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ENANTIOSELECTIVITY IN CAMPHOR PINACOLISATION

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Summary: Total enantioselectivity has been observed in pinacol formation using Li/THF.(+) Camphor and (±) Camphor give the optically active and racemic form of a single pinacol whose stereochemistry has been established as **endo:endo** by X-ray analysis. An **exo:endo** pinacol is formed as the sole product if camphor is added to Li/NH_3. Tentative mechanism is proposed.

The ability of an enantiomer to recognise its mirror image and **either** react exclusively with it **or** refuse to react with it preferring to react with its own kind, is a phenomenon which is rarely encountered.

We wish to report a case of total enantioselectivity of the second type.

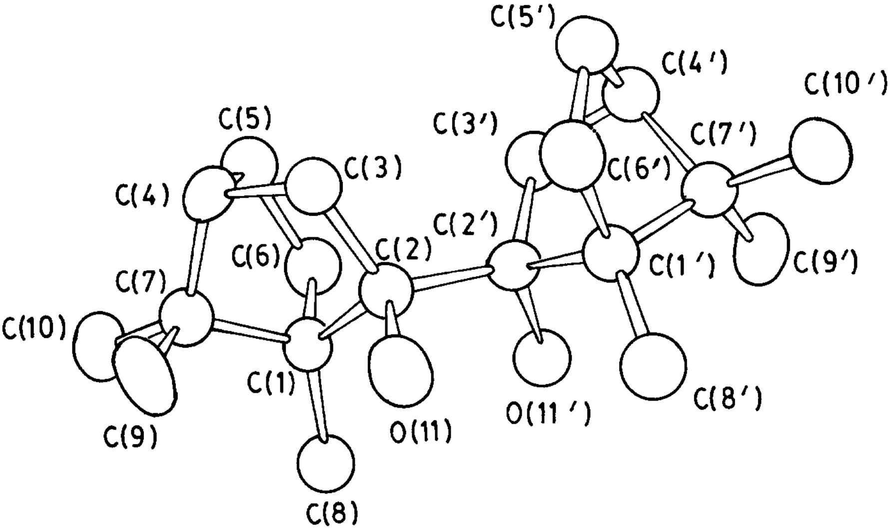
In recent years Paquette has been actively searching for enantioselectivity. Though he had pinned his hopes on pinacol formation[1] the enantioselective reaction he discovered[2] was a different type. The expectation[1] that a single diastereomer would be obtained from optically pure and racemic hexahydrotriquinancen-2-one on pinacolisation with Mg amalgam were not fulfilled. Thus so far no case has come to light of enantioselectivity in pinacolisation of a saturated cyclic ketone. The nearest is a case of reductive dimerisation of an $\alpha\beta$ unsaturated ketone reported by Touboul and Dana[3] who used an electrochemical method.

We wish to report that (+) camphor on stirring with Li in THF at room temperature reacts stereoselectively to give a single pinacol[4]. (±) camphor can in theory give as many as four racemates and two meso pinacols. But under the above reaction conditions it gives only a single racemate. From a comparison of ^1H and ^{13}C NMRs as well as mass spectra, it could be concluded that optically active and racemic forms of the **same diastereomer** were being produced from (+) and (±) camphor respectively. The reaction is hence not only stereoselective but it is **enantioselective** as well. Thus in spite of the presence of equal amounts of (+) and (-) camphor in racemic camphor, the only reaction that takes place is between (+) and (+) and between (-) and (-) to the **total** exclusion of pinacolisation between (+) camphor and (-) camphor.

We turn now to the determination of configuration. All that was needed was to determine that for the compound m.p. 157°C, $[\alpha]_D$-24°($CHCl_3$) obtained in the reductive dimerisation of (+) camphor. This pinacol hs been reported before[5] but the only attempt to determine its stereochemistry was by Rautenstrauch[6]. On reduction of (+) camphor with either Li/NH_3 or Na/NH_3 the latter obtained the above pinacol accompanied by another m.p. 113°C.

The pinacol m.p.157°C was found[6] to have only three methyl signals in ^1H NMR. This was correctly interpreted as being due to the pinacol possessing a C_2-axis of symmetry and hence having the new C-C bond either **exo** to both rings or **endo** to both rings. On steric grounds the latter appeared more likely. This configuration was **tentatively** assigned by Rautenstrauch[6] after comparing the ^1H NMR of the pinacol with ^1H NMRS of borneol and **iso**borneol. He has, however, admitted[6] that the validity of the assignment rests on the assumption that extrapolation from the spectra of the monomeric secondary alcohols is justified. In our opinion the assumption is not justified if one requires a **definite** as against a tentative assignment.

In view of the rarity of this type of enantioselectivity it was desirable to have a **definite** assignment. ^{13}C NMR confirmed that the compound had C_2-axis as only ten signals were seen[7]. 2D NMR as well as ^{1}H NMR at 250 MHz[8] also proved inconclusive. Definite assignment was finally made using X-ray crystallography[9]. The ORTEP drawing given below shows the presence of **endo-endo** coupling. The product from 1R, 4R camphor is seen to be 1R, 2R, 4R, 1'R, 2'R, 4'R camphor pinacol.



ORTEP Stereodrawing of pinacol

m.p. 157°C from (+) camphor

The other pinacol m.p.113°C which accompanied the above pinacol on reaction of (+) camphor with alkali metal/NH_3, following a procedure in which the metal is added last, was obtained to the extent of 95% of the total pinacols if Li was used. The two pinacols were obtained in equal amounts using Na[6].

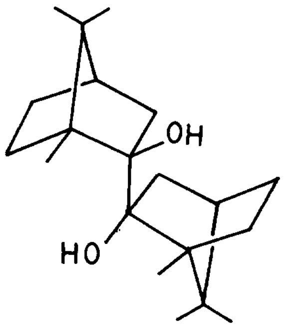
The pinacol m.p.113°C was correctly regarded as having an **exo : endo** linkage since ^{1}H NMR had five clearly resolved methyl signals consistent with an unsymmetrical structure. This was confirmed[10] using ^{13}C NMR wherein nineteen out of the expected twenty signals were detected. The mixture of pinacols is accompanied by reduction products as well as some unreacted camphor. Besides confirming this we have been able to achieve reaction conditions such that one or the other pinacol is formed to the exclusion of the other[10]. It was necessary to rigorously exclude moisture and use sodium benzoate for quenching[11].

(+) camphor gave the symmetrical pinacol, I having the IR, 2R, 4R, 1'R, 2'R, 4'R configuration as the sole dimeric product when to a stirred solution of Li (20 mg. atom) in NH_3 (40 ml.) at - 33°C was added the camphor (10 mmol) in THF (10 ml.) **or** ether (10 ml.) and the reaction was quenched after 5 mins.

(+) camphor gave the unsymmetrical pinacol, II having the 1R, 2R, 4R, 1'R, 2'S, 4'R configuration when the following conditions were used :- To a stirred solution of (+) camphor (10 mmol) in NH_3 (40 ml.) and ether (2 ml.) at - 33°C were added in one lot small pieces of Li (20 mmol) and the reaction worked up after 10 mins.

Such selectivity and the influence on it of reaction conditions was remarkable. However, even more remarkable was the observation that when the reactions were repeated with (±) camphor it was found that both reactions were **totally enantioselective** as well.

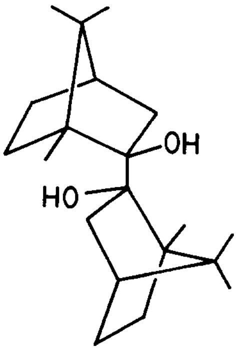
Thus (±) camphor could have given any or all of four racemates and two meso compounds on reductive dimerisation. But under the first set of conditions it gave exclusively the racemic dimer having an **endo : endo** link while under the second set of conditions it gave exclusively the racemic dimer having an **exo : endo** link. In **both** cases **no** reaction took place between (+) camphor and (-) camphor.



I

(1R,2R,4R,1'R,2'R,4'R)

endo : endo



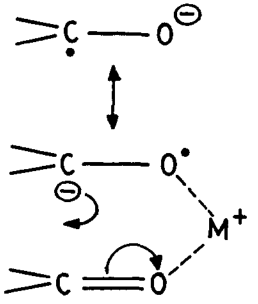
II

(1R,2R,4R, 1'R,2'S,4'R)

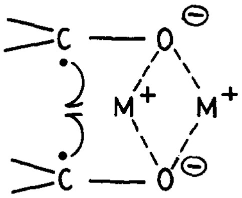
endo : exo

Attention was next turned to examining the factors responsible for change in stereochemistry of pinacolisation. Modifications were tried[10] which gave mixtures of pinacols from (+) camphor. The symmetrical pinacol was found to be accompanied by a small amount of the unsymmetrical isomer simply by reducing the Li quantity to 5 mg. atoms in the first set of conditions. Just extending the time from 5 to 10 mins. also had the same effect[12].

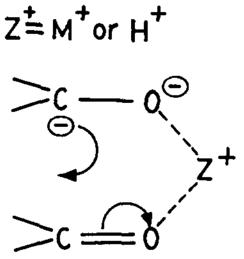
One may reasonably conclude that in presence of excess NH_3 the symmetrical pinacol is formed at high Li concentration while the unsymmetrical pinacol is formed at low concentration of Li. Three possibilities given below are listed in order of increasing dependence on alkali metal concentration13, 14.



A



B



C

Mechanism C is rendered unlikely in view of the observation by Murphy and Sullivan[15] that the yield of pinacol decreases with increasing Li concentration.

One is led to presume that **mechanism A** is in control at low Li concentration in NH_3 while at high metal concentration in same solvent **mechanism B** takes over. It also does so in the Li/THF reaction where the coupling between ketyl radical anions takes place on the metal surface.

References and Notes

1. L. A. Paquette, I. Itoh and W. B. Farnham, J. Am. Chem. Soc. **97**, 7280 (1975).
2. L. A. Paquette, J. Romine, W. Barth and L. Y. Hsu, Tetrahedron Letters, 567 (1985).
3. E. Touboul and G. Dana, Tetrahedron **31**, 1925 (1975) and earlier paper cited.
4. After 48 hrs. stirring under nitrogen, percentage yields were :- pinacol (27), camphor (45), borneol (27) and iso-borneol (7).
5. E. Beckmann, Liebigs Ann. Chim. **292**, 1 (1896).
6. V. Rautenstrauch, B. Willhalm and W. Thommen, Helv. Chim. Acta. **64**, 2109 (1981).
7. ^{13}C NMR ($CDCl_3$) signals were at δ 89.99, 56.06, 50.24, 45.42, 43.81, 28.94, 27.24, 22.04, 21.27 and 14.00.
8. This is also the view of Dr. Ian Fleming of Cambridge University to whom we are grateful for the NMR's.
9. Details can be obtained from Dr. McPhail.
10. K. R. Thakker, Ph.D thesis, Bombay University 1986. Dr. K.R.T. wishes to thank the Department of Science and Technology, New Delhi for generous support.
11. The necessity for using the proper quenching agent in alkali metal/NH_3 reactions has been stressed in a recent review by S. K. Pradhan, Tetrahedron **42**, 6351 (1986).
12. Less camphor was recovered. Independent experiments confirmed that no equilibration was taking place via cleavage of either pinacol. The possibility that pinacols from saturated ketones undergo such cleavage is unlikely.
13. Ref. 11 gives evidence that such dianions are formed from radical anions in a slow reaction wherein alkali metal concentration plays a part. O-protonation by NH_3 can only follow dianion formation.
14. Role of counterions is well known. See Ref. 6 and those cited therein.
15. W. S. Murphy and D. F. Sullivan, J. Chem. Soc. Perkin Trans. I, 999 (1972).

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