Potassium Borohydride Reductions of Ketones absorbed into Polymer Supports: Stereochemical Effects

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The proportions of 6α-alcohol obtained from aqueous potassium borohydride reductions of 3β-hydroxy-5α-cholestan-6-one (1) absorbed into various polymers varied from 0 to 90% depending on the polymer used and whether or not a phase transfer catalyst was added; some other ketones show similar stereochemical effects, the greatest effects probably arising when the substrates are *adsorbed* to the inner surfaces of appropriate polymers.

Since Merrifield introduced the technique of 'solid phase' peptide synthesis in 1963[1] there has been considerable interest in organic reactions where one of the reactive species involved, for example the substrate, is covalently or ionically bound to a polymer support.[2] We now report some examples of reactions of substrates which are simply absorbed into a polymer support. Such reactions have many of the attractions of other polymer-supported systems,[2] but, in the present system, binding the substrate to the polymer and recovering the products from the polymer are particularly simple. More interestingly, however, in some cases this new procedure leads to substantial stereochemical effects.

The reaction selected as a probe for stereochemical effects was the potassium borohydride reduction of ketones. Expecting that large flat molecules, which might adsorb to the inner surfaces of certain polymers, might display the greatest stereochemical effects, most of the present work has been carried out with ketosteroids, in particular the commercially available 3β-hydroxy-5α-cholestan-6-one (1). Reduction of 6-ketosteroids in the 5α-H series with sodium or potassium borohydride usually gives predominantly the 6β-alcohol.[3,4] For example, reductions of ketone (1) with potassium borohydride in methanol or in toluene gave the 6α- and 6β-alcohols in the ratios of 0:100 and 2:98, respectively.[4] Under similar conditions ketone (2)[5] gave the alcohols in the ratios of 0:100 and 1:99, respectively.[4]

Ketosteroids (1)—(3) were hydrophobically bound to various organic polymers; see Table 1. The most satisfactory technique (Method A) was to stir a solution of the substrate in tetrahydrofuran (THF) with the polymer (*ca.* 10 parts by weight). Water was then added slowly during evaporation of the THF until the solvent was just water. The polymer-supported substrate was then filtered off and dried. Examination with an optical microscope indicated that only a small proportion of the substrate was present as crystals; this was confirmed by X-ray powder photographs. Examination with a scanning electron microprobe of cholesteryl chloride bound to Amberlite XAD-4† showed that the substrate was distributed uniformly throughout the beads. The substrates were also bound to various inorganic supports; see Table 1. In this case Method A was unsatisfactory and best results were obtained (Method B) by dissolving the substrate in methylene dichloride, adding the polymer, and then slowly evaporating the methylene dichloride from the stirred suspension. By optical microscopy, only a small proportion of the substrate was present as crystals.

Reductions were carried out by suspendng the polymer-bound ketone in aqueous potasssium borohydride at 60 °C for 2 h. The polymer was then filtered off and washed with water, and the products were recovered by washing with dichloromethane. The products were analysed using g.l.c. The results are summarised in Table 1. Although reduction yields were generally modest, they were usually greater than those obtained in control experiments with no polymer present indicating that here, as in other supported systems,[6] distribu-

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† Amberlite XAD-2, a Rohm and Haas product, is a highly crosslinked macroporous styrene–divinylbenzene copolymer with an internal surface area of ~330 m²/g. Amberlite XAD-4 is a similar polymer but with an internal surface area of ~750 m²/g.

Table 1. Reductions of ketosteroids by aqueous potassium borohydride under various conditions.

Entry	Ketosteroid	Polymer support	Loading Method	Loading % w/w of substrate	Uncatalysed reaction[a] % Reduction[c]	Uncatalysed reaction[a] Proportion of 6α- or 7α- alcohol (%)[c]	TBAB-catalysed reaction[b] % Reduction[c]	TBAB-catalysed reaction[b] Proportion of 6α- or 7α- alcohol (%)
1	(1)	None	—	—	0	—	80	18
2	(1)	Polyethylene	A	13	30	22	80	26
3	(1)	2% Crosslinked polystyrene	A	10	65	34	59	43
4	(1)	Amberlite XAD-2†	A	8	9	—	49	81
5	(1)	Amberlite XAD-4†	A	8	13	53	46	90
6	(1)	Silica gel	B	10	42	62	66	39
7	(1)	Silanised silica gel	B	10	45	47	41	4
8	(1)	Alumina	B	10	100	0	100	0
9	(2)	None	—	—	63	12	73	3
10	(2)	2% Crosslinked polystyrene	A	8	82	15	80	13
11	(2)	Amberlite XAD-4†	A	8	71	53	84	45
12	(3)	None	—	—	26	56	96[d]	61
13	(3)	Amberlite XAD-4†	A	8	16	59	30[d]	74

[a] The polymer-supported ketone was stirred with a large excess of 0.04 M aqueous KBH_4 at 60 °C for 2 h. [b] Reaction carried out as in a but with 1% by weight (compared with weight of substrate) of TBAB added. [c] The crude reaction product was treated with chlorotrimethylsilane + N,O-bis(trimethylsily)acetamide (1:9, v/v) to give the $SiMe_3$ ethers and the mixture was analysed by g.l.c. using authentic samples and dihydrocholesterol as an internal standard. All reactions were carried out in duplicate: reduction yields varied by ±5%, proportions of 6α-alcohol varied by ±2%. [d] Catalyst was tricaprylmethylammonium chloride.
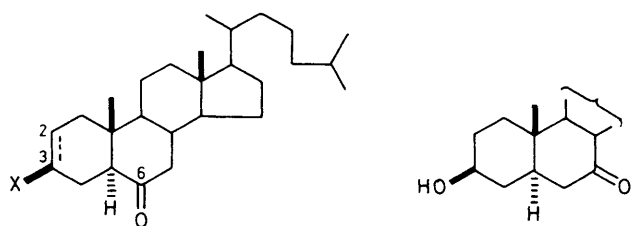
(1) X = OH; saturated at C^2—C^3

(2) X = H; double bond at C^2—C^3

(3)

tion of a reactant on a polymer can facilitate reaction. Phase transfer catalysis has often been used to facilitate penetration of reactive anions into polymers[7] and in the present system addition of a catalytic amount of tetra-n-butylammonium bromide (TBAB) generally raised reaction yields; see Table 1. Since the stereochemical results obtained differed from polymer to polymer and from control experiments with no polymer, it is clear that the reactions took place mainly, if not entirely, within the polymers and not in the surrounding aqueous medium.

The proportions of 6α-alcohol obtained from the reductions of ketone (1) varied from 0 to 90% depending on the polymer used and whether or not TBAB was added; see Table 1, entries 1—8. The greatest proportions of the 6α-alcohol were obtained with Amberlites XAD-2† and XAD-4,† silica gel, and silanised silica gel, all of which are characterised by having large internal surface areas (>200 m² g⁻¹ by N_2 adsorption). With these polymers the substrate probably *adsorbs* onto the inner surfaces of the polymer beads and does so preferentially by the less hindered α-face of the molecule. When the α-face is screened in this way attack must take place from the β-face, leading to the formation of the 6α-alcohol. A similar explanation has been proposed by de Mayo *et al.* to rationalise the stereochemical results obtained in the photoaddition of allene to steroidal enones adsorbed onto silica gel.[8] Other related systems are the reductions of steroidal alkenes and ketones at metal surfaces in hydrogenations[9] and dissolving metal reductions,[10] the reactive species in these cases

coming from within the surface. In the present reaction system smaller stereochemical effects were obtained with polyethylene and lightly crosslinked polystyrene. These polymers, which do not have clearly defined 'surfaces,' may simply provide a microenvironment similar to that found in hexane and in toluene, respectively.

Reductions of other supported 6-ketosteroids, for example ketone (2), showed similar stereochemical trends; see Table 1, entries 9—11. Smaller stereochemical effects were found with other ketosteroids, for example 7-ketone (3); see Table 1, entries 12 and 13.

Reductons of prochiral ketones adsorbed onto chiral polymers are currently being investigated.

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