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REGIOSELECTIVITY AND STEREOSPECIFICITY IN HOMOKETONIZATIONS. CONTROL BY THERMODYNAMIC AND STERIC FACTORS.[1]

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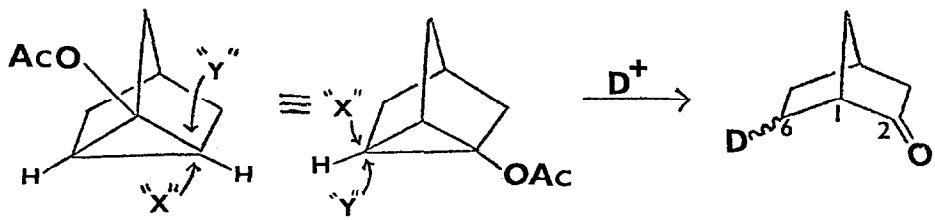
We recently reported[2] the first example of an acid-induced homoketonization that proceeds by predominant inversion of configuration and showed that this high inversion could be diminished, and even completely transformed to high retention, by addition of D_2O to the solvent, which was either DOAc-D_2SO_4 or DCO_2D.[3] The substrate was 1-acetoxynortricyclane (1), which produces 6-deuterionorbornan-2-one (2). It is at once important to establish whether this unprecedented acid opening with inversion (i.e. "x" attack in 1), as well as the reversal brought about by water (i.e. "y" attack), are unique to this substrate. Therefore we synthesized and studied two new homoenol acetates that not only provided this information but



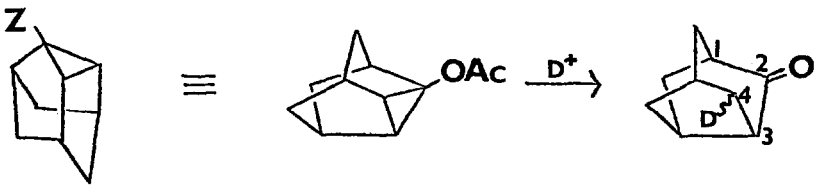
1 2

also revealed new features that can control regioselectivity and stereospecificity in homoketonizations. Specifically we have found: (a) A second case of acid homoketonization with high inversion of configuration, and thereby demonstrate that this newly found path is not unique to 1-acetoxynortricyclane; (b) Pronounced stereochemical perturbation by water is not a general characteristic of acid cleavages; (c) In alkaline homoketonozations[4] thermodynamic stability of the ring-opened polycycle can control regioselectivity; and (d) In acid media steric hindrance can control stereospecificity.

2-Acetoxytriaxane (5) resembles 1-acetoxynortricyclane (1) in symmetry and in steric differences between inversion and retention paths. We prepared 5 from triaxane (3)[5] directly (31%) by action of Pb $(OAc)_4$ in HOAc,[6] and also by ring acetylation[7] to 4 followed by Baeyer-Villiger[8] oxidation (50% overall). Homoketonization of 5 in deuterated media produces noradamantan-2-one[9] with deuterium exclusively at C-4. Its stereochemistry was quantitatively assigned from Eu(fod)$_3$-shifted pmr and, in some runs, was independently confirmed by dmr.[10]

Table I summarizes the results.

The openings in alkali (Runs 1 and 2) gave largely inversion and those in acid (Runs 3-5) gave high retention. The results in Runs 1-4 qualitatively resemble those found earlier for substrate 1 under the same conditions. However the exclusive retention (>99%) in Run 5 sharply contrasts the high inversion (94%) exhibited[2] by 1 under the same conditions. Therefore the



3, Z = H
4, Z = $COCH_3$
5, Z = $OCOCH_3$

5 6

TABLE I. HOMOKETONIZATION OF 2-ACETOXYTRIAXANE IN ALKALINE AND ACID MEDIA AT 25°

Run	Solvent	Reagent	Mass Spectral %d_1[a]	Axial D[b]	Stereospecificity[c]
1	CH_3OD	$NaOCH_3$	92	16[d]	82-85% Inversion
2	$(CH_3)_3COD$	$KOC(CH_3)_3$	84	20.5	72-79% Inversion
3	CH_3OD	D_2SO_4	90	89	99-100% Retention
4	$CD_3CO_2D:D_2O$[e]	D_2SO_4	91	89.5	98-99% Retention
5	CD_3CO_2D	D_2SO_4	88	87.5	99-100% Retention

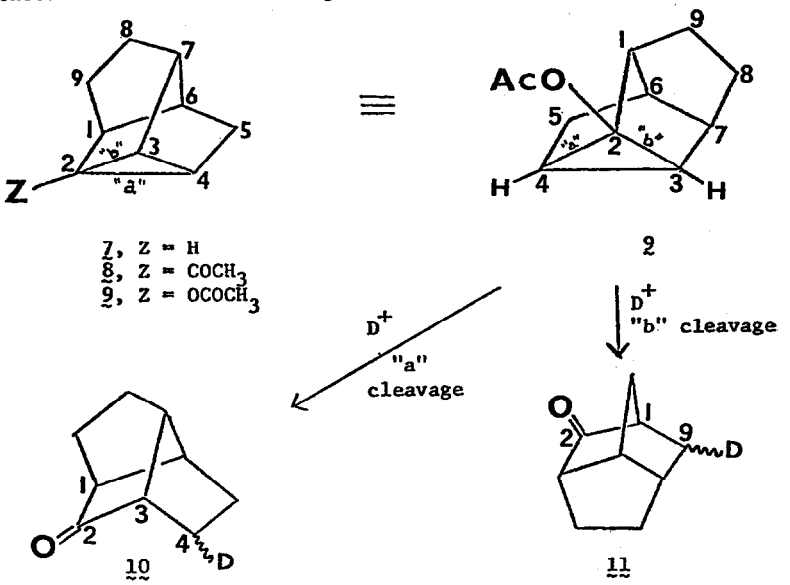
[a]The remainder was d_0; [b]From pmr spectra in CCl_4 containing ca. 0.7-1.5 mole equiv. $Eu(fod)_3$ and the mass spectral data; [c]Range from duplicate or triplicate runs; [d]Dmr on epinoradamantanol obtained by $LiAlH_4$ reduction of the d-ketone (Run 1) showed equatorial-D:axial-D in the ratio 87:13; [e]The ratio was 8:1 by volume.

dramatic stereochemical effect of water found earlier[2] is not a general characteristic even for homoenolic skeletons that appear structurally similar.

Our second substrate was 2-acetoxydeltacycane (9), which we synthesized from deltacyclane (7)[5,11] by treatment with $Pb(OAc)_4$ in HOAc[12] and also by ring acetylation[7] to 8 followed by Baeyer-Villiger[8] oxidation. Homoketonization of this unsymmetrical substrate holds special interest because its two different centers for proton attack (C-3 and C-4) have the same degree of alkylation.[13] Therefore the proportions of the two possible products, brexan-2-one (10) and brendan-2-one (11), can reveal new factors that influence direction of ring opening. Table II shows the relative amounts of both products and the stereospecificity in each.[14] In Run 5 the substrate was the parent homoenol rather than the homoenol acetate.

In $NaOCH_3$-CH_3OD (Run 1) the opening was 100% regioselective to give brendan-2-one (11) with 95-100% inversion of configuration. This exclusive cleavage of bond "b" to give 11 can't reasonably be attributed to steric factors because steric accessibility is virtually the same for attack by inversion at C-3 or at C-4. However the brendane skeleton is more stable than

the brexane skeleton (by ca. 2.24-3.13 kcal/mole)[15] and evidently some of this greater stability is felt at the transition state. Consequently the degree of exothermicity in alkaline homoketonization can dictate regioselectivity, at least in polycyclic structures.



7, Z = H
8, Z = $COCH_3$
9, Z = $OCOCH_3$

2

10

11

In acid (Runs 2-4), regioselectivity was appreciably lower and the same held for the one run (No. 5) on the parent homoenol. In the three acid systems the brendan-2-one (11) was formed with virtually complete inversion of configuration. This constitutes the second known example of acid homoketonization with inversion and shows that this unusual stereochemical path is not unique to one ring structure. Note that the high inversion occurred in acetic acid with

TABLE II. REGIOSELECTIVITY AND STEREOSPECIFICITY IN HOMOKETONIZATION OF 2-ACETOXYDELTACYCLANE IN ALKALINE AND ACID MEDIA AT 25°.

			Brexan-2-one (10)				Brendan-2-one (11)			
				Mass Spectrum				Mass Spectrum		
Run	Solvent	Reagent	%	d_0	d_1	Stereospecificity[a]	%	d_0	d_1	Stereospecificity[a]
1	CH_3OD	$NaOCH_3$	0	--	--	--	100	10[b]	90[b]	95-100% Inv.
2	CH_3OD	D_2SO_4	31	11	89	93-100% Ret.	69	9	91	96-98% Inv.
3	$CD_3CO_2D:D_2O$ (3:1 by vol)	D_2SO_4	22	6	94	97-98% Ret.	78	6	94	97-100% Inv.
4	CD_3CO_2D	D_2SO_4	20	11	89	98-99% Ret.	80	13	87	98-100% Inv.
5[c]	CH_3OH	H_2SO_4	29	--	--	--	71	--	--	--

[a]Lower and higher value from duplicate runs; [b]After washing out a small amount (3-6%) of d_2 that arose by exchange at C-3 in the brendan-2-one. The ease of that bridgehead enolization has been reported. A. Nickon, D. F. Covey, F. Huang, and Y. Kuo, J. Am. Chem. Soc., 97, 904 (1975)
[c]The substrate was the corresponding homoenol, 2-hydroxydeltacyclane, prepared from the acetate.

or without added water. The brexan-2-one (10) was produced exclusively with retention, which is the conventional path in acid media. As with acetoxytriaxane (5)(Table I), but in contrast to acetoxynortricyclane (1), this outcome was unaffected by water. These variations argue against the possibility that, for homoenol acetates, the species that undergoes carbon protonation differs in aqueous and nonaqueous systems and that this difference is responsible for inversion and retention paths.[2] The persistent inversion on acidic cleavages of bond "b" to form 11, especially when "a" cleaves consistently with high retention, is most reasonably ascribed to steric blocking by the C-8, C-9 bridge. Consequently steric factors can control the outcome in acidic media.[16]

Footnotes and References

1. Supported by the National Institutes of Health (Grant GM06304) and by the National Science Foundation (GP11919X).

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3. For stereochemical studies of acid homoketonizations, see:

   a. C. H. DePuy, F. W. Breitbeil, and K. R. DeBruin, J. Am. Chem. Soc., 88, 3347 (1966);
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10. In noradamantan-2-one shifted by Eu(fod)$_3$ all protons are distinct and assignable with spin decoupling. The C-4 axial H signal is free of overlap and readily integrated. For details see: D. Covey, Ph.D. Thesis, The Johns Hopkins University, 1973.

11. a. A. Nickon, H. Kwasnik, T. Swartz, R. O. Williams, and J. B. DiGiorgio, J. Am. Chem. Soc., 87, 1613, 1615 (1965); b. J. J. Mrowka and T. J. Katz, ibid., 88, 4012 (1966); c. L. G. Cannell, Tetrahedron Lett., 5967 (1966); d. R. C. Weglein, Ph.D. Thesis, The Johns Hopkins University, 1973.

12. The yield is low, and other products are formed including 4-acetoxydeltacyclane.

13. For a discussion, see: C. H. DePuy, Accounts Chem. Res., 1, 33 (1968).

14. In Eu(fod)$_3$-shifted pmr spectra, all protons in each ketone were distinct and readily assigned by spin decoupling. The endo protons at C-4 in 10 and at C-9 in 11 are readily integrated for d-assay (Ref. 10).

15. a. T. Swartz, Ph.D. Thesis, The Johns Hopkins University, 1966;
    b. E. M. Engler, J. D. Andose, and P. v. R. Schleyer, J. Am. Chem. Soc., 95, 8005 (1973).

16. New compounds (4, 5, 8, 9) gave satisfactory C and H analyses and appropriate nmr spectra.