

Catalysis of Aerobic C–C Bond Cleavage of 1,2-Bis(4-methoxyphenyl)ethane-1,2-diol by *meso*-Tetraphenylporphyrinatoiron(III). A Model System for Cytochrome P-450_{scc}-dependent Glycol Cleavage

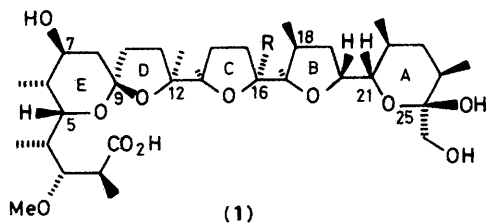
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Catalytic cleavage of 1,2-bis(4-methoxyphenyl)ethane-1,2-diol (**1a**) by chloro(*meso*-tetraphenylporphyrinato)iron(III) in the presence of *N*-benzyl-3-carbamoyl-1,4-dihydropyridine under molecular oxygen at room temperature yielded exclusively 4-methoxybenzaldehyde, reproducing most features of the C–C bond cleavage of a vicinal diol catalysed by cytochrome P-450_{scc}.

Catalysis by metal complexes relevant to heme-containing proteins is of current interest.¹ It has been established that a high-valent oxo-iron porphyrin complex can abstract hydrogen from a substrate in the initial step of hydroxylation, exhibiting a large kinetic isotope effect and allylic rearrangement similar to the reaction with cytochrome P-450. However,

the role of molecular oxygen in catalysis with various cytochrome P-450 species² is not well understood, partly because very few model reactions³ simulating the enzymatic reaction with molecular oxygen are known. We report here the title reaction, which reproduces most features of the cleavage reaction of a vicinal diol catalysed by cytochrome



MonA: R = Et

MonB: R = Me

substituent at C-16.³ In light of the Duax proposal, we were especially intrigued by the dramatically different behaviour of MonA and MonB sodium salts on both silica gel and C-18 reversed phase chromatography.[†] Since to our knowledge no data concerning the complexation or transport properties of MonB have been reported, we felt it would be interesting to determine whether such a small change in the structure of MonA could indeed change binding and selectivity patterns.

MonA and MonB tetrabutylammonium salts were prepared by titration of the free acids with tetrabutylammonium hydroxide. The enthalpy, entropy, and free energy of complexation of both MonA-Bu₄N⁺ and MonB-Bu₄N⁺ with Na⁺ and K⁺ trifluoromethanesulphonates (triflates) were measured in methanol at 25 °C by careful titration calorimetry⁴ using a Tronac isoperibol titration calorimeter controlled by an HP 85 microcomputer. The thermodynamic parameters were extracted from the titration curves by a non-linear least-squares fitting technique assuming 1:1 complexation in each case. The values obtained for MonA differ slightly from those reported by Simon for the MonA tributylammonium salt in methanol-tributylamine solvent.⁵ We have obtained evidence that use of tributylamine as cosolvent and base leads to systematically lowered free energies of complexation owing to incomplete deprotonation of the MonA free acid. This is consistent with the observed differences between the values reported herein and the values of Simon.⁵

As shown in Table 1, MonA-Bu₄N⁺ and MonB-Bu₄N⁺ do indeed differ in both binding and selectivity pattern for Na⁺ and K⁺. MonA⁻ is selective for Na⁺ over K⁺ by $\Delta\Delta G(\text{Na}^+ - \text{K}^+) = -1.41 \pm 0.22$ kcal/mol, with a free energy of complexation for Na⁺ of $\Delta G(\text{Na}^+) = -8.68$ kcal/mol. Changing the ethyl grouping at C-16 to methyl affects both absolute binding strength and selectivity. MonB⁻ is selective for Na⁺ over K⁺ by $\Delta\Delta G(\text{Na}^+ - \text{K}^+) = -0.99 \pm 0.17$

kcal/mol, with a free energy of complexation for Na⁺ of $\Delta G(\text{Na}^+) = -7.98$ kcal/mol. MonB⁻ thus has diminished affinity for both K⁺ and Na⁺ relative to MonA⁻, and binding free energy for Na⁺ is lowered more than binding free energy for K⁺. The difference in selectivity for the two ionophores [$\Delta\Delta G(\text{MonA}(\text{Na}^+ - \text{K}^+) - \Delta\Delta G(\text{MonB}(\text{Na}^+ - \text{K}^+))$] is -0.42 ± 0.28 kcal/mol. Put another way, the selectivity of MonA⁻ is increased relative to MonB⁻ by about 40%. While not a large effect, it is clear that small structural changes in the monensin framework can have a measurable effect on binding and selectivity.

It is interesting to consider the origins of the observed differences between MonA⁻ and MonB⁻. Note that enthalpically, MonB⁻ is actually slightly more selective than MonA⁻ for Na⁺. The enthalpic driving force for complexation of Na⁺ by MonB⁻ is increased by 0.30 ± 0.11 kcal/mol relative to MonA⁻, while the two ionophores have equal heats of binding for K⁺. The diminished selectivity and binding observed for MonB⁻ is a reflection of rather dramatic differences in the entropic contribution to the free energy of complexation. Thus, the entropic driving force for binding of MonB⁻ with Na⁺ ($-T\Delta S$) is diminished by 1.00 ± 0.29 kcal/mol, or 20%, relative to MonA⁻, while the entropic driving force for binding of K⁺ is only lowered by 0.28 ± 0.16 kcal/mol (7%) for MonB⁻ relative to MonA⁻.

A useful interpretation of these results is not possible at this time. The described study does, however, serve to define an absolute lower limit on the possible changes in binding and selectivity that may be achieved by simple manipulation of alkylation pattern about the monensin backbone.

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[†] Separation of MonA and MonB on silica gel is described in reference 3. In our hands, utilizing Merk glass-backed silica gel 60 F254 t.l.c. plates (0.25 mm layer thickness), MonA-Na⁺ has an R_f of 0.31 and MonB-Na⁺ has an R_f of 0.24 with hexane-EtOAc-MeOH (78:20:2) as eluting solvent. Preparative separations of MonA and MonB sodium salts are easily achieved utilizing flash chromatography. Interestingly, if MonA free acid is passed through a flash silica gel column, the sodium salt is isolated after the chromatography. Analytical and preparative separations of MonA and MonB sodium salts by C-18 reversed phase chromatography are reported by M. Beran, J. Tax, V. Schon, Z. Vanek, and M. Podojil, *J. Chromatogr.*, 1983, **268**, 315. On reversed phase chromatography, MonB is the faster moving component utilizing methanol-water as the mobile phase.

co-ordinated alcohol by molecular oxygen affording high-valent alkoxide complexes is known.¹⁰ The alkoxide complex of the diol may be present in a linear monodentate or cyclic bidentate form as shown in Scheme 1. FeCl(TPP) was reduced to Fe^{II}(TPP) in the presence of BNAH slowly in the dark but rapidly under irradiation of visible light. Acceleration of the biomimetic reaction by light may be due to the formation of Fe^{II} by the reduction of Fe^{III}, which is formed in side reactions. §

Although the detailed mechanism of the reaction requires further investigation, the present paper presents the first model system simulating aerobic glycol cleavage with cytochrome P-450_{sc} with evidence against a free-radical chain mechanism.

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