Enhanced Rates of Dihydropyridine to Pyridinium Hydrogen Transfer in Complexes of an Active Macrocyclic Receptor Molecule

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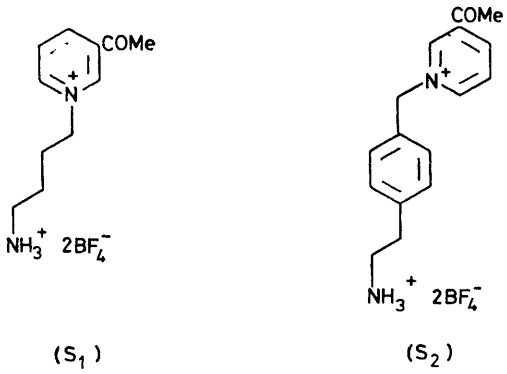
Summary The complexes formed by the dihydropyridine-bearing macrocyclic receptor molecule (I) with the pyridinium substrates (S_1) and (S_2) display enhanced rates of internal H-transfer which may be inhibited by addition of other complexable cations.

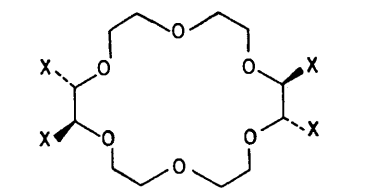
SYNTHETIC molecular catalysts which provide both a receptor site for substrate binding and a reactive site for transformation of the bound substrate are of interest as enzyme models or as new types of efficient and selective chemical reagents. Utilisation of the substrate binding properties of cyclodextrins leads to derivatives displaying

rate enhancement[1] and stereospecificity.[1,2] Macrocyclic compounds containing a hydrophobic cavity[3] and a reactive site have been synthesized. The ability of macrocyclic polyethers to bind polar substrates has recently led to functionalized derivatives which display enhanced rates of thiolysis of aminoester salts[4] and of hydride transfer from a 1,4-dihydropyridine to a sulphonium salt.[5]

We have developed a series of macrocyclic receptor molecules derived from (II), which strongly complex primary ammonium salts.[6,7] We now report that when 1,4-dihydropyridyl side-chains are attached to the macrocyclic binding site as in compound (I), enhanced rates of H-transfer to bound pyridinium salt substrates [(S_1) and (S_2)] are observed. This represents the first example of accelerated 1,4-dihydropyridine (DHP) to pyridinium (P^+) H-transfer in a synthetic molecular receptor–substrate complex. Mitochondrial transhydrogenation between pyridine nucleotides (NADH and $NADP^+$) occurs in biological redox processes.[8] Model systems involving intermolecular H-transfer of this type have been described.[9,10]

Treatment of the tetra-acid chloride of (II) with monobenzyloxycarbonylethylenediamine affords compound (III) (m.p. 214—215 °C; 70% yield). Deprotection with HBr in acetic acid gives (IV) (m.p. 174—177 °C; 95% yield) which on treatment with the *N*-(2,4-dinitrobenzene)pyridinium salt (VII) (glass; 50% yield from *N*-butylnicotinamide)[11] affords the tetrapyridinium salt (V) (hygroscopic solid; 85% yield). Complete reduction of (V) (followed spectroscopically) by treatment of an aqueous sodium carbonate solution (pH *ca.* 12) with sodium dithionite (10 equiv.) for 24 h at room temperature yields the macrocyclic tetra-1,4-dihydropyridine derivative (I).† Extraction of (I) with dichloromethane gives a solution containing about 1 equiv. of complexed Na^+. Removal of Na^+ (followed by atomic absorption spectrometry) is achieved by extraction with a basic (pH *ca.* 10) solution of the imidazolium salt of the tetra-acid (II) which strongly complexes Na^+ ($\log K_S = 5{\cdot}5$ in water).[12] The dried dichloromethane solution is evaporated and the residual material is redissolved in acetonitrile affording the stock solution of (I) used in further experiments. All operations involving compound (I) are performed under argon atmosphere. The tetra-dihydropyridine (I) was characterized by its u.v. spectrum (λ_{max} 345 nm, ϵ $2{\cdot}9 \times 10^4$, in MeCN; Figure 2) which did not contain absorptions from side products (remaining pyridinium unit or tetrahydro or sulphinate derivatives). The





(I) X = $CONH[CH_2]_2N$ (pyridinium) $CONHBu^n$

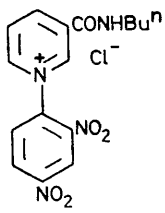
(II) X = CO_2H

(III) X = $CONH[CH_2]_2NHCO_2CH_2Ph$

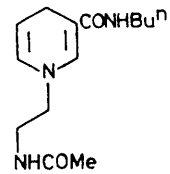
(IV) X = $CONH[CH_2]_2NH_2$

(V) X = $CONH[CH_2]_2N^+$ (pyridinium) $CONHBu^n$ Cl^-

(VI) X = $CONH[CH_2]_2$(3-indole)



(VII)



(VIII)

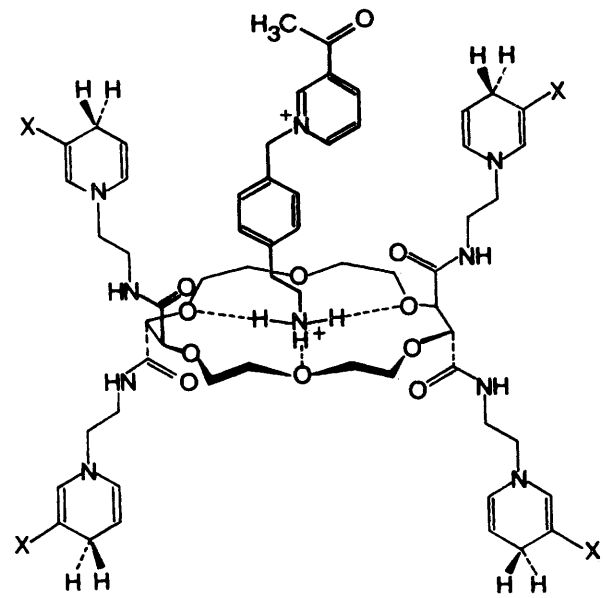


FIGURE 1. Schematic representation of the complex of receptor (I); X = $CONHBu^n$) with substrate (S_2).

† Reduction of nicotinamide pyridinium salts by dithionite gives exclusively the 1,4-dihydropyridine derivative (U. Eisner and J. Kuthan, *Chem. Rev.*, 1976, **72**, 1).

reference compound (VIII) (λ_{max} 345 nm, ϵ 7 × 10^3) was prepared by dithionite reduction of its pyridinium salt precursor.

Since 3-acetylpyridinium salts are reduced by 1,4-dihydronicotinamides at convenient rates,[10] the primary ammonium derivatives $S_1(BF_4^-)_2$ (m.p. 110—115 °C) and

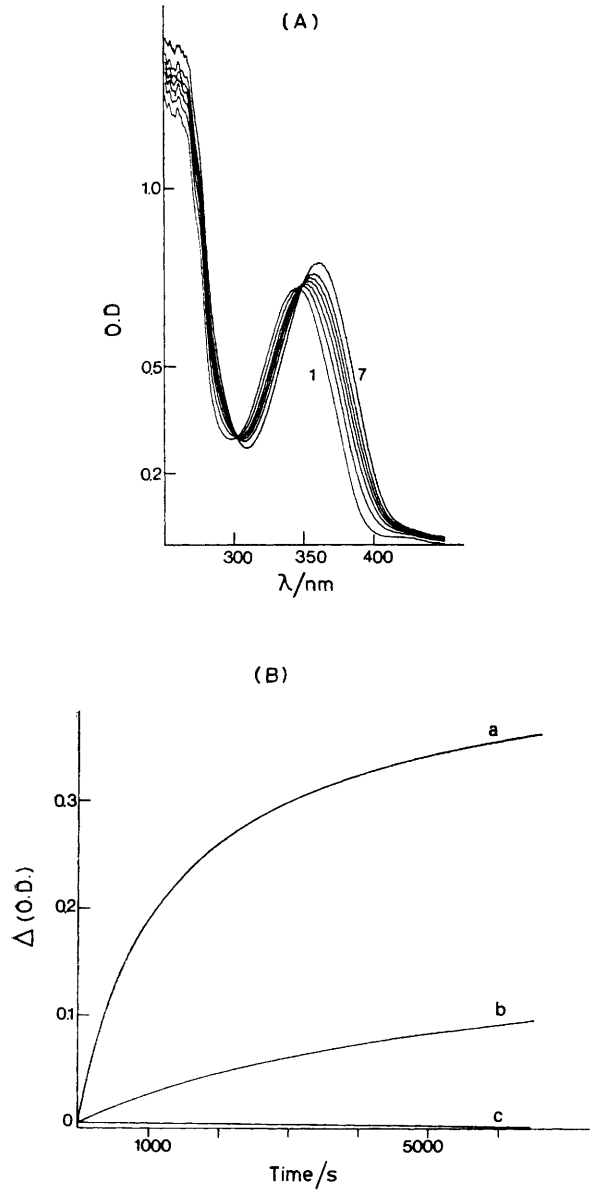


FIGURE 2. Internal H-transfer in the [(I),(S_2)] complex. (A) U.v. spectral changes in the course of the reaction (*ca.* 2·5 × 10^{-3} mol l^{-1}; reaction time: (1) 30 s, (7) 660 min. (B) Time dependence of the absorption at 400 nm for (I) (5·8 × 10^{-4} mol l^{-1}) + (S_2) (3 × 10^{-4} mol l^{-1}) (curve a); in the presence of K^+ (2 × 10^{-3}) mol l^{-1} (curve b); in the presence of $H_3N^+[CH_2]_4NH_3^+$ (7 × 10^{-3} mol l^{-1}) (curve c); in MeCN at 23 °C.

$S_2(BF_4^-)_2$ (m.p. 216 °C) (prepared by straightforward reactions) were chosen as substrates. Compound (I) is expected to form a complex [(I),S] where the substrate is bound by its $-NH_3^+$ group in the macrocyclic unit and held between the dihydropyridine side-chains (Figure 1).

Since [(I),S] undergoes reaction as soon as it is formed, the stability of the complexes was estimated indirectly. When the tetratryptamine derivative (VI) [m.p. 223 °C; 65% yield from the tetra-acid chloride of (II) and tryptamine] is mixed with (S_1) or (S_2), a new band appears in the u.v. spectrum due to indole–pyridinium interaction.[7,13] Titration of (VI) with (S_1) and (S_2) in MeCN yields the stability constants K_S of the complex and the features of the charge transfer (CT) band [for (VI) + (S_1): $K_S = 10^4$ l mol^{-1}, ϵ 370 at 320 nm; for (VI) + (S_2): $K_S = 1{\cdot}5 \times 10^4$ l mol^{-1}, ϵ 235 at 320 nm]. We assumed that the stability of the complexes of (S_1) and (S_2) with (I) should lie in the same range. This method allows measuring the stability of ammonium salt complexes in homogeneous organic media.[14] The [(VI),(S_1)] complex displays a band of higher intensity than [(VI),(S_2)]; indeed, (S_1) should form more easily the face-to-face indole–pyridinium stack required for efficient interaction[13] than (S_2) where the pyridinium unit is at an angle with respect to the direction of attachment of the side-chains.

(a) When substrates (S_1) and (S_2) are mixed with (I) (1 : 2 ratio in MeCN under argon), electronic spectral changes occur which are similar to those observed for the reduction of 3-acetylpyridinium salts by NADH;[10] reduction of (S_1) and (S_2) by (I) to their 1,4-dihydro-derivatives occurs. The reaction rate may be monitored at 400 nm where only the reduced substrates absorb appreciably (Figure 2).

(b) The kinetic analysis shows that the reaction between (I) and (S_1) or (S_2) is first order, thus implying that it proceeds intramolecularly in a preformed complex with the following rate constants: [(I) + (S_1)] $k_1 = 1{\cdot}2 \times 10^{-4}$ s^{-1}; [(I) + (S_2)] $k_1 = 2{\cdot}5 \times 10^{-4}$ s^{-1}.

(c) Substrate (S_2) which gives a weaker CT band than (S_1) when complexed by (VI), reacts about twice as fast with (I). This rather small effect suggests, but does not prove, that the face-to-face geometry of the CT interaction[13] may not be the best geometry for the H-transfer reaction.

(d) Inhibition of the intracomplex reaction is brought about by addition of excess of K^+ (as KBF_4) which is more strongly complexed than a primary ammonium salt[7] and expels the substrate from the $-NH_3^+$ binding cavity. The reaction becomes intermolecular and its rate decreases (Figure 2; curve b). The kinetics are second order with the same rate constant $k_2 = 1{\cdot}2 \times 10^{-2}$ l mol^{-1} s^{-1} for the two systems [(I) + (S_1) + K^+] and [(I) + (S_2) + K^+] as well as for the reference reaction [(VIII) + (S_1)].

(e) At concentrations below 10^{-2} mol l^{-1} the intracomplex reaction becomes appreciably faster than the inhibited reaction, provided the complex is sufficiently stable to form at low concentration. At 5 × 10^{-4} mol l^{-1}, *ca.* 80% of the substrate is complexed and the rate of the intracomplex reaction is *ca.* 10 times faster than the reaction inhibited by K^+ (Figure 2, curves a and b).

(f) When inhibition is caused by excess of $H_3N^+[CH_2]_4NH_3^+,2BF_4^-$ ($tmed^{2+}$) which is also strongly complexed,[7] the reaction becomes very slow, $k_2 < 10^{-4}$ l mol^{-1} s^{-1} for [(I) + (S_2) + ($tmed^{2+}$)]. The complexed diammonium salt may inhibit the bimolecular reaction, for instance, by electrostatic and steric repulsion disfavouring the formation of a positively charged pyridinium group on the ring and

hindering the external approach of the charged substrate.

Systems like [(I),(S_2)] (Figure 1) display some of the characteristic features which molecular catalysts should possess. More rigid receptors (of higher cyclic order) containing properly oriented reactive sites held in position by additional bridges may present larger acceleration factors. They should also provide means of studying the mechanism and geometry of H- transfer reactions.

(*Received*, 31*st October* 1977; *Com.* 1132.)

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