On the Use of the Wilkinson Rhodium Catalyst for the Homogeneous Hydrogenation of Unsaturated Thiophene Derivatives

ANNA-BRITTA HÖRNFELDT,
JAN SIMON GRONOWITZ and
SALO GRONOWITZ

Chemical Center, Division of Organic Chemistry, University of Lund, Lund, Sweden

The strong inhibitory effect of compounds containing divalent sulphur on platinum metal catalysts used for hydrogenation is well-known.[1,2] Therefore difficulties are often encountered in the catalytic hydrogenation of unsaturation in the side-chain of thiophene derivatives. Due to the poisonous effect of the thiophene ring, large amounts of palladium or platinum type catalysts [3,4] must often be used, and high pressures (100 atm) applied for the hydrogenation of double bonds.[3,4] Examples in which more catalyst than substrate has been used are described in the literature.[5] Catalyst preparation and conditions are often very critical in order to obtain reproducible results.

Special types of Raney-nickel catalysts have also been used,[6] but in this case desulphurization is often a competing reaction [7] and high pressure has to be applied.[6] Rhenium heptasulphide has been used as a catalyst for the reduction of the azomethine bond in thiophene derivatives,[8] and for the reduction of nitro to amino group.[9]

Due to the poisonous effect of the ring sulphur on most hydrogenation catalysts, sodium amalgam in alcohol has often been used for the hydrogenation of double bonds in conjugation with the thiophene ring.[3,7]

Recently Wilkinson *et al.*[10] demonstrated that tris(triphenylphosphine)-chlororhodium(I) was an excellent catalyst for the catalytic homogeneous hydrogenation of olefins at atmospheric pressure and room temperature.

In a brilliant series of papers Wilkinson elucidated the mechanism of the homogeneous catalytic hydrogenation and the effect of some structural changes in simple olefins on the reaction rate.[11,12] The usefulness of the Wilkinson catalyst in solving preparative problems in organic chemistry

has been demonstrated in some recent work [13-16] and the method is of great importance for deuterium labelling, as no scrambling occurs.[17]

Wilkinson states that strongly coordinating compounds such as thiophene at high concentration totally prevent reduction at 25°C and 1 atm. However, as no quantitative data on the poisonous effect of thiophene were given, we found it worthwhile to study the homogeneous catalytic hydrogenation of some unsaturated thiophene derivatives with tris(triphenylphosphine)-chlororhodium(I) as catalyst.

The hydrogenations were carried out on a preparative scale in a benzene-hexane mixture as solvent and in the usual Parr-apparatus at a few atmospheres pressure.
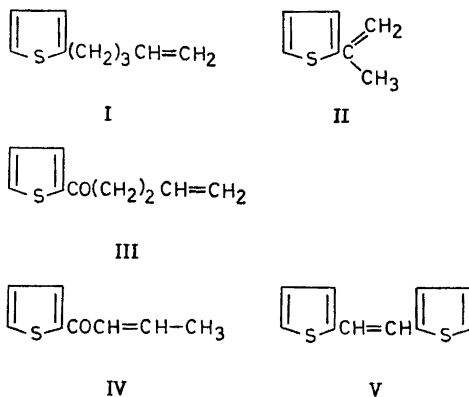
We found that isolated double bonds such as that in 5-(2-thienyl)penten-1 (I) or conjugated double bonds such as that in isopropylidene thiophene (II) are smoothly and rapidly reduced in high yield to the saturated thiophene derivatives. Likewise non-conjugated as well as conjugated unsaturated ketones such as (III) and (IV) were smoothly hydrogenated in a few hours to the saturated thiophene ketones.

Only *trans*-1,2-di(2-thienyl)ethene (V) reacted more slowly. Under the same conditions as used for I—IV, the reduction was not complete after 48 h. However, by increasing the temperature and the catalyst concentration V could also be easily hydrogenated to the ethane in a few hours. The hydrogenated products were identified by their IR- and NMR-spectra or by comparison with authentic samples.

We have made no attempts to work out the most efficient conditions. Our results clearly demonstrate, however, that the poisonous effect of the thiophene ring on the rhodium catalyst is not serious, and that it is the catalyst par excellence for the convenient hydrogenation of ethylenic bonds in thiophene derivatives.

III and IV were prepared directly from the appropriate carboxylic acid and thiophene according to the method of Yurev et al.[18] It should, however, be pointed out that isomerization occurs in the reaction with vinylacetic acid, leading to IV, which was apparently overlooked by Yurev et al.[18] Wolff-Kishner reduction of III yielded I.

Experimental. General hydrogenation procedure. The reactions were carried out in a 250 ml bottle of a low pressure Parr hydrogenation apparatus. 300 mg of tris(triphenylphosphine)-chlororhodium(I) was dissolved in 80 ml of degassed benzene and 30 ml of degassed hexane in the hydrogen-swept flask. The ethylenic thiophene derivative (0.050 mole) was then added and the solution hydrogenated at 3−4 atm. When the theoretical amount of hydrogen had been taken up (approximately 2−3 h) absorption of hydrogen ceased. The product was separated from the catalyst by chromatography on a silica gel column, using benzene as eluent. The benzene was removed and the residue distilled or recrystallized.

Butyl 2-thienyl ketone. 8.3 g (0.050 mole) of 4-(2-thenoyl)butene-1 [18] yielded on hydrogenation 6.7 g (79 %) of butyl 2-thienyl ketone, b.p. 126−128°C/14 mm Hg, $n_D^{20} = 1.5310$, having the same physical and spectral data as an authentic sample prepared by the acylation of thiophene with valeric acid.[19]

5-(2-Thienyl)pentene-1. From 18.3 g (0.11 mole) of 4-(2-thenoyl)butene-1,[18] following the usual procedure of the Wolff-Kishner reduction,[20] 12.0 g (72 %) of 5-(2-thienyl)penten-1 was obtained, b.p. 86−87°C/15 mm Hg, $n_D^{20} = 1.5150$. [Found: C 70.8; H 8.00. Calc. for $C_9H_{12}S$ (152.25): C 71.00; H 7.94].

2-Amylthiophene. 3.04 g (0.020 mole) of 5-(2-thienyl)penten-1 and 125 mg of catalyst yielded upon hydrogenation 2.3 g (75 %) of 2-amyl-thiophene, b.p. 85°C/15 mm Hg, $n_D^{20} = 1.4977$. (Lit.[21] b.p. 82°C/12 mm Hg, $n_D^{20} = 1.4982$).

2-Crotonylthiophene. From 20.6 g (0.24 mole) of vinylacetic acid in 280 ml of anhydrous benzene, 10.2 g of silicon tetrachloride (0.060 mole), 16.8 g (0.20 mole) of thiophene and 52.2 g (0.20 mole) tin tetrachloride in 60 ml of anhydrous benzene following the procedure of Yurev et al.,[18] 5.8 g (19 %) of 2-crotonylthiophene was obtained, b.p. 140°C/15 mm Hg,

having the same spectral properties as an authentic sample.[22]

Propyl 2-thienyl ketone. 8.6 g (0.057 mole) of 2-crotonylthiophene gave upon hydrogenation 6.4 g (74 %) of propyl-2-thienyl ketone, b.p. 120°C/15 mm Hg, $n_D^{20} = 1.5450$, having the same spectral data as an authentic sample.[23]

2-Isopropylthiophene. 12.4 g (0.10 mole) of 2-propylidene thiophene yielded upon hydrogenation 10.0 g (79 %) of 2-isopropylthiophene, b.p. 46−47°C/15 mm Hg, $n_D^{20} = 1.5051$, having the same spectral data as an authentic sample.[7]

trans-1,2-Di-(2-thienyl)ethene. 17.0 g (0.15 mole) of 2-thiophenealdehyde and 32.7 g (0.15 mole) of 2-thenyl diethyl phosphonate (0.14 mole) gave in the modified Wittig reaction carried out according to the general description of Bastian et al.,[3] 26.0 g (97 %) of trans-1,2-di-2-(2-thienyl)ethene, m.p. 133−134°C, after recrystallization from ethanol. (Lit.[24] m.p. 133−134°C).

1,2-Di-(2-thienyl)ethane. 6.7 g (0.035 mole) of trans-1,2-di-(2-thienyl)ethene was] hydrogenated over 600 mg of rhodium catalyst at 40°C, yielding 6.1 g (89 %) of 1,2-di(2-thienyl)-ethane, m.p. 65−66°C after recrystallization from methanol. (Lit.[25] m.p. 64−65°C).

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Scheit[7]). The transformation of RNA phosphate diester groups to triester would make the molecule more disposed to hydrolysis as phosphate triesters are generally more labile than diesters.[8] As a parallel, it might be assumed that the labilization of DNA produced by alkylation of phosphate to triester would be considerably enhanced, if the alkyl was equipped with an OH-group in β-position. This would render DNA susceptible to alkaline hydrolysis through a mechanism similar to that of RNA hydrolysis. In order to test this hypothesis, DNA was alkylated *in vitro* with β-hydroxyethyl methanesulfonate[9] (HOEMS) and, for comparison, β-methoxyethyl methanesulfonate[10] (MOEMS). Observed changes of the secondary structure of the alkylated DNA are described in this paper.

Calf thymus DNA (Type I) (from Sigma Chemical Co.; 0.75 mg/ml) was alkylated (0.4 M alkylating agent) in phosphate buffer (0.4 M) at pH 7.0 for 16 h at 25°C. The DNA was separated from small molecules by chromatography on a Sephadex G-25 column. The DNA fraction was collected and concentrated in vacuum at room temperature. pH was adjusted to 7.0 and 8.5, respectively, with sodium carbonate. Samples of the concentrated DNA were incubated for different times at 37°C.
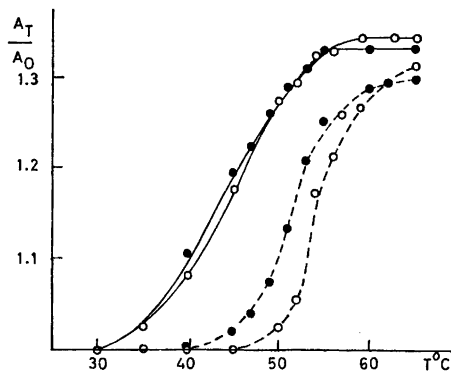
Effects of β-Hydroxyethylation and β-Methoxyethylation on DNA *in vitro*

SOLVEIG WALLES and L. EHRENBERG

Institute of Biochemistry, University of Stockholm, Stockholm, Sweden

Yeast ribonucleic acid is known to be hydrolysed in alkaline solution to mononucleotides.[1] An alkali catalysed interaction between the vicinal 2-OH and the phosphoryl group will give a cyclic ester, which is hydrolysed by P—O fission.[2-4] Alkylated RNA has been found to be hydrolysed even in neutral solution. Kriek and Emmelot[5] observed a degradation of RNA after treatment with diazomethane (*cf.* also Brimacombe *et al.*[6] and Holy and

Fig. 1. Thermal denaturation and its irreversibility of HOEMS-treated calf thymus DNA. Absorbance at 254 mμ as a function of temperature immediately after treatment (O) and after 16 h of incubation at 37°C and pH 8.5 (●). The dashed curves illustrate the corresponding absorbance values measured after cooling from the different denaturation temperatures to 25°C.