HOMOGENEOUS HYDROGENOLYSIS OF THE C–I BOND; PREPARATION OF [5-^{2}H]URACIL

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Reductive dehalogenation of 5-iodouracil by deuterium, catalysed by coordination compounds of transition metals, has been studied. Conditions were found under which the deuteration product contained 80% of [5-^{2}H]uracil and less than 2% of [5,6-$^2H_2$]uracil.

Hydrogenolysis of halogen derivatives is an important method for the preparation of specifically deuterated or tritiated compounds[1,2]. In view of the well-known selectivity[3,4] of homogeneously catalysed hydrogenation reactions, compared to the heterogeneous catalysis, we attempted to apply the homogeneous hydrogenation to reductive dehalogenation. The chosen substrate was 5-iodouracil, to make the results comparable with the thoroughly studied heterogeneously catalysed reductive dehalogenation[5–7], and because this compound is readily accessible, is biologically important an the linkage of its halogen is relatively firm. Homogeneous hydrogenolysis of organic halides proceeds smoothly in the presence of pentacyanocobaltate in an aqueous–methanolic medium[8]. More important, from the preparative point of view, is hydrogenolysis in the system $RhCl_3$ (pyridine)$_3$–$NaBH_4$–N,N-dimethylformamide, which is also usable for the preparation of deuterated compounds[9].

In systems catalyst–hydrogen–5-iodouracil–solvent, the reductive formation of metal occurred in most of the catalytically active complexes studied. Further reaction proceeded in a heterogeneous system or failed to proceed (Table I). Blank experiments, without a catalyst and hydrogen, have revealed that at 350–460 K 5-iodouracil decomposes and uracil appears in the reaction mixture.

Further experiments were carried out with ruthenium complexes and deuterium. At 303–343 K no reductive separation of the metal occurred and pyrolysis of 5-iodouracil was reduced to a negligible extent. The concentrations of the catalyst and the substrate were equimolar (10^{-2} mol l^{-1}). Under these conditions the conversion was 100% in 2 to 8 h. The amount of deuterium incorporated into uracil was rather low, and markedly dependent on the solvent used (Table II, experiments 1–3). Blank experiments without 5-iodouracil showed that under the reaction conditions isotope exchange with the solvent took place; the isotope composition of the solvents

TABLE I

Catalytic activity of transition metal complexes

Catalyst	Ref.	Conversion, %[a]		
		DMF, 8h	DMSO, 8 h	DMA, 20 h
$PdCl_2(C_6H_5CN)_2$	14	52	42	45
$CoCl_2L_2$[c]	15	9[b]	7[b]	17[b]
$CuClL_3$	19	8	10	15
$PdCl_2L_2$	13	66	42	70
$PtCl_2L_2$	20	10	16	50
$NiCl_2L_2$	16	18	5	16
$RuCl_2L_3$	18	20	17	36[b]
$RhClL_3$	17	28	19	70
—		6	5	8

[a] 10^{-1} mol l^{-1} 5-iodouracil, 10^{-3} mol l^{-1} catalyst, 353 K, 0·01 MPa of H_2, DMF designates N,N-dimethylformamide, DMSO dimethyl sulphoxide, DMA N,N-dimethylacetamide; [b] no metal separated out; [c] L = $(C_6H_5)_3P$.

TABLE II

Hydrogenolysis of 5-iodouracil catalysed by $RuCl_2[(C_6H_5)_3P]_3$

Experiment[a]	Solvent[b]	Isotope composition of the product, %			
		$^2H_0$	$^2H_1$	$^2H_2$	$^2H_3$
1	DMA	80·3	19·7	—	—
2	HMPT	68·2	31·0	0·8	—
3	DMF	46·7	53·0	0·3	—
4	DMF[c]	18·0	80·5	1·5	—
5	DMF[c,d]	9·8	86·1	2·0	2·0
6	DMF[e]	36·2	62·4	1·3	—
7	DMA[f]	55·8	42·4	1·6	0·2
8	HMPT[f]	32·1	62·6	3·5	1·8
9	DMF[f]	24·6	73·4	1·4	0·6
10	DMF[g]	56·8	41·8	1·1	0·3

[a] 10^{-2} mol l^{-1} 5-iodouracil, 10^{-2} mol l^{-1} catalyst, 0·1 MPa of $^2H_2$, 343 K; [b] DMA N,N-dimethylacetamide, HMPT hexamethylphosphorictriamide, DMF N,N-dimethylformamide; [c] the solution was bubbled with $^2H_2$; [d] recovered DMF; [e] 5-iodouracil recrystallized from ^2H_2O; [f] solvent repeatedly dried with CaH_2; [g] 20 µl of H_2O was added to the dry solvent.

was: N,N-dimethylacetamide 55·2% $^2H_0$, 34·2% $^2H_1$, 9·2% $^2H_2$, 1·4% $^2H_3$; hexamethylphosphorictriamide 94% $^2H_0$, 3·8% $^2H_1$, 1·5% $^2H_2$; N,N-dimethylformamide 99% $^2H_0$, 0·8% $^2H_1$ < 0·1% $^2H_2$. Comparison of these data (Table II) shows that the contents of deuterium in the isolated uracil were consistent with the extent of the isotope exchange in the solvents (Table II, experiments 1–3 and 7–9), but fails to explain satisfactorily the origin of ^1H-uracil in the reaction in N,N-dimethylformamide (Table II, experiments 3 and 9), when the isotope incorporation into the solvent was very low. By use of an excess of deuterium (bubbling of $^2H_2$ through the reaction mixture) and the solvent recovered from preceding experiments the content of deuterium in the product was increased, but at the expense of specificity of the labelling. The content of deuterium in the product was also increased by using a repeatedly dried solvent, or by employing 5-iodouracil recrystallized from deuterium oxide (exchanged atoms of hydrogen at positions 1 and 3). By contrast, on an addition of mere 20 μl of water (to 5 ml of N,N-dimethylformamide) the content of deuterium in uracil markedly decreased (Table II, experiment 10).

Some catalytic activity for reductive dehalogenation has also been observed with the dichlorobenzoruthenium complex. The reaction rate was somewhat lower than with the dichlorotris(triphenylphosphine)ruthenium complex, the isotope exchange with the solvent was negligible, the maximum incorporation of deuterium into N,N-dimethylformamide being 0·1–0·2%. The results are given in Table III.

The rather high content of ^1H in the product is due to the mechanism of activation of hydrogen by the dichlorotris(triphenylphosphine)ruthenium complex[10] or dichlorobenzoruthenium complex[11]:

$$RuCl_2L + {}^2H_2 \rightleftharpoons Ru^2HClL + {}^2HCl,$$

TABLE III
Hydrogenolysis of 5-iodouracil catalysed by $RuCl_2(C_6H_6)$[a]

Solvent[b]	Conversion %	Reaction time h	Isotope composition of the product			
			$^2H_0$	$^2H_1$	$^2H_2$	$^2H_3$
DMA	70	18	62·8	31·1	3·1	3·0
HMPT	30	25	57·3	34·7	4·4	3·6
DMF	30	15	55·8	39·7	3·5	1·0

[a] 0·38 mmol of 5-iodouracil, 0·12 mmol $RuCl(C_6H_6)$, 5 ml of solvent, 348 K, 0·1 MPa of $^2H_2$; [b] DMA N,N-dimethylacetamide, HMPT hexamethylphosphorictriamide, DMF N,N-dimethylformamide.

where

$$L = [(C_6H_5)_3P]_3 \quad \text{or} \quad C_6H_6 .$$

The formed deuterium chloride underwent very fast isotope exchange with traces of water in the solvent and with the labile hydrogen atoms bound to nitrogen in uracil. Another source of ^{1}H in the product is the isotope exchange with the solvent, and, probably, the isotope exchange of the *ortho*-position hydrogen in the triphenylphosphine ligand[12]. In the heterocatalysed reductive dehalogenation on Pd/$BaSO_4$ in [O^{2}H]ethanol[6] or aqueous potassium hydroxide[7] no isotope exchange was observed and the radiochemical yield of [5-^{3}H]uracil[7] was nearly 100%.

EXPERIMENTAL

Chemicals. The transition metal complexes were obtained by described procedures[13-20] (Table I), dichlorobenzoruthenium was prepared as described in ref.[21]. Deuterium was obtained by electrolysis of KO^{2}H in ^2H_2O (99·9%) and used without further purification. The solvents were purified and dried in the standard ways; dimethylformamide was further dried with calcium hydride and distilled *in vacuo*.

Analytical methods: The reaction mixtures were analysed by HPLC, employing an apparatus Varian 8 500 with an UV detector (Pye-Unicam), a column 258 CH-10 (length 25 cm, ID 2 mm). The eluant was 7% methanol in water, the elution rate 10 ml/h, the temperature 296 K. Mass spectra were measured with an apparatus Jeol JMS D-100. The energy of electrons was 75 eV. The samples were introduced directly into the source of ions at 383–403 K; the liquids were brought in from a capillary. The isolated uracil was examined by IR spectroscopy and the position of ^{2}H was found to agree with the literature[6].

The reaction. Deuterium was introduced over a solution of 5-iodouracil (0·109 g, 0·46 mmol) and the dichlorotris(triphenylphosphine)ruthenium complex (0·128 g, 0·13 mmol) in a degassed solvent (5 ml). The solution was stirred and kept at a constant temperature. A side neck of the flask was equipped with a silicone rubber septum, allowing withdrawal of samples in the course of the reaction. After the reaction had ceased, the solvent was distilled off *in vacuo* (20 Pa). The nearly dry residue was extracted with two 40 ml portions of hot water, the extract was discoloured with activated charcoal and concentrated to crystallize; the product was recrystallized, yield 80–90% (with hexamethylphosphorictriamide only 30–40%).

REFERENCES

1. Evans E. A.: *Tritium and its Compounds*, p. 326. Butterworths, London 1974.
2. Blackburn J. K., Levinson S. H. in the book: *Catalysis in Organic Synthesis*, p. 82. Academic Press, New York 1976.
3. James B. R.: *Homogeneous Hydrogenation*. Wiley, New York 1973.
4. Birch A. J., Williamson D. H.: Org. React. *24*, 13 (1976).
5. Filip J.: Radioisotopy *11*, 203 (1970).
6. Parkanyi C., Šorm F.: This Journal *28*, 2491 (1963).
7. Filip J., Havlíček J.: Energ. *15*, 388 (1969).
8. Kwiatek J., Seyler J. K.: J. Organometal. Chem. *3*, 42 (1965).

9. Love C. J., McQuillin F. J.: J. Chem. Soc., Perkin Trans. 1 *1973*, 2509.
10. Strathdee G., Given R.: Can. J. Chem. *53*, 1402 (1975).
11. Ogata I., Owata R., Ikeda Y.: Tetrahedron Lett. *1970*, 3011.
12. Hallmann P. S., McGarvey B. R., Wilkinson G.: J. Chem. Soc. (A) *1968*, 3143.
13. Both G.: Advan. Inorg. Chem. Radiochem. *6*, 1 (1970).
14. Hudson B., Webster D. E., Wells P. B.: J. Chem. Soc. *1972*, 1204.
15. Cotton T. A., Faut O. D., Goodgame D. M. L., Halm R. H.: J. Amer. Chem. Soc. *83*, 178 (1961).
16. Itatani H., Bailar J. C.: J. Amer. Chem. Soc. *89*, 1600 (1967).
17. Osborn J. A.: J. Chem. Soc. (A) *1966*, 1711.
18. Stephenson T. A., Wilkinson G.: J. Inorg. Nucl. Chem. *28*, 945 (1966).
19. Tayim H. A., Bouldoukian A., Awad F.: J. Inorg. Bull. Chem. *32*, 3799 (1970).
20. Jensen K. A.: Z. Anorg. Algem. Chem. *229*, 242 (1936).
21. Winkhaus G., Singer H.: J. Organometal. Chem. *7*, 487 (1967).

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