STEREOCHEMISTRY OF THE HYDROGENOLYSIS OF 1,2-DISUBSTITUTED FERROCENES IN ACID MEDIA

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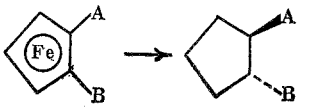
The decomplexation of stable π-cyclopentadienyl metal complexes is an important problem in organic synthesis. The methods for the preparation of such systems as ferrocene and cymanthrene, which may be seen as precursors for cyclopentanes, have been highly developed while the direct introduction of a series of substituents into cyclopentanes is impossible. In addition ferocene and cymanthrene derivatives are rather readily obtained in optically active form. The source of activity may be either a chiral plane or chiral center in the side chain. Hence, promise is found for the synthesis of optically-active substituted cyclopentanes.

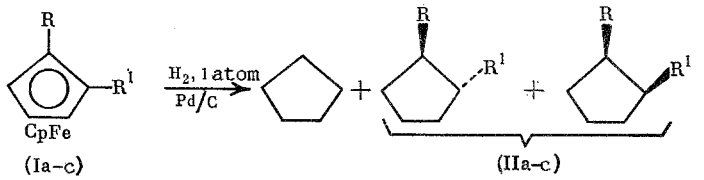
Of the two methods described for the decomplexation of ferrocene and its derivatives using lithium in ethylamine [1] and by hydrogenolysis in acid media [2], only the latter method which leads to cyclopentane derivatives offers hope for converting plane chirality to site chirality using enantiomeric starting compounds and the preparation of optically active products according to the scheme below [3].



The decomposition of plane-chiral ferrocenes by lithium in ethylamine, which involves the formation of a cyclopentadienyl anion, must proceed with loss of optical activity.

In our previous work [4], we showed that a series of mono- and disubstituted ferrocenes with substituents such as alkyl, dimethylaminomethyl, and carboxyl groups readily undergo catalytic hydrogenolysis in acid media with cleavage of both Cp–Fe bonds and retention of the functional groups to give a mixture of one equivalent cyclopentane (from the unsubstituted ring) and one equivalent of its corresponding derivative (from the substituted ring).

In the present work, we studied the stereochemistry of the products of the hydrogenolysis of enantiomeric 1,2-disubstituted ferrocenes (Ia)-(Ic) over Pd/C in CF_3CO_2H at 50°C for 2-6 h.* We were primarily interested in the geometrical configuration of the 1,2-disubstituted cyclopentanes formed and secondarily in whether optical activity is retained in the hydrogenolysis products.



(Ia-c) (IIa-c)

$R = CH_3$, $R^1 = COOH$ (a); $R = CH_3$, $R^1 = CH_2NMe_2$ (b); $R = (CH_2)_6COOEt$, $R^1 = (CH_2)_7CH_3$ (c).

In order to avoid distortion of the diastereomer composition, the products were analyzed by PMR spectroscopy immediately after separation from the reaction mixture without purification by crystallization or chromatography. The reaction leads to the expected 1,2-disubstituted cyclopentanes (IIa)-(IIc). Product (IIb) was isolated as its iodomethylate.

*The reaction time depends on the specific catalyst portion.

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The ^1H NMR spectra of (IIa) and (IIb) and the ^{13}C NMR spectra of (IIa)-(IIc) show doubling of some of the signals. For example, the signals at 0.99 and 1.10 ppm for (IIa) and at 0.82 and 1.05 ppm for (IIb) with integral intensity ratio 70/30 and 80/20, respectively, corresond to the methyl protons in the PMR spectra of these compounds. Thus, (IIa) and (IIb) are isomer mixtures. Comparison of the ^1H NMR spectra of the mixture of the diastereomers of (IIa) obtained and the trans isomer of this compound [5] showed that this isomer specifically predominates in the mixture (70%). We note that, in contrast to 2-methylcyclopentanols [6], $\delta_{Me}^{trans} > \delta_{Me}^{cis}$ ($\Delta\delta$ 0.11 ppm). The similarity of the ^1H NMR spectra of (IIa) and (IIb) indicates that the trans isomer is predominantly formed in the hydrogenolysis of (Ib) (80%). The ^1H NMR spectrum of (IIc) does not yield stereochemical information.

The final conclusion concerning the geometrical configuration of (IIa)-(IIc) was made on the basis of the ^{13}C NMR data. This method has been shown, as in the work of Roberts et al. [7], to give an unequivocal answer to the question of the relative configuraiton of the substituents in 1,2-disubstituted cyclopentanes. If one of the vicinal substituents is a methyl group, as in (IIa) and (IIb), its signal in the case of cis substituent configuration always lies upfield to that for the case of trans configuration. Indeed, the less intense methyl signal in the ^{13}C NMR spectra of (IIa) and (IIb), in accord with their PMR spectra, lie at 16.1 and 16.3 ppm, while the more intense signals lie at 19.7 and 20.0 ppm. When the indicator methyl group is lacking in 1,2-disubstituted cyclopentane, as in the case of (IIc), the assignment of the configuration of the isomers may be made by comparing the $\delta^{1,3}C$ values of the tertiary carbon atoms. In the case of prostaglandins E, Lüthy et al. [8] have shown that the chemical shifts of the carbon atoms of the cyclopentane ring bound to hydrocarbon substituents are lower in the case of cis configuration than in the case of trans configuration.

The ^{13}C NMR spectrum of (IIc) shows two groups of CH signals of different intensity: two signals (1:1) with predominant intensity (2CH) at 46.11 and 46.15 ppm. and a signal of lesser intensity (2CH) upfield at 42.74 ppm. Thus, the trans isomer predominates in the mixture of diastereomers of (IIc), i.e., prostanoic acid itself ($\Delta\delta_{CH}^{trans-cis}$ = 3.37-3.41 ppm).* The isomer ratio (75/25) was determined from the ratio of the integral intensities of these two groups of signals in the spectrum of (IIc) with the paramagnetic additive, tris(acetylacetonato)Cr(III), obtained with a 30 sec delay between pulses.

Products (IIa)-(IIc) are racemic since the conditions used for the decomplexation of plane-chiral ferrocene derivative are unsuitable for the preparation of optically active cyclopentanes.

These results indicate stereoselectivity but not enantioselectivity in the hydrogenolysis of (Ia)-(Ic). The loss of optical activity indicates the multistep nature of the reaction and the generation of an achiral intermediate in one of the step preceding the formation of (IIa)-(IIc), likely as the result of the total cleavage of the Fe–ligand bond. The predominant trans configuration of products (IIa)-(IIc) does not correspond to the cis-stereochemistry of the hydrogenation of aromatic systems, which usually is favored under heterogeneous catalysis conditions.

EXPERIMENTAL

The ^1H and ^{13}C NMR spectra were taken on a Bruker WP-200SY spectrometer. The ^1H NMR spectra were taken at 200.13 MHz and the ^{13}C NMR spectra were taken at 50.33 MHz. $CDCl_3$ and TMS were the solvent and internal standard for (Ib), (IIa), and (IIc), while D_2O and $Me_3Si(CH_2)_3SO_3Na$ were the solvent and internal standard for (IIb). The proton-decoupled spectra were compared with undecoupled spectra with the nuclear Overhauser effect in order assign the signal in the ^{13}C NMR spectra to secondary, tertiary, and quaternary carbons. This assignment was carried out using the DEPT multipulse sequence for (IIc).

Enantiomeric (Ia)-(Ic) were prepared according to our previous procedures [9, 10]. The enantiomeric purity was 77.5% for (Ia) and (Ib) but only 20% for (Ic).

2-Methylcyclopentanecarboxylic acid (IIa). ^1H NMR spectrum (δ, ppm): 0.99 d (CH_3, cis isomer, ^3J = 7.0 Hz), 1.10 d (CH_3 trans isomer, ^3J = 6.5 Hz), 1.15-2.40 m (ring protons), 2.82 q ($C\underline{H}CO_2H$, cis isomer, ^3J = 7.5 Hz). ^{13}C NMR spectrum (δ, ppm): cis isomer: 16.14

*The signals for the two tertiary carbon atoms are, thus, resolved only for the trans isomer but not for the cis isomer.

br. q ($\underline{C}H_3I$, ^1J = 127 Hz), 23.81 br. t, 27.56 br. t, 38.84 br. t ($3CH_2$, ^1J = 130 Hz), 37.49 br. d ($\underline{C}HCH_3$), ^1J = 128 Hz), 48.54 br. d, ($\underline{C}HCO_2H$, ^1J = 131 Hz), 181.90 br. s (CH_2H); trans isomer: 19.69 br. q (CH_3, ^1J = 126 Hz), 2465 br. t, 30.12 br. t, 35.01 br. t ($3CH_2$; ^1J = 130 Hz), 39.48 br. d ($\underline{C}HCH_3$, ^1J = 132 Hz), 51.99 br. d ($\underline{C}HCO_2H$, ^1J = 131 Hz), 183.00 br. s (CO_2H).

Iodomethylate of 2-Methyl-1-dimethylaminomethylcyclopentane (IIb). ^1H NMR spectrum (δ, ppm): 0.82 d (CH_3, cis isomer, ^3J = 7.2 Hz), 1.05 d (CH_3, trans isomer, ^3J = 6.5 Hz), 1.10-2.30 m (ring protons), 3.00-3.55 m (CH_2N), 3.152 s ($N(CH_3)_3$). ^{13}C NMR spectrum (δ, ppm): cis isomer: 16.29 br. q (CH_3, ^1J = 125 - Hz), 38.52 br. d, 39.51 br. d ($\underline{C}HCH_3$, $\underline{C}HCH_2$, ^1J = 151 Hz), 43.49 q. t ($N(CH_3)_3$, $^1J_{C,H}$ = 148, $^1J_{14N,C}$ = 3.7 Hz), 70.98 br. t (CH_2N, ^1J = 151 Hz); trans isomer: 20.01 br. q (CH_3, ^1J = 125 Hz), 41.38 br. d, 43.80 br. d ($\underline{C}HCH_3$, $\underline{C}HCH_2$, ^1J = 130 Hz), 55.77 q. t ($N(CH_3)_3$, $^1J_{CH}$ = 148, $^1J_{14N,C}$ = 3.5 Hz), 73.90 br. t (NCH_2, ^1J = 151 Hz).

2-Octyl-1-(6-ethoxycarbonylhexyl)cyclopentane (IIc). ^{13}C NMR spectrum (δ, ppm): 14.11, 14.25 ($2CH_3$), 22.67, 30.45 ($2CH_2$, ring, cis isomer), 22.78 ($CH_2\underline{C}H_2$), 23.99, 35.39, 35.50 ($3CH_2$, ring, trans isomer), 28.58, 28.78 ($2\underline{C}H_2$, ring, cis isomer), 32.48, 34.58 ($2CH_2$, ring, trans isomer and $\underline{C}H_2CO_2$), 25.14, 28.45, 28.67, 29.29, 29.46, 29.79 (2C) (other 7 CH_2).

CONCLUSIONS

The catalytic hydrogenolysis of enantioimeric 1,2-disubstituted ferrocenes in H_2 at 1 atm over Pd/C in CF_3CO_2H at 50°C leads predominantly to the trans isomers of the corresponding 1,2-disubstituted cyclopentanes; optical activity is lost.

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