Review

Renaissance of the entatic state principle

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ARTICLE INFO

ABSTRACT

This review summarises studies on the entatic state principle since 2000 when a comprehensive review of Comba defined the field in coordination chemistry. It gives a general introduction to the field but also a short overview of recent studies on the entatic state in enzymes as well as the outreach into different fields in chemistry. The review is focused on the realisation and interpretation of the entatic state principle in model complexes. Especially after the flowering of the entatic state principle around the year 2000, a renaissance could be observed in the last years, which is recapitulated herein.

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1. Introduction

Entasis is well-known in aesthetics and architecture for more than 2000 years [1]. Following a definition of Penrose, it is the "swelling given to a column in the middle parts of the shaft" of Doric columns [2]. This bulging of the column leads to a larger strength-to-weight ratio than in a strictly parallel column and hence provides technical and aesthetic advantages.

In general, "entatic" means "stretched or under tension". For bioinorganic chemistry, the entatic state principle is a cornerstone [3–8]. In the entatic state of a metalloprotein, the metal active site is poised in a particular conformation to perform efficient catalysis or electron transfer (ET).

Since its discovery in the 1950s, the entatic state principle has been discussed controversially (see [9] for a historical overview) but we try to give a tentative definition here.

Definition

Comba defined entasis "as the energization due to a misfit" between ligands and metal ions (metalloproteins or simple coordination compounds) or "between complex fragments and the corresponding substrate–catalyst complexes" (Fig. 1) [10]. Both sides of the reaction, starting state and product state, are elevated with regard to the transition state. This may be different in degree of elevation, the transition state may be slightly shifted, but Fig. 1 provides a general simplistic illustration. The strain of reactants and products lowers the relative transition state energy. This is the broadest definition which is narrowed down depending on

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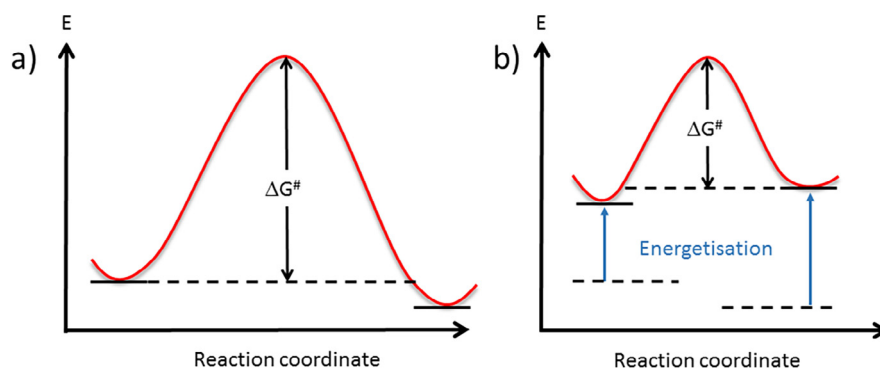
Fig. 1. Simplified illustration of (a) normal reaction and (b) a reaction facilitated by the energetisation of the reactant states. The reactant and product energies as well as the degree of energetisation are arbitrarily chosen.

the regarded topic as we will see later. The energetisation (or strained geometry) can be caused by strain due to the ligand backbones or the electronic preferences of the metal ion and also environmental stresses (solvation, crystal lattice effects) [11]. To be more precise: the entatic state is the result of ligands/proteins enforcing specific structures to metal ions and this may have steric (ligand backbone) and/or electronic (donor atoms) origin. This has been discussed as "the dual complementarity principle" [10–20].

Already in the primary definition, two different interpretations appear: Vallee and Williams regarded the protein as a rigid framework which forces the metal ion into an unusual coordination sphere. This leads to an enhanced electron transfer due to the lower reorganisation energy during the oxidation state change [3]. Malmström formulated the socalled induced-rack theory [4–6]. This theory bases upon the concept that the copper-coordination geometry is strained by the protein conformation. The fine difference between the theories emphasizes that for the entatic state theory, the protein matrix is rigid, whereas the rack-induced state needs some flexibility of the protein structure.

Rorabacher et al. defined it to be an electronic entatic state rather than a simple geometric constraint physically imposed upon the active site by the protein matrix [21]. Using X-ray absorption spectroscopy (XAS) methods at simple solvated Cu(II) ions Hodgson et al. discussed that the concept of a rack-induced state might be not valid as the protein imposes almost no strain on the copper coordination [22,23]. In several theoretical studies, it was proven that Cu(II) ions prefer square-planar and square-pyramidal coordination but that π-donor ligands lead to a stabilisation of trigonal distorted geometries [24–28].

Via NMR studies of apo-azurin, Vila et al. identified metal binding as a major contributor to the rigidity of ET copper centres. Here, the entatic state does not require a preformed metal-binding site of the ligand. These findings reconcile the contradictory requirements of a rigid centre for electron transfer and an accessible, dynamic site required for *in vivo* copper uptake [29]. In blue copper centres, the entatic state is nowadays more regarded as a "soft entatic state" since the binding of the axial methionine is rather weak but decisive for the colour and the redox potential [30]. This is caused by the change of the relative energies of the corresponding orbitals by the Cu–methionine bond length change in a special kind of bistability [31,32].

With ligand field molecular mechanics (LFMM), Deeth et al. investigated small copper Type 1 active site models but also the full proteins [33,34]. They observed a conformational "plasticity" for Cu(II) (related to its Jahn–Teller properties) which allows a multitude of protein conformations with relatively large fluctuations in the calculated metal–ligand bond lengths. The authors stress the point that adequate configurational averaging is required

to reasonably correlate the calculations with experimental properties measured in solution. Inspired by the architectural terminology, they designate this conformational fluctuation as "entatic bulging" with a strain of about 10 kcal/mol. The idea of averaging over a multitude of conformations was continued in QM/MM studies by Besley and co-workers [35]. Moreover, they needed a rather large QM region around the active site to determine the strain energy to be 12.8 kcal/mol and 14.5 kcal/mol for the oxidized and reduced forms of the protein. This reveals that the active site has an intermediate structure and supports the entatic state principle.

Kemeny and Mahanti had already in 1976 the idea that the various coordination orientations in the active site thermally equilibrate fast enough such that a tunneling may occur [36].

The impact of the idea of entatic state is far-reaching as Galperin and Koonin 2012 discussed the role of the entatic state in evolution [37]. Following their argumentation, the emergence of each distinct entatic state conformation was a major evolutionary event which allows efficient catalysis of a new class of reactions or the usage of a new substrate class. Major changes in the protein might have led to the formation of inactive misfolded molecules [38]. Hence, in a rather conservative process, a once found entatic motif led to the preservation of specific structural fold.

The idea of the entatic state was so attractive that it was even translated to enzymes without metals to conceptualise the strain in enzymes for the promotion of enzymatic catalysis [39] and even the steering of the pKA value of regions in enzymes by structural strains [40].

In organic chemistry, some ideas of the entatic state principle appear in a generalised concept in form of the distortion/interaction–activation strain model developed by Bickelhaupt and Houk [41]. In this model, activation energies are represented by the sum of the energies to distort the reactants into geometries which they have in transition states combined with the interaction energies between the two distorted molecules. The authors directly relate it to the Marcus theory where a small reorganisation energy promotes a small activation barrier for thermoneutral reactions [42]. Hence, reorganisation and distortion of the reactants directly translate into each other. Over Marcus theory, the different concepts are connected to each other.

As latest development, the concept of the entatic state has been introduced into the broad field of metal–organic frameworks (MOFs, see Section 3.3) [43–45].

In the following sections, the interpretation of the entatic state principle for different classes of proteins and for coordination compounds is reviewed. Due to the enormous increase in publication activity in the last years, we interpreted this development as a renaissance of the entatic state principle.