Tetrahedron Letters,Vol.24,No.19,pp 1983-1986,1983 0040-4039/83/191983-04$03.00/0
Printed in Great Britain

STEREOSELECTIVE CONTROL IN THE BASE-CATALYZED H-D EXCHANGE REACTION OF 5,6,7,8-TETRAKIS(METHYLENE)-2-BICYCLO[2.2.2]OCTANONE IRONTRICARBONYL COMPLEXES

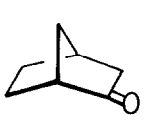
Raphy Gabioud and Pierre Vogel*

Institut de chimie organique de l'Université de Lausanne,
2, rue de la Barre, CH-1005 Lausanne, Switzerland.

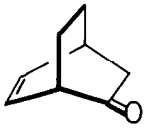
Summary. *The base-catalyzed H-D exchange of H-C(3) in the* endo-*$Fe(CO)_3$ monocomplex and the* endo,exo-*$[Fe(CO)_3]_2$ double complex of 5,6,7,8-tetrakis(methylene)-2-bicyclo[2.2.2]-octanone are highly stereoselective.*

The diastereotopic hydrogen atoms α to a carbonyl group of a chiral ketone can, in principle, show stereoselective keto-enol tautomerism.[1,2] The preference for axial over equatorial attack in the protonation of cyclohexenols was attributed by *Corey* and *Sneen* [3] to the necessity for proper orbital alignment in the enol fragment during protonation. Subsequent work has both reinforced and contradicted this interpretation.[4] A rate constant ratio k_{exo}/k_{endo} of ca 800 was reported for the direct base-catalyzed exchange of the $H_2C(3)$ hydrogen atoms in norbornanone 1.[1,5] Several explanations have been advanced for this stereoselectivity[1,2], e.g.: (1) torsional effects between H-C(3) and H-C(4) bonds, (2) steric hindrance to *endo* protonation of the enolate, (3) the least-motion principle (equivalent to *Corey*'s and *Sneen*'s hypothesis[3] of maximum overlap between the breaking α-(C-H) bond and the carbonyl π system) and (4) π-anisotropy in the enolate intermediate (non-equivalent π electron density extension between the two faces of norbornene[6]).

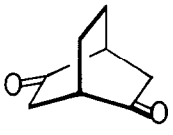
With minor structural modification in the skeleton of 2-bicyclo[2.2.2]octanone, as in 2 and 3, the diastereoselectivity for the H-D exchange at C(3) was lost. In contrast, monodeuteration at C(8) in bicyclo[4.2.2]deca-2,4,9-trien-7-one (4) was stereoselective, probably because of steric factors.[7] We report the base-catalyzed hydrogen-deuterium exchange reactions



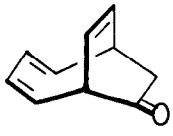
1



2

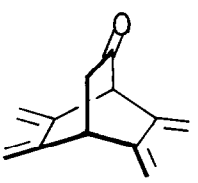


3

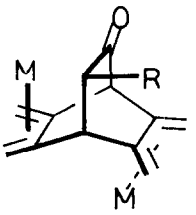


4

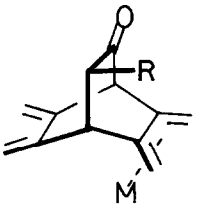
of 5,6,7,8-tetrakis(methylene)-2-bicyclo[2.2.2]octanone (5) and of its irontricarbonyl complexes 6 and 7. As expected, high diastereoselectivity was observed with the *exo,endo*-double complex 6; the less hindered face of the enolate intermediate was deuterated giving 8. To our surprise, however, the *endo* monocomplexed ketone 7 was also monodeuterated with high stereoselectivity yielding 9.



5



R = H : 6
R = D : 8

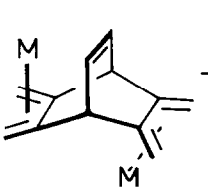


7
9

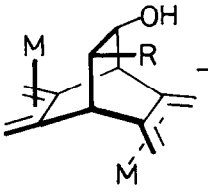
M = $Fe(CO)_3$

Ketones 5, 6 and 7 were prepared in the following way. Hydroboration/oxidation of the *endo,exo*-diiron complex 10 gave the corresponding alcohol 11.[8] In the presence of a 20-fold molar excess of trimethylamine oxide,[9] 11 was oxidized selectively into the monocomplexed alcohol 12 (78 %, acetone, 25^0, 50 min). Further oxidation of 12 into the uncomplexed 5,6,7,8--tetrakis(methylene)-2-bicyclo[2.2.2]octanol was a very slow reaction giving a small amount of 5 and several products of decomposition. CrO_3 oxidation of 11 (pyridine/CH_2Cl_2, 20^0, 10 min) yielded the doubly complexed ketone 6 (64 %). Under the same conditions, 12 furnished the monocomplexed ketone 7 (65 %). When treated with a ten-fold molar excess of trimethylamine oxide in acetone (25^0, 20 min), 6 gave a mixture of the *endo*-irontricarbonyl complexed ketone 7 (50 %) and the uncomplexed ketone 5 (31 %). The selectivity of these irontricarbonyl oxidations is not yet understood. In all cases, the *exo*-$Fe(CO)_3$ group is removed more rapidly than the *endo*-$Fe(CO)_3$ group, this was also true for 10.[10]

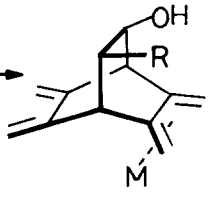
When treated in a 1:1 mixture of $CD_3OD/CDCl_3$ containing 1 % of anhydrous K_2CO_3, ketone 6 was monodeuterated into 8 (40^0, 1h). Prolonged heating of 6 in CD_3OD saturated with K_2CO_3 or containing 5-10 % of CD_3ONa did not exchange the second hydrogen atom at C(3) before decomposition of 6 (40^0, 2 - 4 days). The high diastereoselectivity of the base-catalyzed monodeuteration



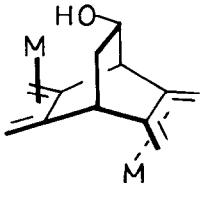
10



R = H : 11 → 6
R = D : 14 → 8



12 → 7
15 → 9



13

6 → 8 can be attributed to a steric factor, i.e. protonation of the enolate intermediate occurs preferentially from its less hindered face. When treated in 1:1 $CD_3OD/CDCl_3$ containing K_2CO_3 or CD_3ONa, the *endo*-complexed ketone 7 gave the monodeuterated ketone 9. The exchange of the second hydrogen atom at C(3) was also observed; at 35° it occurred ca 100 times more slowly than reaction 7 → 9 (by 360 MHz ^{1}H-NMR spectroscopy). The exchange was complete after 16 h in 1:1 $CD_3OD/CDCl_3$ with 1 % K_2CO_3. The lithium enolate of 7 generated by treatment with LDA in hexane at - 78° gave 9 after quenching with D_2O.[11]

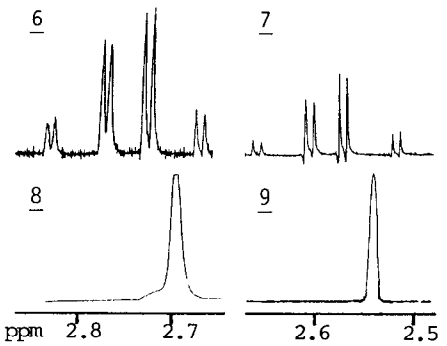
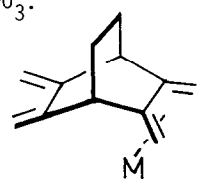


Figure 1: ^{1}H-NMR spectra.

The structures of 5 - 12 were determined by their mode of formation, elemental analyses and by spectroscopic data.[12] The deuterium content in 8 and 9 was determined by 360 MHz ^{1}H-NMR (see Fig. 1 for the $H_2C(3)$ signals of 6 & 7 and for the HDC(3) signals of 8 & 9) and mass spectrometry. The structure of 10 was established by X-ray cristallography,[8] and those of the alcohols 11[8] and 12 by ^{1}H- and ^{13}C-NMR spectroscopy using $Eu(dpm)_3$ and $Yb(dpm)_3$ induced chemical shifts, respectively. Reduction of ketone 6 with $LiAlH_4$ (THF, 20°, 15 min) gave the doubly complexed alcohol 13 (37 %). The deuterium position in 8 and 9 was further confirmed by the following experiments. Hydroboration/oxidation of 10 using $NaBD_4/BF_3$ gave 14 which was oxidized into 8 with CrO_3. Removal of the *exo*-$Fe(CO)_3$ group in 14 by treatment with trimethylamine oxide gave 15 which yielded 9 upon oxidation with CrO_3.[13]

X-ray cristallographic data on the *endo*-$Fe(CO)_3$ complex 16[14] showed that the two faces of the ethano bridge offer the same steric hindrance. If this is also the case in 7, the selectivity of the H-D exchange 7 → 9 cannot be attributed to a difference in the steric hindrance to protonation of the enolate intermediate. π-anisotropy of the enolate (pyramidal anion ?[15]) due to a field effect of the *endo*-$Fe(CO)_3$ group[16] could be invoked instead. Such a hypothesis though requires a rate enhancement for the base-catalyzed H-D exchange of 7 compared with that of 5, but competitive kinetic measurements by 360 MHz ^{1}H-NMR showed very similar rates with 5, 6 and 7. Specific solvation effects could be invoked , but again with this hypothesis alone it is difficult to reconcile the lack of reactivity difference between 5 and 7. The ^{1}H-NMR spectra of 6 and 7 suggest slightly twisted bicyclic skeletons. The vicinal coupling constants between H-C(4) and the two H-C(3) are not the same[12] (see Fig. 1). This distortion may arise from a dipole-dipole interaction between the $Fe(CO)_3$ and ketone groups. This hypothesis is consistent with the observation of a slight stereoselectivity (2:1) in the addition of CH_3MgI to 7. The Grignard reagent preferred the ketone face *syn* to the diene-$Fe(CO)_3$ complex. A skeleton distortion could also be invoked to explain the stereoselective base-catalyzed H-D exchange in 7.



16

Acknowledgments. We are grateful to Hoffmann-La Roche and Co., Basel, To the "Swiss National Science Foundation" and to "Fonds Herbette", Lausanne, for generous financial support.

References and Notes.

1. J. Toullec, Adv. in Phys. Org. Chem. 18, 1 (1982).

2. G. Lamaty, in "Isotopes in Organic Chemistry", E. Buncel, C.C. Lee, Ed., Elsevier Scient. Publ. Co., Amsterdam, Vol. 2, Chap. 2 (1976).

3. E. J. Corey and R. A. Sneen, J.Am.Chem.Soc. 78, 6269 (1956).

4. R. R. Fraser and P. J. Champagne, J.Am.Chem.Soc. 100, 657 (1978) and references cited therein; R. R. Fraser and P. J. Champagne, Can.J.Chem. 58, 72 (1980).

5. G. A. Abad, S. P. Jindal and T. T. Tidwell, J.Am.Chem.Soc. 95, 6326 (1973); N. H. Werstiuk and R. Taillefer, Can.J.Chem. 48, 3966 (1970).

6. S. Inagaki, H. Fujimoto and K. Fukui, J.Am.Chem.Soc. 98, 4054 (1976); G. Wipff and K. Morokuma, Tetrahedron Lett. 4445 (1980); W. H. Watson, J. Galloy, P. D. Bartlett and A. A. M. Roof, J.Am.Chem.Soc. 103, 2022 (1981); A. A. Pinkerton, D. Schwarzenbach, J. H. Stibbard, P. A. Carrupt and P. Vogel, ibid. 103, 2095 (1981); J.-P. Hagenbuch, P. Vogel, A. A. Pinkerton and D. Schwarzenbach, Helv. Chim. Acta 64, 1818 (1981).

7. J. B. Press and H. Shechter, J.Org.Chem. 40, 2446 (1975).

8. Ph. Narbel, A. A. Pinkerton, E. Tagliaferri, J. Wenger, R. Roulet, R. Gabioud, P. Vogel and D. Schwarzenbach, J. Organomet. Chem. 208, 335 (1981).

9. Y. Shvo and E. Hazum, J.Chem.Soc.Chem.Commun. 336 (1974); A. P. Humphries and S. A. R. Knox, J.Chem.Soc.Dalton 1514 (1978).

10. Ph. Narbel, R. Roulet, E. Tagliaferri and P. Vogel, J.Organomet.Chem. 194, 103 (1980).

11. Acid-catalyzed H-D exchanges in 6 and 7 could not be studied as these compounds decomposed rapidly under acidic conditions.

12. Characteristics of 5: m.p. 55-56°, UV(dioxane) 251(11600), 305(440), ^{1}H-NMR($CDCl_3$): 5.38(s,2H), 5.32(s,2H), 4.98(s,4H), 3.75(s,1H), 3.4(t,J=3Hz,1H), 2.4(d,J=3Hz,2H).
Characteristics of 6: m.p. 146-7°, ^{1}H-NMR(360 MHz, CD_2Cl_2): 3.88(s,1H), 3.63(dxd,J=2.9 & 2.5 Hz,1H), 2.79(dxd,J=18 & 2.5Hz,1H), 2.70(dxd,J=18 & 2.9Hz,1H), 2.19(d,J=3Hz,1H), 2.18(d,J=3Hz, 1H), 2.08(d,J=3Hz,1H), 1.89(d,J=3Hz,1H), 0.72(d,J=3Hz,1H), 0.64(d,J=3Hz,1H), 0.54(d,J=3Hz,1H), 0.44(d,J=3Hz,1H).
Characteristics of 7: m.p. 109-110°, ^{1}H-NMR(360 MHz, $CDCl_3$): 5.49(s,1H), 5.41(s,1H), 5.03(s, 1H), 5.01(s,1H), 3.75(s,1H), 3.52(dxd,J=2.9 & 2.6 Hz, 1H), 2.63(dxd,J=18 & 2.9 Hz,1H), 2.55 (dxd,J=18 & 2.6 Hz,1H), 1.98(d,J=3Hz,1H), 1.88(d,J=3Hz,1H), 0.43(d,J=3Hz,1H), 0.27(d,J=3Hz,1H).
Characteristics of 12: m.p. 91-92°, ^{1}H-NMR($CDCl_3$): 5.22(s,1H), 5.13(s,1H), 4.85(s,1H), 4.73 (s,1H), 4.45(m,H-C(2)), 3.32(d,J=3Hz,H-C(1)), 3.20(t,J=3Hz,H-C(4)), 2.50(dxdxd,J=13, 9 & 3 Hz, H-C(3R*)), 1.85(d,J=3Hz,2H), 1.8-1.5(m,H-C(3S*) & OH), 0.34(d,J=3Hz,1H), 0.30(d,J=3Hz,2H).
Characteristics of 13: m.p. 183-184°, ^{1}H-NMR($CDCl_3$): 4.60(dxdxdxd,1H), 3.36(d,1H), 3.28(t,1H), 2.62(dxdxd,1H), 2.19(d,1H), 2.06 & 2.03(d,2H), 1.86(dxdxd,1H), 1.85 & 1.67(d,2H), 0.54 & 0.48 (d,2H), 0.29 & 0.24(d,2H).

13. Details will be given in a full paper.

14. A. A. Pinkerton, G. Chapuis, P. Vogel, U. Hänisch, Ph. Narbel, T. Boschi and R. Roulet, Inorg. Chim. Acta 35, 197 (1979).

15. S. Wolfe, H. B. Schlegel, I. G. Csizmadia and F. Bernardi, Can. J. Chem. 53, 3365 (1975).

16. C. Barras, L. G. Bell, R. Roulet and P. Vogel, Helv.Chim.Acta 64, 2841 (1981) and references cited therein.

(Received in France 10 March 1983)