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# STEREOCHEMISTRY OF THE HYDROGENATION OF METHOXYCYCLOHEXANONES OVER PLATINUM METALS. A POLAR GROUP EFFECT IN THE CATALYTIC HYDROGENATION OF A C-O DOUBLE BOND

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2- and 4-Methoxycyclohexanones give the alcohols of higher cis/trans ratios than the corresponding methylcyclohexanones in the catalytic hydrogenation over platinum metals. This trend is most clearly seen over iridium and platinum among the six platinum metals. Hydrogenation with platinum gives the alcohols of higher cis/trans ratios in t-butyl alcohol than in other solvents.

Recently, it has been recognized that an alkoxyl group located at an allylic[1,2] or homoallylic[3,4] position has a considerable influence on the stereochemistry of hydrogenation of a C-C double bond. The addition of hydrogen to the double bond has been found to occur predominantly from the opposite side versus the alkoxyl group, particularly over the metals of low olefin isomerization activity such as osmium and iridium.[1] Polar group effects on hydrogenation stereochemistry are also seen even when the group is located far away from reaction center, as well known in the catalytic hydrogenation of 3-oxo-4-ene steroids over palladium.[5]

Although such effects may not always be of the same nature, similar effects are expected to be observed in the hydrogenation of other functional groups as well.

In this letter, we wish to report a polar effect of methoxyl group observed in the catalytic hydrogenation of a C-O double bond. The hydrogenation of 2- and 4-methoxycyclohexanones has been performed over the six platinum metals in ethanol at 25°C and an atmospheric pressure of hydrogen. The cis/trans isomer ratio of the alcohols produced is presented in Table 1, in comparison with those obtained from hydrogenation of the corresponding methylcyclohexanones under the same conditions. In general the methoxycyclohexanones give rise to the alcohols of higher

Table 1. Cis/trans Isomer Ratio of the Alcohol from Hydrogenation of Methoxy- and Methylcyclohexanones in Ethanol a)

| Catalyst | Cyclohexanone 2-Methoxy | Cyclohexanone 2-Methyl | $\frac{r_{OMe}}{r_{Me}}$ b) | Cyclohexanone 4-Methoxy | Cyclohexanone 4-Methyl | $\frac{r_{OMe}}{r_{Me}}$ b) |
|---|---|---|---|---|---|---|
| Ru | 2.2 | 1.8 | 1.2 | 2.5 | 2.0 | 1.3 |
| Rh | 2.2 c) | 2.0 d) | 1.1 | 3.9 e) | 3.0 f) | 1.3 |
| Pd | 3.6 g) | 1.5 h) | 2.4 | 3.7 i) | 1.4 j) | 2.6 |
| Os | 2.8 | 2.7 | 1.0 | 1.9 | 1.1 | 1.7 |
| Ir | 8.2 k) | 1.4 | 5.9 | 6.3 | 1.1 l) | 5.7 |
| Pt | 30 m) | 3.5 n) | 8.6 | 17 o) | 1.7 p) | 10 |

a) The ketone (0.2 ml) was hydrogenated in 5 ml ethanol at 25°C and atmospheric pressure, using 10 mg of the catalyst. The ketone was added after the catalyst had been shaken with hydrogen in the solvent. Unless otherwise noted, the products were analyzed after complete hydrogenation by glpc using the column packed with PEG 20M or diglycerol. The separation of cis- and trans-4-methoxycyclohexanols was obtained with their acetylation products. The products other than the alcohol (A: cyclohexane, B: methylcyclohexane, C: methoxycyclohexane, D: ethoxymethylcyclohexane, E: ethoxymethoxycyclohexane, F: cyclohexanol) are given below in per cent. b) The ratio of the cis/trans ratio of the alcohol from methoxycyclohexanone ($r_{OMe}$) to that from methylcyclohexanone ($r_{Me}$). c) Analyzed at 45% hydrogenation. A, 7.3; C, 28.3. d) B, 4.3; D, 19. e) C, 0.6; E, 3.6. f) Analyzed at 67% hydrogenation. B, 1.2; D, 6.1. g) Analyzed at 23% hydrogenation. A, trace; C, 15; E, 65. h) D, 75. i) E, 97. j) Analyzed at 86% hydrogenation. D, 98. k) Analyzed at 64% hydrogenation. l) B, trace; E, 3.5. m) Analyzed at 69% hydrogenation. A, 2.0; C and an unidentified product, 2.5; F, 1.3. n) B, 0.6; D, 17. o) Analyzed at 57% hydrogenation. C, 9.0; E, 10.5. p) B, 11; D, 27.

cis/trans ratios than the corresponding methylcyclohexanones. It should be noted, however, that the effect of the methoxyl group to favor the formation of the cis-alcohols is definitely more pronounced in the hydrogenation over iridium and platinum than over the other platinum metals, as seen from the values of $r_{OMe}/r_{Me}$ in Table 1. It is also to be noted that the methoxyl group at the C-4 has as great an effect as the methoxyl group at the C-2.

Similar polar group effects have been reported in the reduction of 4-substituted cyclohexanones with sodium borohydride and aluminum isopropoxide.[6)] In these reductions, however, the effect of 4-methoxyl group appears less pronounced than in the catalytic hydrogenation with iridium and platinum metals.

Table 2 shows the effect of solvents on the product stereochemistry in the platinum-catalyzed hydrogenation of the methoxy- and methylcyclohexanones where the most remarkable effect of the methoxyl group has been observed. It is seen that the stereochemistry is considerably influenced by the nature of solvents, but the solvent effect is very similar for the methoxycyclohexanones and for the methylcyclohexanones. Thus the cis/trans ratio of the alcohol produced increases in the order EtOH < i-PrOH < t-BuOH, irrespective of the ketones hydrogenated. Hydrogenation in less polar solvents, isopropyl ether and cyclohexane, or hydrogenation in acetic acid always gives the alcohols of smaller cis/trans ratios than in t-butyl alcohol. These results suggest that stereochemistry controlling step is the same for the methoxycyclohexanones and methylcyclohexanones, notwithstanding the great differences in the cis/trans ratio of the alcohol formed. The solvent effect observed here seems rather characteristic of the hydrogenation with platinum, since over other platinum metals different trends have been observed.[7)]

The hydrogenation of 4-methoxy- and 4-methylcyclohexanones has also been compared using a rhodium catalyst in isopropyl alcohol/hydrochloric acid, which is, to our knowledge, one of the best hydrogenation systems for obtaining high yields of axial alcohols from unhindered ketones.[8)] The results shown in Table 2 indicate that under this condition the polar nature of the methoxyl group did not affect the stereochemistry of hydrogenation, a smaller cis/trans ratio being obtained from 4-methoxycyclohexanone than from 4-methylcyclohexanone. Thus, with 4-methoxycyclohexanone the alcohol of a high cis/trans ratio can be obtained in the hydrogenation over platinum in t-butyl alcohol, while with 4-methylcyclohexanone hydrogenation over rhodium in isopropyl alcohol/hydrochloric acid gives the cis-alcohol in high yield.

The profound effects of the methoxyl group as well as of the solvents on the stereochemistry of the hydrogenation catalyzed by platinum suggest that the product

Table 2. Effect of Solvent on the Cis/trans Isomer Ratio of the Alcohol from Hydrogenation of Methoxy- and Methylcyclohexanones[a]

| Catalyst | Solvent | Cyclohexanone | | | |
|---|---|---|---|---|---|
| | | 2-Methoxy | 2-Methyl | 4-Methoxy | 4-Methyl |
| Pt | EtOH | 30[b] | 3.5[b] | 17[b] | 1.7[b] |
| Pt | i-PrOH | 50[c] | 6.7[d] | 17[e] | 2.4[f] |
| Pt | t-BuOH | 67[g] | 13[h] | 22[i] | 3.5[j] |
| Pt | i-Pr$_2$O | 28[k] | 4.5[l] | 19[m] | 1.7[n] |
| Pt | Cyclohexane | 17[o] | 4.9[p] | 8.2[q] | -[r] |
| Pt | AcOH[s] | 29[t] | 3.7[u] | 8.5[v] | 1.0[w] |
| Rh | i-PrOH/HCl[x] | - | - | 6.7[y] | 11[z] |

a) The ketone was hydrogenated in 5 ml of the solvent under the same conditions as described in Table 1. For the notations of the products other than the alcohol, see footnote a in Table 1. b) Reproduced from Table 1. c) A, 15; C, 5.9; F, 5.4. d) B, 0.5. e) C, 23. f) B, 26. g) A, 4.9; C, 3.9; F, 4.7. h) B, trace. i) C, 15. j) B, 21. k) A, 3.8; C, 4.9; F, 5.6. l) B, trace. m) C, 14. n) B, 20. o) A, not determined; C, 7.1; F, 8.7. p) B, trace. q) C,30 r) Deactivated during hydrogenation probably because of the formation of water by hydrogenolysis. s) The products were analyzed after neutralization with aqueous KOH, followed by extraction with ether. t) A, 4.2; C, 4.0; F; 4.1. u) B, trace. v) C, 34. w) B, 16. x) Conc. HCl, 0.05 ml, was added. y) C, 1.1. z) B, 0.7, an unidentified product, 0.5.

controlling step and/or the nature of the transition state for it may differ from those in the hydrogenation over the other metals.[9] It is suggested that the polarization of the carbonyl group on adsorption to the catalyst or a polar addition of hydrogen to the adsorbed carbonyl group plays an important role in determining the product stereochemistry over platinum. Strong solvation around a polarized carbonyl group may lower the stereoselectivity as well as the rate of hydrogenation, as would be the case in the hydrogenation in ethanol.

Interestingly, hydrogenation of 5α-cholestan-3-one over platinum in t-butyl alcohol gave 5α-cholestan-3β-ol (an equatorial alcohol) predominantly. On the other hand, hydrogenation of the same ketone over rhodium in isopropyl alcohol/hydrochloric acid gave 5α-cholestan-3α-ol (an axial alcohol) in high yield.10) These results are also indicative that the product controlling step over platinum might be different from those over other metals. Studies on the hydrogenation of steroid ketones are in progress and will be described elsewhere.

The platinum catalyst used in this study was prepared by reduction of platinum hydroxide with hydrogen in water.11) The water became strongly acidic after the reduction. The platinum black thus formed was washed with water by decantations and subjected to further reduction with hydrogen, followed by washing with water, and then dried over silica gel. Another platinum catalyst, obtained by reduction of an Adams platinum oxide with hydrogen but made carefully free of alkaline substances,12) gave nearly the same results as the platinum catalyst used in this study, with respect to the stereochemistry of the hydrogenation and the solvent effect on it. The other platinum metals were prepared by the procedures described previously.12)

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although the effect of solvents for the iridium-catalyzed hydrogenation appears not always alike to that found for platinum (unpublished observations).

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