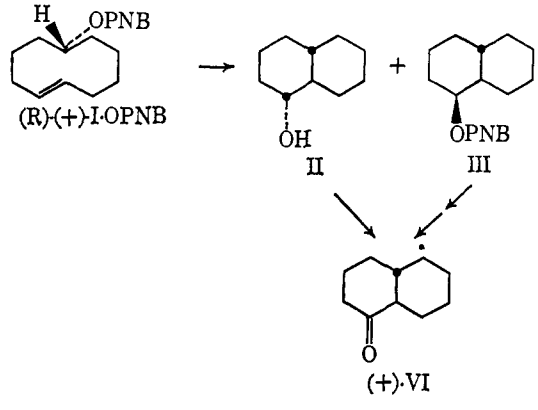
OH), $[\alpha]^{30}_{365}$ 21.1° (*c* 1.6, $CHCl_3$), was converted[6] to (+)-I-OCH_3, $[\alpha]^{30}_{365}$ 24.2° (*c* 0.9, $CHCl_3$). Cleavage[7] of the double bond followed by esterification of the diacid gave (−)-dimethyl 5-methoxysebecate, $[\alpha]^{30}_{365}$ −0.90° (*c* 3.56, $CHCl_3$).[5] This acid was shown to have the *R* configuration by comparison with (S)-(+)-dimethyl 5-methoxysebecate, $[\alpha]^{30}_{365}$ 2.85° (*c* 3.02, $CHCl_3$), derived from (S)-(−)-β-methoxyadipic acid, $[\alpha]^{30}_{365}$ −23.8° (*c* 6.03, $CHCl_3$),[4,8] as follows. Optically active (S)-(−)-β-methoxyadipic acid[8] was converted to (S)-(+)-3-methoxy-1,6-hexanediol by reduction with $LiAlH_4$. The active methoxyglycol was converted to the ditosylate which was added to a DMF solution of 2 equiv of sodium diethylmalonate. Saponification and decarboxylation followed by esterification gave (S)-(+)-dimethyl 5-methoxysebecate. These correlations show that (+)-I-OH, and the related (+)-I-OPNB, have the *R* configuration.

The absolute configurations of II and III derived from active I-OPNB were established by conversion to active *trans*-α-decalone of known configuration.[9]

Solvolysis of (*R*)-(+)-I-OPNB in 90% acetone at 100° gave active II and III which were separately converted to (+)-*trans*-α-decalone (VI) (both samples showed a negative Cotton effect in methanol).[9] In a parallel experiment it was found that (−)-*trans*-α-decalone (positive Cotton effect in methanol) is derived from (*S*)-(−)-I-OPNB. This establishes that cyclization of I-OPNB involves inversion of C_1 as in IV. Thus, the *p*-nitrobenzoate ion migrates a considerable distance in the I → III rearrangement. The observed stereoselectivity may result from the fact that return to the *trans,trans* isomer (II-OPNB) requires an even longer migration route and therefore does not compete with solvent capture.



The results of the ^{18}O experiments are summarized in Table I. In these experiments ether- and carbonyl-^{18}O-labeled I-OPNB was solvolyzed and the distribution of the label in the rearrangement product (III) was determined[2,10]—scrambling does not occur prior or subsequent to the rearrangement and no label is lost.[2] Carbonyl-labeled ester was described earlier;[2] ether-labeled ester was prepared from *trans*-5-cyclodecenone-^{18}O ($LiAlH_4$ reduction followed by esterification) which was obtained by base-catalyzed exchange of the ketone[11] and $H_2{}^{18}O$ in dioxane.

Table I. Carboxyl Oxygen Equilibration for the I-OPNB → III Rearrangement in 90% Acetone at 100°

Labeled I-OPNB (amt)[a]	Amt[a] of ether-^{18}O for III	% equilibration
Ether-^{18}O (3.95 ± 0.04)[b]	2.57 ± 0.01[b]	70 ± 1[b]
Ether-^{18}O (3.95 ± 0.04)	2.54 ± 0.02	71 ± 2
Carbonyl-^{18}O (2.47 ± 0.01)	0.90 ± 0.01	73 ± 1
Carbonyl-^{18}O (3.98 ± 0.04)[c]	1.35 ± 0.02	69 ± 2

[a] Atom % excess ^{18}O. [b] Uncertainties determined from limiting values for a series of determinations. [c] Data in this row taken from ref 2.

The ^{18}O experiments confirm that rearrangement does not result in complete oxygen equilibration. This is a remarkable result considering the long migration route (IV) and points up a most interesting property of the ion-pair intermediate(s) involved in this transformation. Evidently the carboxyl oxygen atoms are not equivalent in ion pairs related to unreactive secondary alkyl esters. In some ways the present result is similar to the report[12] that the α-phenylethyl α-naphthoate ion pair gives ester with both inversion and retention of configuration with incomplete (~60%) oxygen equilibration. The required relocation of the ions for forming inverted product appears to be similar to that involved in the I → III rearrangement.

(5) Satisfactory elemental analyses were obtained for all new compounds, and ir and nmr spectra of active compounds were indistinguishable from those of authentic racemic samples.
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(12) E. H. White and D. J. Woodcock, "Chemistry of the Amine Group," S. Patai, Ed., John Wiley & Sons, Inc., New York, N. Y., 1968, p 450.

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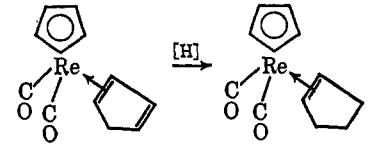
Stereospecific Hydrogenation of Nickelocene[1]

Sir:

Organometallic complexes containing partially coordinated ligands have often been hydrogenated and the amount of hydrogen consumed taken as a measure of the extent of uncoordinated unsaturation in the ligands, *e.g.*[2]



Analogous examples have been reported for complexes of iron,[3] chromium,[3] cobalt,[4] and molybdenum.[5] Nickelocene, $(\pi\text{-}C_5H_5)_2Ni$, is similarly hydrogenated

(1) Presented at the 157th National Meeting of the American Chemical Society, Minneapolis, Minn., April 13–18, 1969.
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Table I. Proton Nmr Data for π-C_5H_5Ni-π-C_5H_7 and π-C_5H_5Ni-π-$C_5H_5D_2$[a]

π-C_5H_5Ni-π-C_5H_7			π-C_5H_5Ni-π-$C_5H_5D_2$		
δ, ppm	Multiplicity	Assignment[b]	δ, ppm	Multiplicity	Assignment[b]
5.12	1	C_5H_5	5.22	1	C_5H_5
4.98	3[c]	H_a	5.08	3[c]	H_a
3.83	1	H_b	3.91	2[c]	H_b
1.15	AA'BB'	*exo*-Methylene	1.23	1	*exo*-Methylene[d]
0.67	multiplet	*endo*-Methylene	...	..	

[a] 100 MHz, C_6D_6 solvent, tetramethylsilane internal standard. [b] Relative intensities are in accord with these assignments (see text). [c] $J_{H_a-H_b} = 2.7$ Hz, $J_{H_a-H_{methylene}} \cong J_{H_b-H_{methylene}} \leq 1.0$ Hz. [d] H–D coupling not observed.

with Raney nickel,[6] producing π-C_5H_5Ni-π-C_5H_7 (I). Although the stereochemistry of free olefin hydrogenation has been exhaustively studied,[7,8] the stereochemical nature of metal-complexed olefin hydrogenation has apparently escaped attention.

We wish to report the results of stereochemical studies on nickelocene hydrogenation. We have found that the hydrogenation is stereospecific, with the hydrogen atoms entering from the most hindered side of the cyclopentadienyl ring. This mode of addition sharply contrasts that observed in metal-free olefin systems.[7,8] The stereochemical corridor of the entering hydrogen atoms suggests participation of the nickel nucleus in the hydrogen-transfer step.

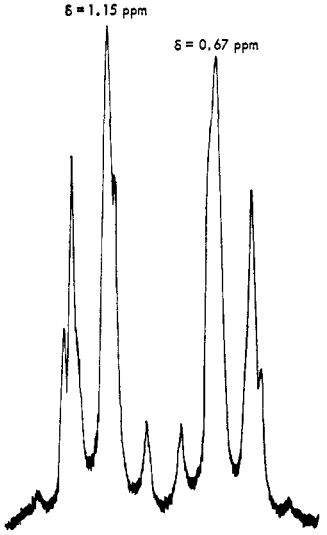

Figure 1. Decoupled methylene region of the 100-MHz nmr spectrum of π-$C_5H_5Ni\pi$-C_5H_7.

Nickelocene and hydrogen react directly in tetrahydrofuran solution at 50° and 400 psi to afford I in 50–60% yield. The use of deuterium affords 45–50% yields of π-C_5H_5Ni-π-$C_5H_5D_2$ (II), based on nickelocene charged. That two and only two deuteriums are incorporated was shown by high-resolution mass spectrometry. The hydrogen and deuterium reactions proceed after induction periods of approximately 30 and 60 min, respectively, suggesting either *in situ* generation of a hydrogen-transfer agent or removal of hydrogenation inhibitor. Addition of Raney nickel, palladium on charcoal, or $[(C_6H_5)_3P]_3RhCl$[9] to the reaction mixture eliminates the induction period and allows the hydrogenation to take place at lower temperatures. These data indicate that the nickel metal formed in the direct reaction functions as a catalyst for further hydrogenation of nickelocene. The stereospecificity observed in the direct reactions is preserved in the experiments employing added catalyst.

Proton nmr data for the dihydro and dideuterio complexes are displayed in Table I. Both complexes exhibit a sharp singlet corresponding to the five equivalent cyclopentadienyl protons, a triplet due to the unique allylic proton H_a, and a further resonance assigned to the pair of equivalent allylic protons H_b. (These assignments are in agreement with those made by earlier workers.[10]) The relative intensities of these resonances are 5:1:2 for both complexes, precluding the presence of deuterium in the C_5H_5 or allylic positions of II. The H_b resonance of II occurs as a doublet, but this fine structure is not observed for I owing to minor coupling with the methylene protons. That this coupling is negligibly small was demonstrated by double irradiation experiments (*vide infra*).

The *endo* and *exo* protons of I, having different proximities to the nickel atom, exhibit different chemical shifts,[11] allowing analysis of this portion of the decoupled spectrum as an AA'BB' system.[12] Decoupling of the H_b resonance collapses the H_a resonance to a sharp singlet, but sharpens the methylene pattern only slightly indicating $J_{H_bHCH_2} \leq 1.0$ Hz (Figure 1). Iterative analysis of the decoupled methylene region yields the following parameters: $\delta_A = \delta_{A'} = 0.67$ ppm, $\delta_B = \delta_{B'} = 1.15$ ppm, $J_{AA'} = J_{BB'} = 7.5$ Hz, $J_{AB} = J_{A'B'} = -16.3$ Hz, and $J_{AB'} = J_{A'B} = 2.7$ Hz.

We propose that the δ 1.15 and 0.67 resonances of I are due to the *exo* and *endo* protons, respectively. An upfield shift is to be expected for the *endo* protons owing to the added shielding by the nonbonding d electrons of nickel.[13] Our assignment is supported by the broadness of the high-field methylene triplet. This feature cannot be explained by spin–spin coupling, as shown by the persistence of this broadening in the doubly irradiated spectrum (Figure 1). This broadening, however, is consistent with relaxation of the

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endo-proton nuclear spins by interaction with the nickel atom.

The simplicity of the methylene resonance of π-C_5H_5Ni-π-$C_5H_5D_2$ demonstrates the *cis* stereochemistry of the incorporated deuteriums, since a *trans* orientation should afford both *endo* and *exo* resonances analogous to I. The chemical shift of the methylene protons of II corresponds closely to that of the low-field BB′ multiplet of I. The deuterium atoms have replaced the protons giving rise to the high-field resonance, and, therefore, can be assigned the *endo* configuration.

The departure from the usual stereochemistry in catalytic hydrogenation observed in this study may prove to be a general feature of organic ligands coordinated to transition metals. We plan to examine this possibility.

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Studies on the Hepatic Microsomal N-Dealkylation Reaction. Molecular Oxygen as the Source of the Oxygen Atom

Sir:

The TPNH-dependent oxygenases associated with the endoplasmic reticulum of mammalian hepatic cells catalyze the oxidative dealkylation of a wide variety of N- and O-alkyl compounds, including amines, amides, carbamates, sulfonamides, and aromatic ethers.[1] The most likely mechanism[1,2] for this enzymatic reaction involves hydroxylation of the carbon atom adjacent to the heteroatom as the initial reaction step. With a tertiary amine as substrate, a carbinolamine would be produced. This unstable intermediate would then dissociate to form the dealkylated amine and an aldehyde, the observed reaction products (eq 1). Alternatively it has been suggested[3,4] that oxidative dealkylation may proceed by the initial formation of an N-oxide which in turn could rearrange to the carbinolamine intermediate (eq 2). In support of this pathway it can be mentioned that enzymatic N-oxidation is a known reaction[5] and further that the dealkylation of N-oxides to form dealkylated amine and aldehyde is a known chemical reaction.[4]

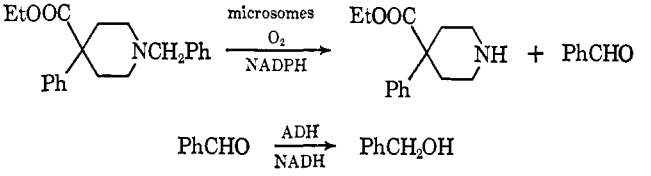
$$R_2NCH_2R \xrightarrow{[O]} [R_2NCHOHR] \longrightarrow R_2NH + O{=}CHR \quad (1)$$

$$R_2NCH_2R \xrightarrow{[O]} R_2\overset{\uparrow}{\underset{O}{N}}CH_2R \longrightarrow [R_2NCHOHR] \quad (2)$$

One difference between these two possible reaction pathways would be the source of the oxygen atom. If the reaction is indeed a typical microsomal hydroxylation (mechanism 1) the carbonyl oxygen in the aldehyde produced should derive from molecular oxygen. This would not be true in the case of mechanism 2. The probable[6] mechanism for the Fe^{II}-catalyzed dealkylation of tertiary amine oxides requires that the oxygen in the carbinolamine be derived from solvent water and not from N-oxide oxygen. The same situation exists for the earlier mechanism suggested by Craig, *et al.*[7] Thus it became of considerable interest to establish the source of carbonyl oxygen in the enzymatic dealkylation reaction.

Oxygen-18 studies, however, present a serious difficulty, *i.e.*, aldehydes in water solution rapidly exchange carbonyl oxygen with solvent water oxygen.[8] For this and other reasons it seemed impractical to investigate either N-demethylation or N-deethylation initially. We therefore turned to enzymatic N-debenzylation with the hope that the benzaldehyde formed would exchange with water slowly enough to allow the oxygen to be trapped as benzyl alcohol by a coupled enzymatic reduction. This possibility was investigated as follows. When benzaldehyde-^{18}O (37 atom %) was dissolved in phosphate buffer (pH 7.4), allowed to stand 15 min, and then reduced by the addition of horse liver alcohol dehydrogenase (LADH) and 1 equiv of NADH the benzyl alcohol recovered contained only 1.1 atom % ^{18}O. When, however, benzaldehyde-^{18}O (37 atom %), LADH, and NADH were added simultaneously to buffer, the resultant benzyl alcohol contained 7 atom % ^{18}O (19% recovery of ^{18}O). Thus, although the exchange reaction readily occurs, ^{18}O can be partially trapped if reduction to benzyl alcohol occurs rapidly enough.

Thus encouraged, we next carried out the following coupled enzymatic dealkylation–reduction sequence using oxygen-18-labeled molecular oxygen.



A solution containing washed liver microsomes[9] from 6 g of rat liver, 5 mg of alcohol dehydrogenase, 100 mg of NADH, 70 mg of $NADP^+$, 200 μmoles of isocitric acid, and 1 mg of isocitric dehydrogenase in 20 ml of 0.1 *M* phosphate buffer (pH 7.4) was prepared in a 125-ml reaction flask. The solution was then frozen in liquid nitrogen and 50 μmoles of N-benzyl-4-phenyl-4-carbethoxypiperidine hydrochloride was added. After evacuation and the addition of 1 mmol of $^{18}O_2$ (95 atom %), the closed flask was heated at 37° with stirring for 0.5 hr. The reaction product, benzyl alcohol, was recovered by extraction, purified by gas–liquid partition chromatography, and found (by mass spectroscopy) to contain 29 atom % of ^{18}O. Repetition of the experiment yielded benzyl alcohol containing 26 atom % ^{18}O. A control experiment in which the substrate was benzaldehyde instead of the N-benzylamine

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