The Bovine Serum Albumin–2-Phenylpropane-1,2-diolatodioxo-osmium(VI) Complex as an Enantioselective Catalyst for *cis*-Hydroxylation of Alkenes

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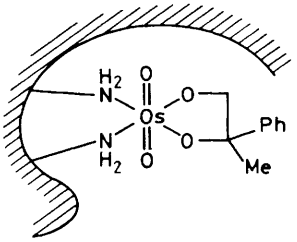
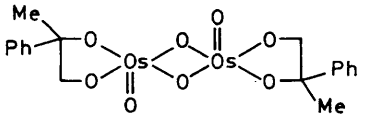
The 1:1 complex between an osmate ester and bovine serum albumin was found to be effective as an enantioselective catalyst in the *cis*-hydroxylation of alkenes, affording diols in up to 68% e.e. and turnover of the catalyst with t-butyl hydroperoxide.

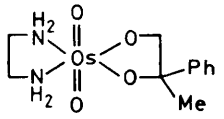
The introduction of a catalytic group into a globular protein by means of chemical modification has attracted interest recently as an approach to enantioselective catalysts.[1] However, many problems have been encountered in the design of



(1) – BSA complex



(2)



(3)

catalytically active substances that can modify a specific site in the protein. We have developed a simpler approach by taking advantage of the strong affinity for a wide range of metals,[2] of a specific protein, bovine serum albumin (BSA).[3] In this communication, we describe that the osmate ester (**1**), an acknowledged catalyst for the *cis*-hydroxylation of alkenes,[4] can be embedded in BSA, and the stoicheiometric complex serves as a good enantioselective catalyst.

When an equimolar mixture of aqueous osmium tetroxide (OsO_4) and a solution of BSA in a carbonate buffer containing an excess of an emulsified alkene, *e.g.*, α-methylstyrene, was chromatographed on Bio-Gel P-6, the elution pattern of osmium was nearly identical with that of BSA.† Further, the reductive hydrolysis of the BSA-containing fractions with sodium hydrogen sulphite[5] gave the diol corresponding to the alkene, 2-phenylpropane-1,2-diol, albeit in low yield. These two complementary observations indicate that 2-phenylpropane-1,2-diolatodioxo-osmium(VI) (**1**) is firmly associated with BSA.

To examine the nature of the interaction between BSA and (**1**) a spectrophotometric investigation was conducted. From the difference spectrum of the (**1**)–BSA complex against native BSA a characteristic absorption maximum at 295 nm was recorded, which was absent in either the spectrum of OsO_4 or that of dimeric 2-phenylpropane-1,2-diolatodioxo-osmium(VI) (**2**). In contrast, the 2-phenylpropane-1,2-diolatodioxoethylenediamineosmium(VI) complex[6] (**3**) which was designed and prepared as a model of the (**1**)–BSA complex in question was found to have a similar spectrum; λ_{max} (294 nm) and ε were in reasonable agreement with those observed for the (**1**)–BSA complex. Therefore, it seems very likely that BSA co-ordinates to (**1**) *via* the primary amino residues.

As mentioned above, the reductive hydrolysis of the (**1**)–BSA complex gave less hydroxylation product than the amounts of OsO_4 or BSA used. The oxidative hydrolysis,[7] however, proved more successful, in that both the turnover of catalyst and the asymmetric induction of the diol were achieved. In a typical experiment the (**1**)–BSA complex was prepared *in situ* by adding an equimolar quantity of OsO_4 to BSA in a carbonate buffer (pH 11) containing an excess of α-methylstyrene. The subsequent oxidation of the styrene was carried out by the addition of t-butyl hydroperoxide to the solution which was maintained at 25 °C for 8 h, to give 2-phenylpropane-1,2-diol (40 equiv.) in 68% e.e. (*S*-configuration) together with an undesirable side product, acetophenone (76 equiv.).‡ It is noteworthy that the (**1**)–BSA complex represents a striking contrast to osmate esters co-ordinated to ligands of low molecular weight, which usually give tarry products on oxidative hydrolysis.[4] The reason for success in the oxidative hydrolysis of the (**1**)–BSA complex remains uncertain, but the bulkiness of the protein might prevent polymerization of the osmate complex.

Table 1. Enantioselective *cis*-hydroxylation of alkene with t-butyl hydroperoxide catalysed by osmate–BSA complexes.[a]

Alkene	Turnover number[c]	*cis*-Diol[b] e.e.(%)[d]	Configuration[d]	Reference
Styrene	38	6	(*S*)-(+)	e
α-Methylstyrene	40	68	(*S*)-(+)	f
trans-β-Methylstyrene	20	18	1(*S*),2(*S*)-(+)	g
Oct-1-ene	9	9	(*S*)-(−)	h

[a] Reaction conditions: [alkene] = 100 mM, [t-butyl hydroperoxide] = 100 mM, and [osmate–BSA complex] = 0.2 mM in 0.05 M carbonate buffer, pH 10.9, 25 °C for 8 h. [b] Satisfactory spectral data were obtained for all diols. [c] Turnover numbers of osmate–BSA complexes corresponding to the amounts of produced diols. [d] Enantiomeric excesses and configurations were based on the literature data (see last column). [e] J. A. Dale and H. S. Mosher, *J. Org. Chem.*, 1970, **35**, 4002. [f] E. L. Eliel and J. P. Freeman, *J. Am. Chem. Soc.*, 1952, **74**, 923. [g] F. Fischer, *Chem. Ber.*, 1961, **94**, 893. [h] E. Spath, F. Kuffner, and L. Enstellner, *Ber.*, 1933, **66**, 591.

The catalytic oxidation of some other alkene substrates was carried out and the results are given in Table 1. The observed e.e. of the diols obtained was not as good as that for α-methylstyrene, but it should be noted that the product diols were all of *S*-configuration.

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† BSA was assayed by use of the biuret reaction and the presence of osmium was determined by inductively coupled plasma atomic emission spectrometry.

‡ The presence of the diol and the ketone was determined by g.l.c. The pure diol was then isolated by t.l.c. and the e.e. estimated from the optical rotation.