	k_3	(see under **12**-ODNB)				
12-ODNB	k_1	60.0	2.37	28.4	0.79	1
			2.67			
		71.5	10.3			
			11.0			
		79.5	27.8			
			29.3			
		40.0[a]	0.152			
		50.0[a]	0.643			
17-ODNB	k_1	60.0	6.46	26.3	−3.4	2.5
			6.53			
		71.5	25.3			
			27.9			
		79.5	60.8			
			62.1			
19-ODNB	k_1	60.0	4.94	25.7	−5.8	2
			5.24			
		71.5	18.4			
			19.1			
		79.5	46.0			
			46.4			

[a] Extrapolated values calculated on the basis of the activation parameters.

Table IV. Solvolysis Products of **10**-ODNB and **12**-ODNB[a]

compd	amt, mg	reaction condn	quantity isolated, mg (%)	products, mg (%)			
				10	**12**	**10**-ODNB	**12**-ODNB
10-ODNB	90	80 °C, 120 h, 2,6-lutidine (0.5 mL), 80% aq acetone (20 mL)	35 (72)	15 (54) (60)[b]	13 (46) (40)[b]		
	100	60 °C, 12 h, 2,6-lutidine (0.5 mL), 80% aq acetone (20 mL)	55 (84)	18 (49) (59)[b]	17 (45) (41)[b]		5 (6)
	99	60 °C, 4 h, 2,6-lutidine (0.5 mL), 80% aq acetone (20 mL)	54 (84)	8 (28)	14 (52)	9 (15)	4 (5)
12-ODNB	133	80 °C, 72 h, 2,6-lutidine (0.5 mL), 80% aq acetone (20 mL)	47 (58)	24 (70) (53)[b]	10 (30) (27)[b]		(20)[c]

[a] Products were isolated by preparative thin layer chromatography on silica gel (elution with hexane–ether, 4:1). [b] Product ratios as determined by VPC analysis on a 20% Apiezon L column (9 ft × 0.25 in.) at 180 °C. [c] Rearrangement products.

rise to a third 3,5-dinitrobenzoate (~4%) which has remained unidentified. Independent control experiments showed all four trishomocycloheptatrienols, **20**, and **21** to be stable to the reaction conditions. On this basis, it is of some interest that the relative amounts of **20** and **21** produced from **17**-ODNB and **19**-ODNB are strikingly similar, whereas the distributions of the corresponding dinitrobenzoates are not.

Under methanolysis conditions, all four substrates gave methyl ethers as major products. In the studies involving **12**-ODNB and **19**-ODNB, small amounts of alcohol and methyl 3,5-dinitrobenzoate, evidently arising from low levels of competitive acyl-oxygen fission, were also detected. The pertinent data are summarized in Tables VI and VII.

Discussion

Rate Comparisons. The topology of the *anti,anti*-trishomocycloheptatriene framework common to both **10** and **12** is unique in that all three cyclopropyl groups can adopt an

Table V. Solvolysis Products of **17**-ODNB and **19**-ODNB[a]

compd	amt, mg,	reaction condn	quantity isolated, mg (%)	Products, mg (%) **20**	**21**	**20**-ODNB	**21**-ODNB	other
17-ODNB	202	80 °C, 31 h, 2,6-lutidine (0.5 mL), 80% aq acetone (20 mL)	108 (54)	10 (21)	11 (23)	61 (56)		
	250	80 °C, 42 h, 2,6-lutidine (0.5 mL), 80% aq acetone (20 mL)	151 (94)	18 (25)	23 (33)	50 (31)	18 (11)	
19-ODNB	202	80 °C, 42 h, 2,6-lutidine (0.5 mL), 80% aq acetone (20 mL)	121 (68)	16 (27)	22 (37)	13 (9)	32 (23)	6 (4)

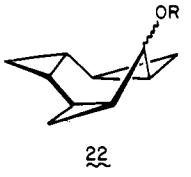
[a] Products were isolated by preparative thin layer chromatography on silica gel (elution with hexane–ether solvent combinations: 90/10, 80/20, 70/30, and 60/40).

Table VI. Methanolysis Results[a]

compd	amt, mg	reaction condn	quantity isolated, mg	products
10-ODNB	19	80 °C, 96 h, 2,6-lutidine (0.1 mL), methanol (10 mL)	8.3	**10**-OMe (3.5 mg, 58%), **12**-OMe (2.4 mg, 42%)[b]
12-ODNB	35	80 °C, 95 h, 2,6-lutidine (0.1 mL), methanol (10 mL)	16	**10**-OMe (4.1 mg, 60%), **12**-OMe (2.8 mg, 40%), CH_3ODNB (3 mg)[c]
17-ODNB	57.6	80 °C, 72 h, 2,6-lutidine (0.1 mL), methanol (10 mL)	28	**20**-OMe (5.3 mg, 55%) **21**-OMe (4.7 mg, 41%), **17** (1%), others (3%)[d]
	114	80 °C, 72 h, 2,6-lutidine (0.5 mL), methanol (20 mL)	35	**20**-OMe (13 mg, 56%), **21**-OMe (10 mg, 44%)
19-ODNB	27.5	80 °C, 96 h, 2,6-lutidine (0.1 mL), methanol (5 mL)	11	**20**-OMe (2.5 mg, 38%), **21**-OMe (3.1 mg, 48%), **19** (5%), others (9%)[d]
	105	80 °C, 100 h, 2,6-lutidine (0.5 mL), methanol (20 mL)	38	**20**-OMe (15 mg, 54%), **21**-OMe (13 mg, 46%), others (1%)

[a] Products were isolated by preparative thin layer chromatography on silica gel unless otherwise indicated. [b] VPC analysis indicated this ratio to be 67:33. [c] Isolated as a crystalline solid, mp 105–108 °C (lit. mp 109 °C). [d] The yields cited were obtained by VPC analysis (9 ft × 0.25 in. Apiezon L column, 180 °C).

"equatorial" relationship relative to the central seven-membered ring (cf. **22**). Molecular models show that this conformation is relatively free of serious nonbonded interactions, especially when compared to the inverted form **23**. In the latter



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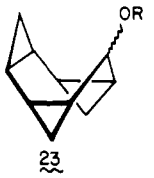
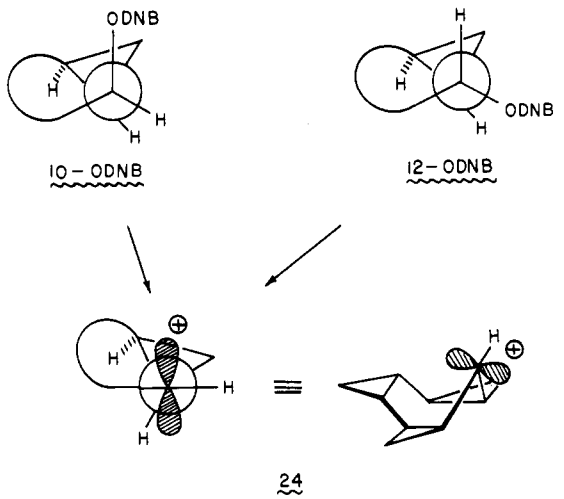


23

structure, various pairs of hydrogen atoms are brought into very close proximity, especially the endo cyclopropyl protons located on the underside of the molecule (as drawn). Because of the magnitude of these nonbonded interactions, distortions toward a somewhat less sterically demanding planar conformation are conceivable. All in all, however, **10** and **12** can be expected to exhibit a strong propensity to maintain the lower energy conformation **22**, as has been previously demonstrated to be favored by the parent hydrocarbon.[17]

These structural considerations suggest that the ionizations of **10**-ODNB and **12**-ODNB will result in generation of the cyclopropylcarbinyl cation **24**, which is geometrically constrained to an angle (~70°) more closely akin to the perpendicular arrangement as long as the triad of cyclopropane rings instills sufficient rigidity into the cycloheptane ring to maintain the approximate ground-state conformation (Scheme III). The normal preference of cyclopropylcarbinyl cations is for the

Scheme III



24

bisected geometry where conjugative stabilization reaches a maximum. Usually, this is reflected in pronounced kinetic acceleration. Examples are known where cyclopropylcarbinyl cations with rigidly fixed perpendicular geometry have been generated.[18] Not only is resonance interaction between the three-membered ring and the developing cation center inhibited, but adverse inductive effects also become paramount. Rate depressions of several powers of ten and an absence of rearrangement products are observed in such circumstances.

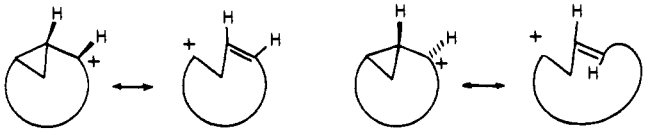
Table VII. Spectral Data of the Methyl Ether Products

compd	method	yield, %	*m/e* obsd[a]	ν_{max} (neat), cm^{-1}	^1H NMR, δ ($CDCl_3$, 60 MHz) olefinic	>C*H*O-	methylene	methoxyl	cyclopropane
10-OMe	A	77	164.1205	2985, 1090, 815		3.83 (t, *J* = 4 Hz, 1 H)		3.33 (s, 3 H)	1.3–0.3 (m, 11 H) 0.1–0.0 (m, 1 H)
12-OMe	B	87	164.1204	2985, 1085, 980, 810		2.2 (m, 1 H)		3.40 (s, 3 H)	1.3–0.0 (m, 12 H)
17-OMe	B	93	164.1205	2990, 1085, 825		3.80 (br d, *J* = 4 Hz, 1 H)		3.50 (s, 3 H)	1.4–0.4 (m, 11 H) 0.2–0.0 (m, 1 H)
19-OMe	B	*b*	164.1204	2985, 1090, 815		3.10 (d, *J* = 6 Hz, 1 H)		3.43 (s, 3 H)	1.6–0.2 (m, 12 H)
20-OMe	A	74	164.1205	2925, 1085, 910[c]	6.0–5.2 (m, 4 H)	3.4 (m, 1 H)	2.9–2.0 (m, 4 H)	3.27 (s, 3 H)	2.7–0.6 (m, 3 H) 0.4–0.0 (m, 1 H)
21-OMe	A	84	164.1205	2920, 1105, 970, 705[c]	5.7–5.1 (m, 6 H)	4.1–3.7 (m, 1 H)	3.1–1.9 (m, 6 H)	3.28 (s, 3 H)	

[a] Calcd for $C_{11}H_{16}O$, *m/e* 164.1201. [b] Prepared from a mixture of **17** and **19** and purified by preparative VPC. [c] Determined in CCl_4 solution.

On this basis, **10**-ODNB and **12**-ODNB, if adequately locked in a conformational sense, should be subject to substantive kinetic rate retardation and to formation of products possessing the intact *anti,anti*-trishomocycloheptatriene skeleton. The latter observation has already been made. That the kinetic behavior of this pair of 3,5-dinitrobenzoates is suppressed becomes immediately obvious upon inspection of the examples given in Figure 1.

Trishomotropilidene **10**-ODNB solvolyzes more rapidly than its epimer **12**-ODNB by a factor (860) whose value is substantially larger than that encountered in the somewhat structurally related *exo*- and *endo*-bicyclo[5.1.0]oct-2-yl 3,5-dinitrobenzoate isomer pair.[22] The latter exo derivative is further differentiated by its tendency to undergo rearrangement predominantly by means of a cyclopropylcarbinyl–cyclopropylcarbinyl pathway, with negligible conversion to a homoallylic ion. One reason for **10**'s high rate may be the conformationally enforced axial orientation of the leaving group whose nonbonded interactions with H_4 and H_5 are relieved in progressing to carbonium ion **24**. However, it seems unlikely that this factor alone could give rise to a 280-fold kinetic difference, if cyclohexyl systems serve as relevant analogy.[23] On the other hand, the relative orientations between both *flanking* internal (i.e., more highly substituted) cyclopropane bent σ bonds and the leaving group seem to offer a rational explanation of the kinetic results. As seen in the Newman projections (Scheme III), the electron densities in these bonds are more available for anchimeric assistance to loss of the leaving group in **10**-ODNB. Phrased differently,[24] there is available to **10** resonance forms (cf. A ↔ B) which attempt



A B C D

to place a cis double bond in an eight-membered ring. In the case of **12**, the double bond would be trans (C ↔ D) and consequently much less energetically desirable. This argument agrees as well with the customary assumptions that cyclopropane inductive effects are constant regardless of the orientation angle and that a smooth, continuous geometric function governs cyclopropylcarbinyl reactivity.[18c,25]

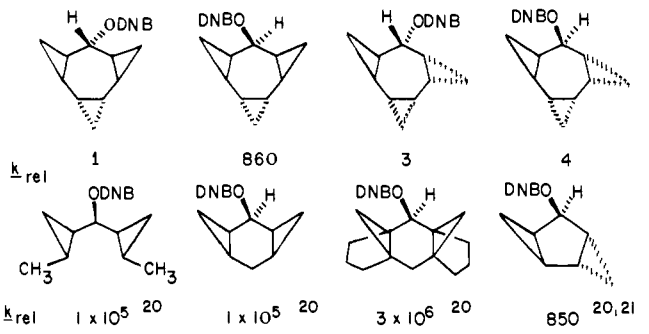
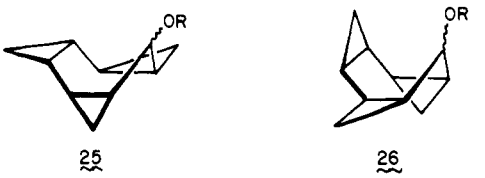


Figure 1. Relative rates of solvolysis of selected biscyclopropylcarbinyl 3,5-dinitrobenzoates in 80% aqueous acetone at 25 °C.[19]

Using similar lines of reasoning, we see that the *syn,anti*-trishomocycloheptatriene ring system common to **17** and **19** has a cyclopropyl triad arrangement which causes conformation **25** to be more stable. In these circumstances, the leaving group is flanked by both an "equatorial" and an "axial" three-membered ring. Ring flipping within **25** to generate **26**



25 26

does not generate nonbonded interactions as severe as those in **23**; however, they are not negligible and this process is clearly disfavored.

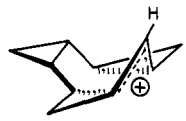
As can be seen from models, both **17**-ODNB and **19**-ODNB possess the ability to attain a "bisected" conformation between the leaving group and at least one cyclopropane ring with a modicum of structural readjustment. Given the energy differences which exist between bisected and perpendicular cyclopropylcarbinyl cations, enhanced solvolytic behavior should in principle be observed in these two examples. However, the rate constants prove to be closely comparable to that found for **12**-ODNB (Figure 1). These results are reminiscent of the behavior of the epimeric spirocyclic *p*-nitrobenzoates **27**.[18b]

In the present instance, the tendency of **17** and **19** to rearrange is viewed as unusual. There can be little doubt that this

27

occurs because the orbital alignment is proper and because these isomers are significantly more strained.

Product Studies. The conversion of **10**-ODNB and **12**-ODNB to a similar set of products argues for the intervention of a common intermediate in the solvolysis reactions. The experimental data suggest that this species is carbocation **24,** which is efficiently trapped by nucleophiles more rapidly than possible rearrangement processes. Of interest is the finding that **10** is the alcohol product which predominates, despite its clearly less stable nature (cf. earlier equilibration study). The process leading to **10** is equivalent to capture of **24** from its more hindered upper surface (as drawn above). This selectivity would appear to result from electronic delocalization into the proximal cyclopropane rings within **24,** as illustrated most concisely by **28.** This factor has previously been cited as being



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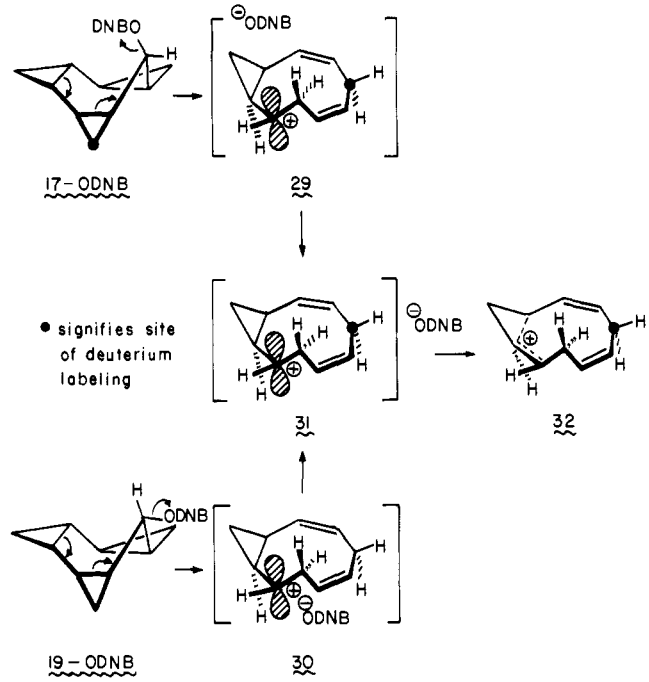
chiefly responsible for the somewhat accelerated ionization rate of **10**-ODNB. More extensive delocalization to generate a trishomotropylium cation is considered to be unimportant. A boat conformation such as that present in **24** = **28** is viewed to be too highly folded to permit the internal cyclopropane bond interconnecting C_4 and C_5 to become properly aligned for orbital interaction. This would appear to be realizable only when the seven-membered ring adopts a more shallow boat topology such that the pendant cyclopropanes assume more or less pseudoaxial positions.

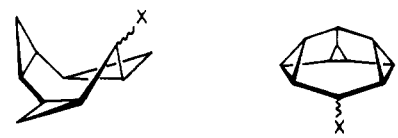
Both **17**-ODNB and **19**-ODNB are seen to solvolyze to the same rearranged alcohols **20** and **21** and to their 3,5-dinitrobenzoates. The nearly identical nature of the alcohol product mixtures points to the intervention of a common cationic intermediate or pair of intermediates in this reaction mode. On the other hand, **20**-ODNB and **21**-ODNB are isolated in dissimilar ratios (3:1 vs. 1:2), thereby signaling the fact that different intimate ion pairs are likely formed first. These findings are consistent with initial ionization of **17**-ODNB and **19**-ODNB predominantly to **29** and **30,** respectively (Scheme IV). The twofold cyclopropane ring opening is made possible by the enhanced conformational flexibility of these epimers which facilitates access to a somewhat more planar seven-membered ring, and by the cis relationship of two contiguous cyclopropane rings. As noted in the scheme, the specific involvement of these two cyclopropane moieties was clearly established in the case of **17**-ODNB by deuterium labeling as indicated. At the solvent-separated ion pair stage (**31**), water is captured with very high stereoselectivity, presumably because of steric factors. Thus, the related ketone *cis,cis*-bicyclo[7.1.0]deca-4,7-dien-2-one has been shown to undergo lithium aluminum hydride reduction with 98% stereoselectivity to give the epimer of **20**.[16c] That **31** is capable of stereospecific cyclopropylcarbinyl → homoallylic isomerization to give **32** has previously been demonstrated by Winstein and his coworkers.[16] It is, of course, not surprising that the positive charge would want to be delocalized predominantly to the cyclopropyl carbon bearing the vinyl substituent. That alcohol **20** is isolated at all may mean that **31,** as originally produced, is twisted into a conformation not quite favorable to utilization of the more substituted arm of the cyclopropane ring.

Scheme IV



When the four products isolated from solvolysis of **17**-ODNB-d_2 were examined spectroscopically, the site of isotopic labeling was clearly apparent. As concerns **20**-d_2 and its dinitrobenzoate, the upfield portions of their ^{1}H NMR spectra were seen to mirror closely the signals which characterize the four cyclopropyl protons in the protio analogues. In contrast, the patterns associated with the olefinic protons were substantively altered. Additionally, the downfield multiplets due to the doubly allylic and α-hydroxyl protons were reduced from an area of 5 to an intensity of 3. This is as expected for substitution by a pair of deuteriums at the doubly allylic carbon. Spectral analysis of **21**-d_2 and its dinitrobenzoate was greatly facilitated as the result of large alterations in the olefinic proton patterns, of the essentially unperturbed nature of >C*H*OH multiplicity relative to unlabeled **21,** and of a halving in intensity of the doubly olefinic proton multiplet (consult Experimental Section).

The principal objective of this research was to gain insight into the geometric dependence of long-range interaction in potential trishomotropylium cations. The consequences of adopting the geometric arrangements illustrated by **4** and **5** have now been elucidated. Clearly, there exists a geometric deterrent to completely extended cyclic conjugation in these systems and trishomoaromatic ions are not formed. There remains the need to consider the advantages available to the all-cis isomers **6** = **33** and to the related "anchored" homologues **34.** The degrees of conformational freedom available



33 34

to these two systems are enormously different and should prove worthy of scrutiny in view of the recognized dependence of cyclopropyl participation on geometry.

Experimental Section

Infrared spectra were recorded on a Perkin-Elmer Model 467 spectrophotometer. The ^{1}H NMR spectra were determined with Varian T-60 and Bruker HX-90 instruments and apparent splittings are given in all cases. The ^{13}C spectra were also run to the Bruker

spectrometer. Mass spectra were measured with an AEI-MS9 spectrometer at an ionization energy of 70 eV. Preparative scale VPC separations and product distribution analyses were carried out on a Varian Aerograph Model A-90-P3 instrument equipped with thermal conductivity detectors. Microanalytical determinations were performed at the Scandinavian Microanalytical Laboratory, Herlev, Denmark.

***anti*-2,3-Bishomotropone (8).**[11] A magnetically stirred mixture of 2,3-homotropone (**7**,[10] 10.8 g, 90 mmol), trimethyloxosulfonium iodide (29.3 g, 133 mmol), tetra-*n*-butylammonium iodide (3.5 g), dichloromethane (160 mL), and aqueous sodium hydroxide solution (70 g of NaOH in 140 mL of H_2O) was heated at gentle reflux under nitrogen for 2 days. The cooled reaction mixture was diluted with water and continuously extracted with petroleum ether. The organic phase was washed with water, dried, and evaporated. Chromatography of the residue on silica gel gave 3.77 g (31%) of **8** as a colorless oil: ^{1}H NMR (δ, $CDCl_3$) 6.53 (dd, J, = 12 and 7 Hz, 1 H), 5.32 (dd, J = 12 and 1 Hz, 1 H), 2.2–1.1 (series of m, 7H), and 0.72 (m, 1 H).

***syn,anti*-2,4-Bishomocycloheptatrienol (9).** A solution of **8** (7.0 g 52 mmol) in anhydrous ether (300 mL) was cooled to −78 °C and treated with 25% diisobutylaluminum hydride in heptane (50 mL, 176 mmol). The reaction mixture was stirred at −78 °C for 3 h and at room temperature for 1 h prior to the addition of 1 N sodium hydroxide solution (50 mL). After being stirred for 1 h, the inorganic solids were removed by filtration and the filtrate was concentrated. The residual material was crystallized and recrystallized from petroleum ether to give 4.6 g (66%) of **9**, mp 55–56 °C (lit.[8c] mp 57–58 °C).

Simmons–Smith Cyclopropanation of 9. To a mixture of zinc-silver couple (1.3 g) and anhydrous ether (10 mL) was added 2 drops of diiodomethane followed by a solution of **9** (120 mg, 1 mmol) and diiodomethane (2.6 g, 10 mmol) in the same solvent (10 mL) under a nitrogen atmosphere. After being heated at gentle reflux for 8 h, the cooled reaction mixture was decanted into ice-cold saturated ammonium chloride solution. The product was extracted into ether and the combined organic layers were washed with cold saturated ammonium chloride and sodium bicarbonate solutions before drying. Evaporation of the solvent left a yellow oil (110 mg), ^{1}H NMR analysis of which revealed it to be a multicomponent mixture. Through preparative-scale VPC, it proved possible to isolate small amounts of **10**, the spectra of which were superimposable upon those of the sample described below.

***anti,anti,anti*-Trishomocycloheptatrienol (12).** In a 25-mL flask equipped with a dry nitrogen inlet, water-cooled reflux condenser, pressure-equalizing addition funnel, and magnetic stirring bar, diiodomethane (1.34 g, 5.0 mmol) in anhydrous ether (5 mL) was added dropwise to a stirred slurry of zinc–silver couple (650 mg) in ether (10 mL). The mixture was brought to gentle reflux for 15 min. Following the dropwise addition of *anti,anti*-2,4-bishomocycloheptatrienol (**11**,[8c] 209 mg, 1.54 mmol) in ether (5 mL), the slurry was heated at reflux for 12 h and subsequently processed as described above. Recrystallization of the residue from petroleum ether afforded 87 mg (38%) of **12** as a colorless solid: mp 84–87 °C; ^{1}H NMR (δ, CCl_4) 2.62 (br s, 1 H), 2.43 (t, J = 8 Hz, 1 H), 1.25–0.25 (m, 9 H), and 0.25 to −0.25 (m, 3 H); ^{13}C NMR (ppm, $CDCl_3$) 78.8, 22.8, 15.2, 15.0, 13.6, and 10.1; *m/e* calcd 150.1045, obsd 150.1048.

The alcohol was converted to its *p*-nitrobenzoate under standard conditions: colorless solid, mp 143–144.6 °C.

Anal. Calcd for $C_{17}H_{17}NO_4$: C, 68.21; H, 5.73; N, 4.68. Found: C, 67.87; H, 5.89; N, 4.61.

See below for preferred alternative synthesis of **12.**

***anti,anti*-2,4,6-Trishomotropone (13). A. Homologation of 8.** A mixture of oil-free sodium hydride (3.96 g, 81 mmol) and trimethyloxosulfonium iodide (17.4 g, 79 mmol) was treated dropwise with dimethyl sulfoxide (90 mL) at room temperature. After 1 h of stirring, tetrahydrofuran (27 mL) was introduced, the reaction mixture was cooled to 0–5 °C, and precooled solution of **8** (10.0 g 75 mmol) in dimethyl sulfoxide (90 mL) and tetrahydrofuran (27 mL) was added in one portion. Stirring was maintained for 1 h at 0–5 °C, 2 h at room temperature, and 10 min at 40–45 °C before the mixture was poured onto ice and extracted with ether. The organic layer was washed with water, dried, and evaporated to yield a yellow oil (4.8 g). Trituration with petroleum ether afforded 3.9 g (35%) of **13** as a colorless solid: mp 64–65 °C (lit.[11] mp 65 °C); ^{1}H NMR (δ, $CDCl_3$) 2.20 (ddd, J = 8.5, 8.5, and 7.5 Hz, 2 H), 1.1–0.5 (series of m, 9 H), and 0.05 (m, 1 H).

B. Homologation of 7. By a method similar to that utilized above, 220 mg of a 3:2 mixture of **8** and **13** was obtained from 1.94 g (16 mmol) of **7** and 3.52 g (16 mmol) of the oxosulfonium iodide.

When 2,3-homotropone (1.45 g, 12 mmol) was treated with a somewhat greater amount of the oxosulfonium iodide (5.8 g, 26 mmol), a trishomotropone epoxide was isolated (205 mg, 10%, bp 74–75 °C (0.5 mm)); ν_{max} (neat) 3000, 1394, 1320, 1030, 950, 905, and 820 cm^{-1}; ^{1}H NMR (δ, $CDCl_3$) 2.47 (s, 2 H), 1.43 (d of t, J = 8 and 6 Hz, 2 H), and 1.0–0.1 (series of m, 10 H).

Diisobutylaluminum Hydride Reduction of 13. A cold (−78 °C) solution of **13** (120 mg, 0.81 mmol) in anhydrous ether (5 mL) was treated with 2 mL of a 25% solution of diisobutylaluminum hydride in heptane. The reaction mixture was stirred at 78 °C for 2 h and at room temperature for 1 h. Sodium hydroxide solution (2 mL of 1 N) was added and, after 1 h, the inorganic solids were separated by filtration. Concentration of the filtrate gave 120 mg (99%) of a colorless oil, ^{1}H NMR and VPC analysis of which showed it to consist of a 5:1 mixture of **10** and **12.**

Lithium Aluminum Hydride Reduction of 13. To a stirred suspension of lithium aluminum hydride (200 mg, 5.3 mmol) in anhydrous ether (25 mL) was added dropwise a solution of **13** (210 mg, 1.4 mmol) in the same solvent (10 mL). The mixture was stirred at 0 °C for 1 h and at room temperature for 20 h before the excess hydride was carefully decomposed with water (2 mL). Workup in the predescribed manner gave 195 mg (93%) of a colorless oil shown to be **10** of >95% purity: ν_{max} (neat) 3480, 3000, 1450, 1405, 1035, 995, and 885 cm^{-1}; ^{1}H NMR (δ, $CDCl_3$) 4.33 (d of t, J = 9 and 4 Hz, 1 H), 1.67 (br d, J = 9 Hz, 1 H), 1.4–0.4 (series of m, 11 H), and 0.26 (m, 1 H); ^{13}C NMR (ppm, $CDCl_3$) 64.9, 23.0, 16.5, 15.4, 10.7, and 8.0; *m/e* calcd 150.1045, obsd 150.1048.

The *p*-nitrobenzoate was obtained as colorless crystals, mp 102–103 °C.

Anal. Calcd for $C_{17}H_{17}NO_4$: C, 68.22; H, 5.72. Found: C, 67.98; H, 5.71.

The 3,5-dinitrobenzoate was isolated as a pale yellow, crystalline substance, mp 154–155 °C.

Anal. Calcd for $C_{17}H_{16}N_2O_6$: C, 59.30; H, 4.68; N, 8.13. Found: C, 59.51; H, 4.74; N, 7.92.

Epimerization of 10. A 190-mg (1.3 mmol) sample of **10** was heated under reflux for 72 h with aluminum isopropoxide (500 mg) in isopropyl alcohol (20 mL) containing 0.1 mL of acetone. After the usual workup, 188 mg of an oil was obtained, the ^{1}H NMR spectrum of which showed it to be almost completely pure **12.** Crystallization and recrystallization from petroleum ether gave a pure sample (160 mg, 82%) as colorless crystals, mp 90–91 °C; for special data, see above.

The 3,5-dinitrobenzoate was obtained as pale yellow crystals, mp 157–158 °C.

Anal. Calcd for $C_{17}H_{16}N_2O_6$: C, 59.30; H, 4.68; N, 8.13. Found: C, 59.66; H, 4.72; N, 8.18.

Manganese Dioxide Oxidation of 10. In a 200-mL flask equipped with a nitrogen inlet, condenser, and magnetic stirring bar was placed a slurry of **10** (190 mg, 1.3 mmol) and activated manganese dioxide (5 g) in cyclohexane (100 mL). The mixture was heated at reflux for 24 h, cooled, and filtered through a short silica gel column (dichloromethane elution). The eluate was concentrated to give 150 mg (79%) of **13** (95% purity by VPC analysis).

Manganese Dioxide Oxidation of 12. In a 15-mL flask equipped with a nitrogen inlet, condenser, and magnetic stirring bar was placed a slurry of **12** (60 mg, 0.40 mmol) and manganese dioxide (340 mg, 4.0 mmol) in cyclohexane (10 mL). The mixture was heated at reflux for 24 h, cooled, and filtered through a pad of Celite. The inorganic solids were washed with 15 mL of ether. The combined filtrates were concentrated to yield 58 mg (98%) of an off-white solid. Recrystallization from petroleum ether (1 mL) gave 24 mg (41%) of **13,** mp 62.5–63 °C.

***tert*-Butyldimethylsilyl Ether (14) of 9.** *tert*-Butyldimethylsilyl chloride (18.8 g, 0.125 mol) and imidazole (21.2 g, 0.312 mol) were added in rapid succession to a stirred solution of **9** (11.3 g, 0.083 mol) in dry dimethylformamide (150 mL) under nitrogen at 0–5 °C. After 25 h at room temperature, the reaction mixture was poured onto water and ice (500 mL) and the product was extracted into ether. The combined organic layers were washed with 5% hydrochloric acid and water prior to drying. Evaporation of solvent followed by distillation (bp 70–75 °C, 0.05 mm) gave 18.3 g (88%) of **14** as a colorless oil: ν_{max} (neat) 1645, 1250, and 830 cm^{-1}; ^{1}H NMR (δ, $CDCl_3$) 5.63 (dd, J

= 12 and 4 Hz, 1 H), 5.27 (dd, J = 12 and 3 Hz, 1 H), 4.77 (t, J = 3 Hz, 1 H), 1.2–0.6 (m, 7 H), 0.90 (s, 9 H), 0.53 (m, 1 H), and 0.07 (s, 6 H); *m/e* calcd 250.1753, obsd 250.1757.

Dichlorocarbene Addition to 14. Chloroform (36 mL, 0.44 mol) was added dropwise during 4.5 h to a stirred mixture of **14** (18.0 g, 0.072 mol), benzyltriethylammonium chloride (1.0 g), benzene (36 mL), and aqueous sodium hydroxide (45 g of NaOH in 90 mL of H_2O). After being stirred for 43 h, the reaction mixture was poured onto ice and water and the product was extracted into dichloromethane. The combined organic layers were washed with water, dried, and evaporated to give unpurified **15** as a yellow oil (27 g): ν_{max} (neat) 1470, 1460, 1255, and 1075 cm^{-1}; ^1H NMR (δ, $CDCl_3$) 4.07 (br d, J = 8 Hz, 1 H), 1.6–0.5 (series of m, 10 H), 0.93 (s, 9 H), and 0.17 (br s, 6 H).

Reduction of 15. A solution of **15** (19.0 g, 0.057 mol) and *tert*-butyl alcohol (30 mL) in tetrahydrofuran (300 mL) was added dropwise to a rapidly stirred slurry of lithium wire (7.5 g, 0.108 g-atom) cut into small pieces in tetrahydrofuran (150 mL) at a rate sufficient to maintain gentle reflux. The reaction mixture was heated at reflux for 4 h, cooled, and filtered. The inorganic solids were rinsed with petroleum ether (50 mL) and the combined filtrates were washed with water, dried, and evaporated. There was obtained an oily product which was purified by distillation at 80–85 °C (0.1 mm) to give 8.2 g (43%) of **16** as a colorless oil: ν_{max} (neat) 1250 and 830 cm^{-1}; ^1H NMR (δ, $CDCl_3$) 4.35 (br d, J = 6 Hz, 1 H), 1.3–0.4 (series of m, 12 H), 0.93 (s, 9 H), and 0.10 (s, 6 H); ^{13}C NMR (ppm, $CDCl_3$) 68.6, 26.0, 23.4, 21.7, 15.9, 15.1, 14.3, 12.6, 12.4, 9.5, 8.7, −4.3, and −4.9; *m/e* calcd 264.1909, obsd 264.1917.

***syn,anti,syn*-2,4,6-Trishomocycloheptatrienol (17).** Tetra-*n*-butylammonium fluoride (25 g, 0.096 mol) was added to a stirred solution of **16** (5.29 g, 0.02 mol) in tetrahydrofuran (350 mL) under a nitrogen atmosphere. The reaction mixture was heated at reflux for 21 h, cooled, and concentrated. The residual oil was partitioned between water (100 mL) and ether (100 mL) and the aqueous phase was extracted with ether. The combined organic layers were washed with water, dried, and concentrated to furnish a colorless oil, distillation of which (bp 95–103 °C, 1.5 mm) gave 2.71 g (90%) of pure **17**: ν_{max} (neat) 3360, 1045, 1000, and 835 cm^{-1}; ^1H NMR (δ, $CDCl_3$) 4.42 (m, 1 H), 1.8 (br s, 1 H), 1.6–1.1 (m, 2 H), 1.1–0.4 (series of m, 9 H), and 0.2 (m, 1 H); ^{13}C NMR (ppm, $CDCl_3$) 68.1 22.3, 21.7, 15.8, 14.3, 14.0, 13.4, 12.2, 8.8, and 8.4; *m/e* calcd 150.1045, obsd 150.1048.

The *p*-nitrobenzoate was prepared in the standard manner: colorless crystals, mp 125–126 °C.

Anal. Calcd for $C_{17}H_{17}NO_4$: C, 68.22; H, 5.72. Found: C, 68.09; H, 5.81.

The 3,5-dinitrobenzoate was a pale yellow solid, mp 92–93 °C.

Anal. Calcd for $C_{17}H_{16}N_2O_6$: C, 59.30; H, 4.68. Found: C, 59.34; H, 4.75.

***anti,syn*-2,4,6-Trishomotropone (18).** In a 500-mL flask equipped with a nitrogen inlet, condenser, and magnetic stirring bar was placed a slurry of **17** (420 mg, 2.8 mmol) and activated manganese dioxide (10 g) in cyclohexane (200 mL). The mixture was heated at reflux for 24 h, cooled, and filtered through a short silica gel column (elution with dichloromethane). The eluate was concentrated to give 322 mg (78%) of **18** (>95% purity by VPC analysis). A pure sample of the ketone was isolated by preparative VPC methods (5 ft × 0.25 in. 5% SE-30, 140 °C): ν_{max} (neat) 1680, 1380, 1195, and 1020 cm^{-1}; ^1H NMR (δ, $CDCl_3$) 1.9–0.57 (series of m, 11 H) and 0.10 (m, 1 H); ^{13}C NMR (ppm, $CDCl_3$) 205.5, 29.8, 27.8, 17.3, 15.5, 15.2, 14.3, 12.7, 11.2, and 10.4; *m/e* calcd 148.0888, obsd 148.0891.

Anal. Calcd for $C_{10}H_{12}O$: C, 81.04; H, 8.16. Found: C, 81.21; H, 8.08.

Epimerization of 17. By means of the above procedure, alcohol **17** (360 mg, 2.4 mmol) was epimerized in 96% yield to a mixture of **17** and **19** (350 mg) rich in the latter epimer (80%). Direct reaction with 3,5-dinitrobenzoyl chloride, followed by recrystallization from petroleum ether and ether, gave crystals mp 112–113 °C, of **19**-ODNB.

Anal. Calcd for $C_{17}H_{16}N_2O_6$: C, 59.30; H, 4.68; N, 8.13. Found: C, 59.28; H, 4.70; N, 8.34.

Saponification of the pure ester (135 mg, 0.39 mmol) with potassium hydroxide (2.0 g) in anhydrous methanol (10 mL) at room temperature for 1 day returned 43 mg (73%) of pure *anti,anti,syn*-2,4,6-trishomocycloheptatrienol (**19**) as a colorless oil; ν_{max} (neat) 3350, 3300, 1450, 1025, and 1005 cm^{-1}; ^1H NMR (δ, $CDCl_3$) 3.60 (br d, J = 7 Hz, 1 H), 1.83 (s, 1 H), and 1.5–0.1 (series of m, 12 H); ^{13}C NMR (ppm, $CDCl_3$) 73.60, 24.76, 21.41, 15.00, 14.18, 13.45, 12.53, 10.92, 9.61, and 4.81; *m/e* calcd 150.1045, obsd 150.1048.

Kinetic Studies, Preparation of Reagents. Acetone was purified by distillation from potassium permanganate and redistillation after drying over anhydrous potassium carbonate. Doubly distilled water was utilized and methanol was distilled from magnesium methoxide. The 80% aqueous acetone was prepared on a volume–volume basis.

General Kinetic Procedures. For each run, approximately 40 mg (0.12 mmol) of 3,5-dinitrobenzoate was weighed into a 10-mL volumetric flask which was subsequently filled to the mark with 80% aqueous acetone (ca. 0.01 M). After thorough mixing, the solutions were divided into nine glass ampules (1.00-mL aliquots each) which were sealed. All ampules were simultaneously immersed into a constant-temperature bath. After an appropriate time interval (5–30 min), one ampule was removed and placed in an ice–water mixture, at which point an accurate timer was started. The remaining ampules were removed and cooled at appropriate intervals to cover a time span of 1.5 half-lives. The final two ampules were removed after approximately 10 and 20 half-lives to provide the average infinity point.

The individual aliquots were diluted with 1 mL of acetone and titrated with standardized 0.011 N sodium hydroxide solution to a blue end point (3 drops of 0.04% aqueous bromothymol blue as indicator). In the case of **10**-ODNB and **12**-ODNB, the infinity titers revealed the liberation of 99–103% of 3,5-dinitrobenzoic acid; however, **17**-ODNB and **19**-ODNB liberated only 90–93 and 85–89% of the theoretical values, respectively. First-order rate data for **12**-ODNB, **17**-ODNB, and **19**-ODNB were determined by measurement of the amount of 3,5-dinitrobenzoic acid generated relative to the experimental infinity point using the method of least squares. The reported rate constants comprise the average of two runs which agreed within 6% at all temperatures.

Plots of the disappearance of **10**-ODNB vs. time did not describe a straight line, thereby indicating the likely operation of an internal return process. Accordingly, analysis was made using standard triangular kinetic scheme methodology. Since it became necessary to include a data point for t = 0 and $\ln X$ = 0, the absolute time of the data points had to be used. These values were obtained by extrapolating the time vs. log X curves to log X = 0 and adding the value of the time axis intercept to the experimental time values. Initial values of k_1 were obtained by extrapolating the $\ln X$ vs. t curves to zero time. The value of k_2 was initially estimated to be roughly the same as k_1. Rate constant k_3 was determined titrimetrically using authentic samples of **12**-ODNB.

Preparative-Scale Solvolyses of the 3,5-Dinitrobenzoates, General Procedure. A solution of **10**-ODNB (90 mg, 0.26 mmol) and 2,6-lutidine (0.5 mL) in 20 mL of 80% aqueous acetone was heated at 80 °C for 120 h. The solution was concentrated under reduced pressure and the resulting suspension was extracted with dichloromethane. The organic phase was washed in turn with sodium bicarbonate solution, water, 1 N hydrochloric acid, water, and again with sodium bicarbonate solution before drying. Solvent removal left 35 mg of yellowish oil. Product distribution was determined using VPC and NMR techniques. Thin layer chromatographic separation (80% hexane–20% ether) gave 15 mg of **10** and 13 mg of **12**.

By similar methodology, product analyses for the other three 3,5-dinitrobenzoates was carried out. The results are summarized in Table IV.

Control Experiments Involving the Trishomocycloheptatrienols. A solution of **10** (19 mg), 2,6-lutidine (0.03 mL), and 3,5-dinitrobenzoic acid (14 mg) in 1 mL of 80% aqueous acetone was heated at 80 °C for 85 h. Isolation of the alcohol showed it to be stable to these reaction conditions.

Comparable treatment of **12**, **17**, and **19** for 76–96 h gave analogous results.

Acid-Catalyzed Isomerization of 17 to *cis,cis,trans*-2,5,8-Cyclodecatrien-1-ol (21). A solution of **17** (80 mg, 0.53 mmol) in a mixture of dioxane (40 mL), water (9 mL), and 70% perchloric acid (1 mL) was heated at 75 °C under nitrogen for 5 h. After being cooled, the reaction mixture was poured into water (200 mL) and the product was extracted into petroleum ether. The combined organic phases were washed with water and saturated sodium bicarbonate solution prior to drying. Removal of solvent left 63 mg (79%) of a colorless oil whose spectra were superimposable upon those of authentic **21**.[16]

For **20**: ν_{max} (CCl_4) 3600, 3020, 1640, 1450, 1025, 915, and 710 cm^{-1}; ^1H NMR (δ, $CDCl_3$) 5.9–5.3 (m, 4 H), 3.3–2.0 (m, 5 H), 1.8 (s, 1 H), 1.8–0.7 (m, 3 H), and 0.05 (d of t, J = 6 and 4 Hz, 1 H); *m/e*

calcd 150.1045, obsd 150.1048.

For **20**-ODNB: ν_{max} (neat) 3095, 1725, 1540, 1340, 1270, 1165, 905, 720, and 710 cm^{-1}; ^1H NMR (δ, $CDCl_3$) 9.07 (s, 3 H), 5.9–5.3 (m, 4 H), 4.50 (m, 1 H), 3.8–2.0 (series of m, 4 H), 2.0–0.9 (series of m, 3 H), and 0.30 (d of 1, J = 6 and 4 Hz, 1 H); *m/e* calcd 344.1008, obsd 344.1014.

For **21**: ν_{max} (CS_2) 3600, 3005, 1030, 1140, and 700 cm^{-1}; ^1H NMR (δ, $CDCl_3$) 5.6–5.1 (m, 6 H), 4.5–4.1 (m, 1 H), 3.3–2.0 (series of m, 6 H), and 1.7 (br s, 1 H); *m/e* calcd 150.1045, obsd 150.1048.

For **21**-ODNB: mp 98–99 °C (from petroleum ether); ν_{max} (neat) 3100, 1725, 1540, 1340, 1270, 1165, 980, 720, and 710 cm^{-1}; ^1H NMR (δ, $CDCl_3$) 9.07 (br s, 3 H), 6.0–5.2 (m, 7 H), and 3.6–2.0 (series of m, 6 H); *m/e* calcd 344.1008, obsd 344.1014.

Saponification of 20-ODNB and 21-ODNB. A solution of **20**-ODNB (58 mg, 0.17 mmol) and potassium hydroxide (2 g) in 10 mL of anhydrous methanol was stirred at room temperature for 1 day prior to dilution with water and extraction with dichloromethane. The combined organic layers were washed with water, dried, and evaporated. There was obtained 24 mg (96%) of **20** as a colorless oil.

By means of an analogous procedure, 90 mg of **21**-ODNB afforded 25 mg (64%) of **21**.

Methanolysis of the 3,5-Dinitrobenzoates. A 19-mg (0.055 mmol) sample of **10**-ODNB was dissolved in anhydrous methanol (10 mL) containing 0.1 mL of 2,6-lutidine and the solution was heated at 80 °C for 4 days. After removal of the methanol under reduced pressure, the remaining suspension was extracted with petroleum ether. The combined organic layers were washed with 1 N hydrochloric acid, water, and saturated sodium bicarbonate solution prior to drying. Removal of the solvent left 8.3 mg of a light yellow oil. This material was then subjected to ^1H NMR and VPC analysis. The results are summarized in Table VI.

The other three dinitrobenzoates were treated comparably with analogous results (Table VI).

Independent Synthesis of the Methyl Ethers, Method A. A 60-mg sample of 50% sodium hydride in oil was washed with petroleum ether and dried under a stream of nitrogen. A solution of **10** (43 mg) in 5 mL of dry tetrahydrofuran was introduced and the mixture was stirred at room temperature for 5 h. Methyl iodide (0.2 mL) was added and stirring was maintained for an additional 24 h. After workup, 35 mg (77%) of **10**-OME was obtained as a colorless oil. Consult Table VII for spectral data.

Method B. A 79-mg sample of 50% sodium hydride in oil was washed with petroleum ether and dried under a stream of nitrogen. A solution of **12** (50.6 mg, 0.34 mmol) in dry tetrahydrofuran was introduced and the resulting mixture was brought to gentle reflux for 2 h prior to the addition of methyl iodide (280 mg, 2 mmol). After 10 h at room temperature, the reaction mixture was diluted with water and ice and the product was extracted into dichloromethane. The combined organic layers were washed with water, dried, and concentrated to give 49 mg (87%) of **12**-OME as a colorless oil (see Table VII).

***syn,anti,syn*-2,4,6-Trishomocycloheptatrienol-*6a*-d_2.** Reduction of a 1.65-g (4.9 mmol) sample of **15** with 0.75 g of lithium metal in 3 mL of *tert*-butyl alcohol-*O*-*d* as described above afforded 0.80 g (61%) of **16**-d_2, bp 80–87 °C (0.1 mm). Desilylation with tetra-*n*-butylammonium fluoride (4.0 g) as predescribed gave 412 mg (90%) of **17**-d_2.

For **16**-d_2: ν_{max} (neat) 1250, 1065, and 830 cm^{-1}; ^1H NMR (δ, $CDCl_3$) 4.35 (br d, J = 6.0 Hz, 1 H), 1.3–0.4 (series of m, 10 H), 0.93 (s, 9 H), and 0.10 (s, 6 H); *m/e* calcd 266.2035, obsd 266.2041.

For **17**-d_2: ν_{max} (neat) 3350, 1045, 1010, and 830 cm^{-1}; ^1H NMR (δ, $CDCl_3$) 4.42 (m, 1 H), 2.1 (br s, 1 H), 1.6–1.1 (m, 2 H), 1.1–0.4 (series of m, 7 H), and 0.2 (m, 1 H).

Dinitrobenzoate **17**-ODNB-d_2 was prepared in 57% yield: mp 90–92 °C; ^1H NMR (δ, $CDCl_3$) 9.07 (s, 3 H), 5.90 (m, 1 H), 1.7–0.5 (m, 9 H), and 0.5–0.0 (m, 1 H); *m/e* calcd 346.1134, obsd 346.1138.

Solvolysis of 17-ODNB-d_2. A solution of 250 mg (0.72 mmol) of the 3,5-dinitrobenzoate and 0.5 mL of 2,6-lutidine in 20 mL of 80% aqueous acetone was heated at 80 °C for 45 h and worked up in the usual manner. The resultant oil (154 mg) was subjected to preparative layer chromatography on silica gel (elution with 10–40% ether in petroleum ether). There were isolated 42 mg of **20**-ODNB-d_2, 10.5 mg of **21**-ODNB-d_2, 15 mg of **21**-ODNB-d_2, 15 mg of **21**-d_2, and 10 mg of **20**-d_2.

For **20**-d_2: ^1H NMR (δ, $CDCl_3$) 5.8–5.2 (m, 4 H), 3.3–2.0 (m, 3 H), 1.7 (s, 1 H), 1.8–0.7 (m, 3 H), and 0.05 (d of 1, J = 6 and 4 Hz, 1 H).

For **20**-ODNB-d_2: ^1H NMR (δ, $CDCl_3$) 9.07 (s, 3 H), 6.0–5.3 (m, 4 H), 4.50 (m, 1 H), 3.3–2.8 (m, 1 H), 2.6–2.0 (m, 1 H), 2.0–0.9 (m, 3 H), and 0.07 (d of 1 J = 6 and 4 Hz, 1 H); *m/e* calcd 346.1134, obsd 346.1140.

For **21**-d_2: ^1H NMR (δ, $CDCl_3$) 5.6–5.0 (m, 6 H), 4.5–4.1 (m, 1 H), 3.0–2.0 (series of m, 4 H), and 1.65 (br s, 1 H); *m/e* calcd 152.1170, obsd 152.1174.

For **21**-ODNB-d_2: ^1H NMR (δ, $CDCl_3$) 9.07 (br s, 3 H), 6.0–5.1 (m, 7 H), and 3.0–2.0 (series of m, 4 H); *m/e* calcd 346.1134, obsd 346.1138.

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(25) Most relevant to the present topic is the earlier observation that cyclopropylcarbinyl cations having 60° geometry appear considerably less stable than their counterparts with 0–30° geometries.[18c]
(26) The conformational features of the trishomocycloheptatriene hydrocarbon parent of **33** have been previously assessed.[17]

Sulfoxylate Ion (HSO_2^-), the Hydride Donor in Dithionite-Dependent Reduction of NAD^+ Analogues

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Abstract: At high pH interaction of dithionite with NAD^+ analogues results in formation of a sulfinate adduct. Its rate of formation is linearly dependent on dithionite concentration. Hence, sulfinate radicals do not appear to be involved in this process. A linear free energy relationship for adduct formation is obtained, the rate of which increases with increasing redox potential of the NAD^+ analogue. The deprotonated adducts are found to be very stable both thermodynamically ($K_d < 10^{-7}$ M) and kinetically ($k_{off} < 10^{-4}$ s^{-1}). Formation of NADH analogues is therefore not observed at pH >11. Conversion of adducts, formed from stoichiometric amounts of NAD^+ analogue and dithionite at high pH, to NADH analogues can be studied by pH jump, stopped-flow spectrophotometry: (1) After protonation of the sulfinate function, formation of oxidized NAD^+ analogue is observed in a fast initial phase (k for NAD^+ = 4.62 s^{-1}), the rate of which increases with decreasing redox potential of nicotinamide. (2) In a much slower, second phase, formation of NADH analogue is observed, which takes more than 20 min to completion. NADH formation can be prevented by adding formaldehyde, which traps the active reducing species. (3) If NAD sulfinate is mixed at pH 5 with an equimolar amount of the high-potential analogue 3-acetylpyridine-NAD^+ almost quantitative formation of 3-acetylpyridine-NADH is observed with no detectable formation of NADH. These results lead us to propose that sulfoxylate ion (HSO_2^-), a hydride donor formed after heterolytic dissociation of the protonated sulfinate adduct, is the active reducing species. Neither the sulfinate adduct itself nor sulfinate radicals appear to be productive in NADH formation. Hence, dithionite appears to be a selective, ambivalent reducing agent. While flavins are reduced by the homolytic dissociation product, sulfinate radical, nicotinamides are reduced by the heterolytic dissociation product, sulfoxylate ion. The factors controlling the nicotinamide pathway are both the high thermodynamic instability of the nicotinamide radical and the high stability of the sulfinate adduct.

Introduction

The question of $1e^-$ vs. $2e^-$ transfer in both flavin- and nicotinamide-dependent oxidoreduction is a currently disputed matter.[2-5] In particular, the possibility of sequential $1e^-$ transfer involving caged radical pair intermediates has been emphasized as a means of avoiding the high energy of the free nicotinamide radical.[2b,3,4,6] While electrochemical and pulse radiolysis studies are important for generating and characterizing free radicals, they suffer from the disadvantage that $1e^-$ transfer becomes mandatory when it might well be irrelevant under biologically meaningful conditions. Clearly, it is desirable to study reactants with readily available $1e^-$ and $2e^-$ shuttles because only then is a choice for a given pathway possible.

Dithionite is such a reactant which in fact has long been used as a general reducing agent in biochemical systems. Only very recently, however, Mayhew has shown that its $2e^-$ shuttle for the reaction

$$S_2O_4^{2-} + 2H_2O \rightleftharpoons 2HSO_3^- + 2H^+ + 2e^- \qquad (1)$$

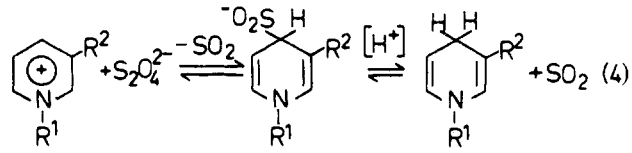
is characterized by an $E_0' = -386$ mV at 2 M sulfite[7] while the $1e^-$ shuttle derived from dissociation of dithionite into two sulfinate radicals

$$S_2O_4^{2-} \rightleftharpoons 2\dot{S}O_2^- \qquad K_d = 10^{-8}\ M \qquad (2)$$

$$\dot{S}O_2^- + H_2O \rightleftharpoons HSO_3^- + H^+ + e^- \qquad (3)$$

is characterized by an $E_0' = -660$ mV at concentrations smaller than K_d. At higher concentrations of dithionite E_0' increases by 29 mV for every tenfold increase in dithionite.[7] In the concentration range where it is usually applied (up to 10 mM) dithionite is thus both a strong $1e^-$ and $2e^-$ reductant.

Free flavins and flavodoxin are reduced by dithionite via consecutive $1e^-$ steps[8,9] and no intermediates have been observed. Nicotinamides, however, form sulfinate adducts, presumably via nicotinamide-C(4), which are stable at high pH but can be converted to 1,4-dihydronicotinamides by protonation of the sulfinate function (eq 4).[10-13] Although this reaction has been described as early as 1935,[14] its mechanism has been elusive so far.[15] In this study we present evidence that sulfinate adducts are not the immediate precursors leading to formation of the corresponding NADH analogues. The evidence suggests that sulfoxylate ion (HSO_2^-) is formed, which is postulated to be the active reducing species.



(4)

Experimental Section

Materials. NAD^+, 3-acetylpyridine-NAD^+, and thionicotinamide-NAD^+ were purchased from Boehringer, Mannheim, West Germany. 1-Methylnicotinamide and 10-methyl-5-deazaisoalloxazine were synthesized according to published procedures.[2a,16,17] Sodium dithionite was either from Baker Chemicals, Phillipsburg, N.J., or

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