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A quantitative UV–VIS probe of enantioselectivity in metalloporphyrin catalyzed oxygenation using aluminium model complexes

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UV–VIS spectroscopy is used to study the selective binding of enantiomeric pairs of chiral epoxides to an αααββ binaphthyl-strapped Al porphyrin; the binding selectivity correlates to the enantioselectivity in the epoxidation of alkenes catalyzed by its Fe analog.

Catalytic asymmetric epoxidation and hydroxylation constitute appealing strategies for synthesizing optically active organic compounds.[1] Much effort has been devoted to the design and preparation of catalysts with novel chiral structures in order to generate good enantioselectivity. Although efficient methods have been developed for asymmetric epoxidation of allylic alcohols,[2] enantioselective epoxidation of unfunctionalized alkenes and hydroxylation of simple alkanes, in general, have been less successful.[3] Owing to the lack of directing functional groups, only weak non-bonding interactions can be used to induce enantioselectivity in oxygenation of unfunctionalized alkenes and alkanes. Evaluating the energy differences of these weak interactions and predicting the enantioselectivity have been virtually impossible.

A paramagnetic NMR relaxation technique was recently used to study the complexation of epoxides to a chiral Cu porphyrin,[4] and correlation was found between the favorable mode of epoxide binding and the direction of chiral induction in the epoxidation. This experiment suggested that the transition state of oxygen transfer in metalloporphyrin-catalyzed epoxidations resembles the product epoxide bound to the metalloporphyrin. However, this method provides no information on the *degree* of chiral induction (*i.e.* the enantiomeric excess of the epoxidation reaction), which is critical for evaluating the efficiency of a chiral catalyst and designing systems with improved selectivity. Herein we present the first quantitative method to probe enantioselectivity in metalloporphyrin-catalyzed oxygenations, by studying the complexation of oxygenation products to an aluminium porphyrin using UV–VIS spectroscopy. This method allows for quantitative measurement of the binding constants of a pair of epoxide or alcohol enantiomers to the Al center. The relative binding selectivity correlates to the enantioselectivity observed in Fe porphyrin catalyzed epoxidation and hydroxylation.

Porphyrins H_2–**1**, Al–**1** and Fe–**1** (Fig. 1) were synthesized by condensing the corresponding ααββ-tetrakis(*o*-aminophenyl)-porphyrin with a binaphthyl diacid chloride. The Fe complex efficiently catalyzes the epoxidation of unfunctionalized alkenes with high enantioselectivity for simple terminal alkenes.[5] The ^{1}H NMR spectrum of Al–**1** shows two sets of resonances for the protons on the two sides of the porphyrin, reflecting a five-coordinate Al center and the resulting disruption of C_2 symmetry. Reversible binding of O or N ligands to this complex gives a distinct red shift in the Q-band region of UV–VIS spectra. This is a useful feature that allows us to conduct ligand titrations and to measure the complexation constants for different ligands.[6] The UV–VIS titration with enantiomerically pure (*S*)- and (*R*)-styrene oxides† in CH_2Cl_2 shows that Al–**1** preferentially binds (*S*)-styrene oxide, which is the major enantiomer obtained in Fe–**1** catalyzed epoxidation of styrene. The binding constants of (*S*)- and (*R*)-styrene oxide to Al–**1** are K_S = 14 dm^3 mol^{-1} and K_R = 1 dm^3 mol^{-1} [eqn. (1) and (2)].‡

This suggests that the (styrene oxide)–Al–**1** complex is a good transition state analog of the Fe–**1** catalyzed epoxidation of styrene (Scheme 1), and that the factors governing the enantioselective binding of Al–**1** are also responsible for the facial selectivity in Fe–**1** catalyzed epoxidations.

It is significant that enantiopure samples are not necessary for this method because the binding constants for two enantiomers can be determined by performing a series of measurements using samples of varying enantiomeric purities.§ For example, the formal binding constants (K_{obs}) can be obtained with (1*R*,2*S*)/(1*S*,2*R*) = 50/50 (racemic), 70/30, and 90/10 mixtures of (1*R*,2*S*)- and (1*S*,2*R*)-*cis*-β-methylstyrene oxide. The binding constants for pure (1*R*,2*S*)- and (1*S*,2*R*)-isomers are calculated to be 0.22 and 0.96 dm^3 mol^{-1}, respectively. The more

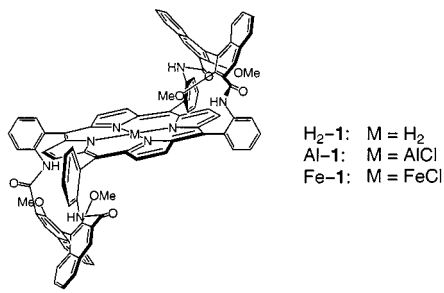
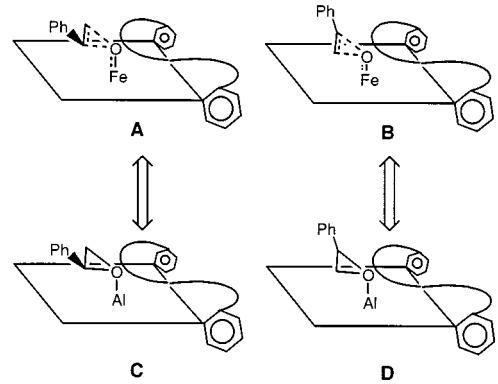


Fig. 1 Binaphthyl-strapped porphyrins.



Scheme 1 Epoxide–Al–**1** complexes as epoxidation transition state analogs: **A** proposed epoxidation transition state forming (*S*)-styrene oxide (favored); **B** transition state forming (*R*)-styrene oxide (disfavored); **C** (*S*)-styrene oxide–Al–**1** complex (more stable) and **D** (*R*)-styrene oxide–Al–**1** complex (less stable). The S curve is the schematic designation of the chiral (*R*)-binaphthyl group.

Table 1 Comparison of the enantioselectivities in Al–**1** complexation and Fe–**1** catalyzed epoxidation[a]

Epoxidation product	Binding to Al–**1**		Fe–**1** catalyzed epoxidation	
	(*S*/*R*)	$\Delta\Delta G^\circ_{R-S}$/ kcal mol^{-1}	(*S*/*R*)	$\Delta\Delta G^\ddagger_{R-S}$/ kcal mol^{-1}
Styrene oxide	14.0 ± 1.7	1.56 ± 0.07	4.71 ± 0.35	0.92 ± 0.04
2-Naphthyl oxirane	4.5 ± 0.5	0.89 ± 0.06	2.43 ± 0.12	0.53 ± 0.04
cis-β-Methyl styrene oxide	4.4 ± 0.5[b]	0.88 ± 0.07	2.33 ± 0.12[b]	0.50 ± 0.04
trans-β-Methyl styrene oxide	3.2 ± 0.3[c]	0.69 ± 0.06	1.67 ± 0.08[c]	0.30 ± 0.03

[a] UV titration and epoxidation were both conducted at 298 K in CH_2Cl_2. [b] *S*/*R* = (1*S*,2*R*)/(1*R*,2*S*). [c] *S*/*R* = (1*S*,2*S*)/(1*R*,2*R*).

favorably bound enantiomer, (1*S*,2*R*)-epoxide, is again the major isomer formed in the Fe–**1** catalyzed epoxidation. The complexation constants of *cis*-β-methylstyrene oxides to Al–**1** are significantly smaller than those of styrene oxides, suggesting that steric exclusion is a major factor governing the enantiofacial selectivity in the epoxide binding. Table 1 compares the selectivities ($S/R = K_S/K_R$) of a number of epoxides obtained in ligand binding studies and Fe–**1** catalyzed epoxidations,¶ as well as the corresponding free energy differences $\Delta\Delta G^\circ$ and $\Delta\Delta G^\ddagger$, for binding and reactivity respectively. These data show that the selectivities in epoxide to Al–**1** complexation and Fe–**1** catalyzed epoxidation are in agreement, *i.e.* greater binding selectivity correlates to higher enantioselectivity in the epoxidation. A plot of $\Delta\Delta G^\ddagger$ against $\Delta\Delta G^\circ$ shows an excellent linear correlation (Fig. 2), demonstrating that the epoxide–metalloporphyrin complex can serve as a transition state model for metalloporphyrin catalyzed epoxidations.[7] The slope of *ca.* 0.6 suggests that the interaction in the epoxidation transition state is slightly less than that in the Al complex. More significantly, the quantitative correlation allows us to use Al porphyrin complexes to screen different chiral structures and substrates and predict the *degree* of enantioselectivity of epoxidation before conducting the actual reaction.

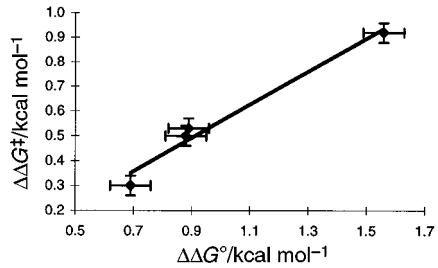


Fig. 2 Linear correlation between $\Delta\Delta G^\ddagger$ and $\Delta\Delta G^\circ$.

We have also applied this method to model the Fe porphyrin catalyzed asymmetric hydroxylation with chiral alcohol-bound Al complexes. Enantiomerically pure (*R*)- and (*S*)-*sec*-phenethyl alcohol have been used as model compounds to study ethylbenzene hydroxylation. Binding studies show that (*R*)-*sec*-phenethyl alcohol coordinates to Al–**1** more strongly than the (*S*)-alcohol by a factor of 2.1 (K_R = 16.0 dm^3 mol^{-1}, K_S = 7.4 dm^3 mol^{-1}). When we carried out the actual hydroxylation of ethylbenzene with Fe–**1** as the catalyst, we found that (*R*)-alcohol is formed preferentially, giving an enantiomeric excess of 20%. Although more data are needed to verify the correlation between the alcohol binding and hydroxylation, the qualitative agreement suggests that this UV–VIS technique can be a useful method to study the mechanism and enantioselectivity of metalloporphyrin catalyzed hydroxylation.[8,9]

In summary, we have demonstrated a UV–VIS spectroscopic method to probe the enantioselectivity in catalytic asymmetric oxygenation reactions. This technique quantifies the differential binding of enantiomers to a chiral metalloporphyrin; it not only can be used to measure the selectivity in enantiomer binding and compute the relative energy differences involved, but also can be applied to screen and predict the stereoselectivity of catalysts before carrying out the reaction. We believe the application of this technique to related fields will have a significant impact in chiral ligand design and catalyst development.

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Notes and references

† Aluminium porphyrin catalyzed polymerization of propylene oxide and ethylene oxide has been reported (T. Aida and S. Inoue, *Macromolecules*, 1981, **14**, 1166). However, in our experiment, no polymerization of styrene oxide was observed: both Al–**1** and styrene oxide can be recovered quantitatively after the UV titration. This is probably due to the hindered porphyrin structure which substantially slows down the polymerization or oligomerization.

‡ We have attempted to use NMR titration to determine the binding constants, but we were not able to observe distinct chemical shift changes at room temperature because of the relatively small binding constants and rapid ligand exchange on the NMR time-scale.

§ In a system involving a mixture of *R*- and *S*-ligands, the formal binding constant $K_{obs} = K_R R + K_S (1\text{-}R)$ where *R* is the percentage/100 of *R* enantiomer in the mixture. The binding constants of pure *R* and *S* isomers K_R and K_S can thus be calculated from the formal binding constants of two different samples:

$K_S = (K_{obs}'R'' - K_{obs}''R')/(R''\% - R')$

$K_R = [K_{obs}'(1 - R'') - K_{obs}''(1 - R')]/(R' - R'')$

¶ Catalyst modification occurs during Fe–**1** catalyzed epoxidation, resulting in a rise of ee in the early stages of reaction.[5] We have taken the *initial* enantioselectivities of the epoxidation, which better reflect the stereoselectivity of the original Fe catalyst.

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