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The Origin of Cooperativity in Double-Wheel Receptors. Freezing of Internal Rotation or Ligand-Induced Torsional Strain?

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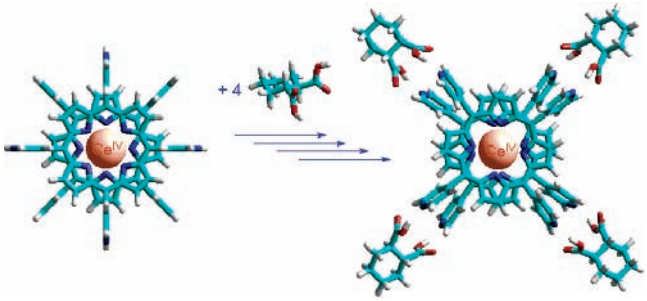
ABSTRACT



A model is proposed for the homotropic cooperative binding of a ditopic ligand to a double-wheel receptor with the aim of understanding the origin of cooperativity. Application of the model to the case of Ce(IV) bisporphyrinate double-decker complexes indicates that cooperativity is mainly due to ligand-induced torsional strain.

Cooperativity is the basis of enzyme control and many other vital biological processes.[1] Not surprisingly, one of the main goals of supramolecular chemistry is the design of artificial allosteric systems capable of efficient regulation of drug release, catalysis, and information transduction.[2] Positive homotropic cooperativity is particularly important in view of the nonlinear amplification of affinities and selectivities toward ligands but, unfortunately, is also the most difficult to reproduce. Shinkai and co-workers, however, have recently introduced a successful new paradigm for the construction of homotropic allosteric systems: the double-wheel receptor.[2d,e] This consists of two "wheels", each bearing two or more identical binding sites, connected by an "axle", so that the wheels can rotate relative to each other. Simultaneous binding of a first ditopic ligand to both wheels would suppress their internal rotational freedom so that the successive ligands would be bound more efficiently. Several receptors of this type, namely, cerium(IV) bis(porphyrinate) double-decker complexes,[3] a meso-meso linked porphyrin dimer,[4] a buta-diynil and a *p*-terphenyl porphyrin tetramer,[5] an ethynil and

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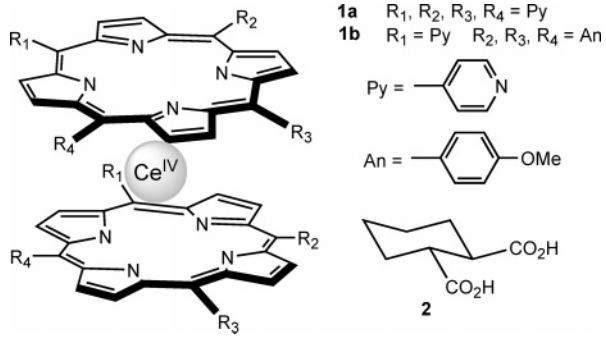
a butadiynil linked trityl dimer,[6] have been prepared and proved to be highly cooperative, with a Hill coefficient (n_H) generally approaching the maximum allowed value.[1,7]

Despite the success of the design, however, the presumed mechanism of cooperativity has been taken for granted without being investigated in detail. In fact the assessment of the mechanism is an important issue, because its knowledge would allow the rational design of the structure of the receptor for maximum cooperativity. Indeed if the mechanism were based on the loss of entropy accompanying the freezing of internal rotation, optimum design would require a structure in which the internal rotation is free and both the "wheels" have the highest possible moment of inertia.[8]

Owing to our interest in cooperative systems,[9] we decided to investigate the problem in more detail with the aim of understanding the relation between the loss of conformational entropy upon restriction of torsional motion and the observed degree of cooperativity as measured by the Hill coefficient. We focused our attention on the archetypal case, namely, the cerium(IV) bis[tetrakis(4-pyridyl)porphyrinate] double-decker **1a**, which binds certain dicarboxylic acids such as (1*R*,2*R*)-cyclohexane-1,2-dicarboxylic acid, **2**, in a positive allosteric manner ($n_H \approx 4.0$).[3a] Our first objective was to estimate the entropy associated with the internal rotation of the two "deckers". This requires the knowledge of the corresponding potential energy curve and the reduced moment of inertia about the rotational axis.[8,10]



Receptor **1a** consists of two coaxial symmetric tops of C_4 symmetry whose potential energy curve can be approximately represented by eq 1, where V_0 is the height of the barrier, σ_{int} is the internal symmetry number ($\sigma_{int} = 4$), and φ is the torsion angle, chosen so that $\varphi = 0°$ corresponds to a minimum.[10]

$$V = \frac{V_0}{2}(1 - \cos \sigma_{int}\varphi) \tag{1}$$

The value of V_0 has not been directly determined yet; however a conservative estimate, based on experiments carried out on the parent compound **1b**,[11] is of at least 15 kcal mol^{-1}.[12,13] The energy difference between the eclipsed ($\varphi = 45°$) and staggered ($\varphi = 0°$) conformations of **1a** calculated at the B3LYP/6-31G(d) (C, H, N), SDD (Ce) level of theory by the Gaussian 03 program (18.6 kcal mol^{-1}) is consistent with the above estimate.[12,14]

Then, since $V_0 \gg RT$, the internal rotation is in fact predominantly a torsional oscillation about the value $\varphi = 0°$.[10] Accordingly, eq 1 can be expanded in a Maclaurin series truncated after the second-order term, yielding the curve of a harmonic oscillator with a force constant of $V_0\sigma_{int}^2/2$.[15] The wavenumber of the oscillator in cm^{-1} is immediately calculated by eq 2, where V_0 is the barrier height in joules per molecule, I_r is the reduced moment of inertia in kg m^2, and c is the speed of light in cm s^{-1}.

$$\tilde{\nu} = \frac{\sigma_{int}}{2\pi c}\sqrt{\frac{V_0}{2I_r}} \tag{2}$$

The reduced moment of inertia ($I_r = 1.36 \times 10^{-43}$ kg m^2) has been evaluated from the geometry of **1a** optimized in the staggered conformation (see above).[12] The entropy of the torsional motion at 25 °C is then easily evaluated from $\tilde{\nu}$, by the Einstein equation ($S_{298} = 7.5$ cal mol^{-1} K^{-1}).[8,10]

Now the question is: can this entropy value justify the observed degree of cooperativity? The answer to this question requires a plausible model for the observed cooperative behavior. Various models can be envisaged, but maximum cooperativity is obtained with the model outlined in Scheme 1, which has some of the features of both the Koshland−Némethy−Filmer (KNF) and the Monod−Wyman−Changeux

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(12) See Supporting Information.

(13) There is a cooperative receptor, namely, cerium(IV) bis[5,15-bis-(3,5-dimethoxyphenyl)-10,20-bis(4-pyridyl)porphyrinate], in which an even higher barrier (18.1 kcal mol^{-1}) has been directly determined.[3b]

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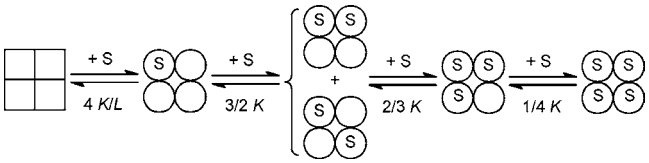
Scheme 1. Proposed Model for Cooperative Binding of Substrate S to Receptor **1a**



(MWC) models.[1,16,17] Like the KNF, it assumes that, in the absence of ligand, the receptor exists in one conformation and that upon binding, the ligand induces a conformational change in the subunit to which it is bound. However, unlike the KNF but analogously to the MWC, this change is not transmitted only to an adjacent binding site but, concertedly, to all of the binding sites so as to make them equivalent. It is assumed, therefore, that the binding of the first ligand occurs with a microscopic association constant K/L with $L > 1$, whereas all successive ligands bind with an identical microscopic constant, K. The allosteric constant, L, is thus a measure of the price that has to be paid to induce the conformational change. The saturation function, Y, for such a model is given by eq 3 where [S] is the free substrate concentration.[12] Equation 3 describes a sigmoidal curve when the system is cooperative ($L > 1$), whereas it reduces to the usual hyperbolic saturation curve in the absence of cooperativity ($L = 1$).

$$Y = \frac{K[\mathrm{S}](1 + K[\mathrm{S}])^3}{L - 1 + (1 + K[\mathrm{S}])^4} \qquad (3)$$

A standard measure of cooperativity is the Hill coefficient at half-saturation, defined by

$$n_{\mathrm{H}} = \left(\frac{d \log [Y/(1 - Y)]}{d \log [\mathrm{S}]}\right)_{Y=1/2} \qquad (4)$$

Application of eq 4 to the saturation function defined by eq 3 shows that the Hill coefficient only depends on the allosteric constant L as illustrated in Figure 1.[12]

The model outlined in Scheme 1 can be used to establish if freezing of internal rotation is the main source of cooperativity. Since no more entropy can be lost than that initially present in the internal rotation,[8,18] restriction of torsional motion of the two "deckers" cannot cost, in free energy terms, more than $-T\Delta S^\circ = 2.2$ kcal mol^{-1} at 25 °C, yielding log $L \leq 1.6$.

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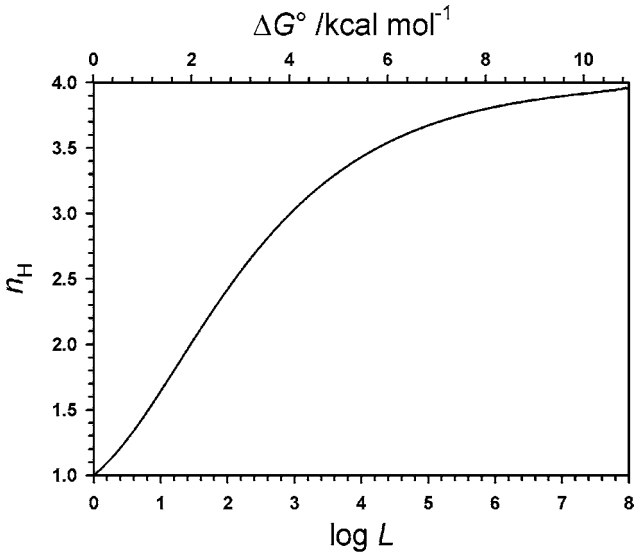

Figure 1. Plot of Hill coefficient as a function of log L (bottom axis) and ΔG° ($= -RT \ln 1/L$) at 25 °C (top axis).

This in turn implies, by interpolation in Figure 1, that $n_{\mathrm{H}} \leq 2.1$. Since the experimental Hill coefficient is ~4.0,[3a] a major fraction of the overall driving force required for cooperativity (ca. 8−10 kcal mol^{-1}) has to be found elsewhere. A plausible alternative is that proper alignment of pyridyl groups upon binding requires a deviation of the torsional angle φ from the energy minimum, thus inducing a significant torsional strain (eq 1). This has been confirmed by B3LYP/6-31G(d) (C, H, N, O), SDD (Ce) optimization of the geometry of the complex **1a**·(**2**)$_4$, displaying a torsional angle $\varphi = 20.6°$.[12] Thus, *a significant barrier height can be beneficial to cooperativity*. This conclusion has profound implications in the optimum design for cooperative double-wheel receptors because, since they behave as torsion balances, conversion of the binding energy into torsional energy depends not only on the barrier height but also on the distance of the binding groups from the torsional axis, the latter affecting the torque exerted by the ligand. This paves the way for further explorations of the structure of double-wheels receptors.

Supporting Information Available: Estimation of V_0 for **1a**, calculation of the reduced moment of inertia of **1a,** derivation of eq 3 and Figure 1, B3LYP/6-31G(d) (C, H, N), SDD (Ce) optimized geometries of the staggered and eclipsed conformations of **1a**, and B3LYP/6-31G(d) (C, H, N, O), SDD (Ce) optimized geometry of the complex **1a**·(**2**)$_4$. This material is available free of charge via the Internet at http://pubs.acs.org.

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