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An Artificial Allosteric System : Regulation of a Biomimetic Reduction (NADH Model) by Potassium ions

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Key Words : NADH model ; allosteric regulation ; charge transfer interaction and transition state.

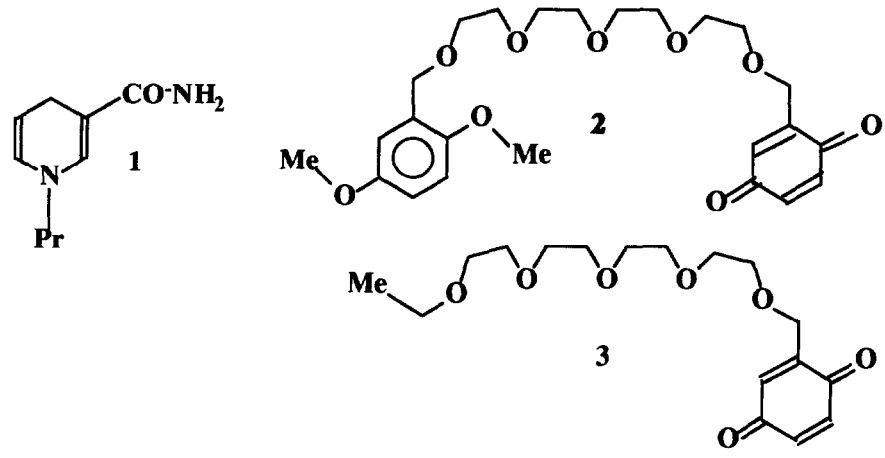
Abstract : An acyclic glycol ether ligand with both a quinone and a dimethoxybenzene as terminal groups, reacts with the NADH model 1-propyl -1,4 dihydronicotinamide. The reduction of the quinone exhibits a 30 fold kinetic enhancement in the presence of potassium ions. An effective charge transfer interaction in the transition state of the reduction is probably responsable of this activation effect. The results are discussed in terms of a potassium induced conformational change that mimics allosteric effects.

The activity of allosteric enzymes is regulated by conformational changes induced by the reversible binding of some agents[1]. Synthetic models which mimic allosteric cooperativity have been described : models that are relevant to oxygen binding and transport have been devised by Tabushi[2] and Traylor[3]; Rebek and others[4] have described some cooperative metal binding systems. In previous papers, we have described the allosteric regulation by potassium ions of : (i) : the formation of an intermolecular charge-transfer complex[5], (ii) : the intramolecular spin exchange and dipolar splitting in a biradical[6]. We have also described the allosteric regulation by a neutral molecular substrate (thiourea) of the latter phenomena (ii)[7].

The biomimetic reductions with 1-alkyl -1,4 dihydronicotinamides as coenzyme NADH models, have been a subject of considerable interest in these years[8]. Much attention has been focused on the activation of substrates via metal ion coordination, hydrogen bonding and general acid catalysis. In a particular model, Murakami has shown a direction in which the reductant undergoes activation via CT electronic interaction in the transition state[9].

We present here (Figure 1), a system in which a reduction by the NADH model 1-propyl -1,4 dihydronicotinamide **1**, is activated by potassium ions via an induced conformational modification which favors the formation of a charge-transfer complex in the transition state.The selected system was quinone **2**[10] in which the quinonic subunit was the substrate of the reaction with **1**[11]. Quinone **3** has been synthesized for comparative studies[12]. The reactions of respectively **2** and **3** with **1** in acetonitrile afford the corresponding hydroquinones .

Figure 1 . The reagent **1**, the "enzyme-susbstrate " system **2**, and the comparative model **3**

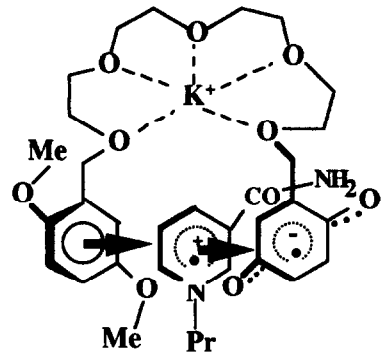


The disappearance of the 340 nm and 440 nm absorption bands characteristic of compounds **1** and **2** respectively was monitored at 25°C in acetonitrile[13]. This led to the following observations : (i) : the rate of the reaction of **2** with **1** was increased by a factor 30 in the presence of one equivalent of potassium ion ; (ii) : on the contrary, K^+ had no effect on the rate of the reaction of **3** or p.benzoquinone with **1** . The last observation showed that K^+ was unable to promote electrophilic assistance to the reduction of the substrates . The present results not only emphasise the crucial role of K^+ during the reduction of **2**, but also demonstrate the specific fonction of the dimethoxyaryl subunit which is present in **2** but not in **3** or p. benzoquinone.

As reported by us [5], one equivalent, of K^+ was able to induce a change of the conformation of L, via a 1:1 complex in which the polyether chain is wrapped around the alkali cation . It is likely probable that the same process occured during interaction of K^+ with **2** and **3**. However, this conformational change had an effect on the rate of reduction only in the case of **2** .

Our data allow to propose for the reduction of **2** that the reaction is activated by a charge-transfer interaction in the transition state . This interaction is only possible with the K^+ induced folded conformation . This allosteric regulation is depicted in Scheme I . Such a mechanism is supported by the elegant work of Murakami[9] and also by our own demonstration of the occurence of a "sandwich CT intercalation of a π- acceptor substrate in the K^+ induced folded conformer of L, the bis dimethoxyaryl analog of **2**[5] .

Scheme I . Proposed Mechanism of Allosteric Activation of the Reaction of 2 with 1, Mediated by K^+



To our knowledge, this is the first simple synthetic model of an allosteric effect applied to a chemical reaction .

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(10) 2 was obtained in 33% yield from L^5, via a one-pot reaction with $Ce(NH_4)_2(NO_3)_6$ in acetonitrile at 0°C. Purification and isolation of 2 was accomplished by column chromatography [SiO_2 / hexane-diethylether]. As did all new compounds, 2 gave expected ^1H NMR and mass spectra and C, H analyses.

(11) 1 has been previously described by several autors[9]

(12) 3 was obtained in 6,5% yield from the reaction of 2,4 dimethoxybenzyl alcohol with ditosylated tetraethyleneglycol followed by the reaction of the monotosylated compound with sodium ethylate.

(13) Transient CT band were observed (see Fukuzumi[14] for similar observations). For instance, without K^+, the disappearance of the 340 nm band corresponds to 32 $nM.L^{-1}.min^{-1}$, since it corresponds to 967 $nM.L^{-1}.\ min^{-1}$ in the presence of K^+.

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