CATHODIC CLEAVAGE REACTIONS STUDIED BY REDOX CATALYSIS.

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The synthesis of peptides is usually carried out by stepwise coupling of amino-acids to a peptide moiety; in every stage of the synthesis, the amino-acid and the peptide bear at least two functional groups each (an amine and a carboxyl or a carboxyl derivative). For any coupling to follow a selective pathway it is essential to block the carboxyl group of one of the reactions and the amino group of the other one:

$$H_3^{\oplus}NCHRCO_2^{\ominus} \longrightarrow H_2NCHRCOP_1$$

$$H_3^{\oplus}NCHR'CO_2^{\ominus} \longrightarrow P_2NHCHR'CO_2H$$

The groups P_1 and P_2 are called "protecting" or "blocking" groups. In order to prevent an acid-base reaction between the new reactants, which would inactivate them towards peptide bond formation, the carboxyl moiety is usually converted into a more active species,

$$P_2NHCHR'CO_2H \longrightarrow P_2NHCHR'COX,$$

prior to reaction with the amine component, to yield a fully protected peptide:

$$P_2NHCHR'COX + NH_2CHRCOP_1 \xrightarrow{-HX} P_2NHCHR'CONHCHRCOP_1$$

In order to add another amino-acid residue to this peptide, one of the protecting groups must be removed, e.g. P_2. Let us now suppose that it is desired to add a further amino-acid which bears a functional group in its side chain, e.g. a carboxyl group; if this is so, then a third blocking group is required for the next step of the synthesis:

$$P_4NHCHCOX + NH_2CHR'CONHCHRCOP_1 \longrightarrow P_4NHCHCONHCHR'CONHCHRCOP_1$$
$$\quad\quad|\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad|$$
$$\quad(CH_2)_nCOP_3\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad(CH_2)_nCOP_3$$

Each coupling reaction therefore alternates with cleavage of a protecting group, and at the end of the synthesis one may end up with a molecule bearing several different protecting groups which have to be removed. Unfortunately this is seldom possible in a single step; together with a decrease of reactivity often associatad with larges molecules, then requiring forcing cleavage conditions, the sequence of deblocking reactions required usually leads to drastic decrease of the overall yield.

Several of the groups commonly used for amine, carboxyl, sulphydryl and hydroxyl protection are removable by chemical reduction but each requires different reaction conditions. Previous studies [1,2] have shown that electrochemistry offers an appropriate means for the selective removal of protecting groups.

It is the objective of this investigation to study the electrochemical cleavage of the tosyl group from alcohols and initially three esters were prepared namely, $TosOCH_3$, $TosOC_2H_5$ and $TosOCH_3(CH)_2$, where Tos is H_3C  SO_2.

The cyclic voltammograms obtained with these compounds in DMF/Bu_4NBF_4 at a vitreous carbon electrode are completly irreversible as shown in figure 1, even at sweep rates of the order of 1000 V/s, which suggests that a chemical step with a rate constant higher than $10^4\ s^{-1}$ follows initial electron transfer. The coulometric study showed that, for all the esters, the number of electrons involved per molecule is equal to two and is therefore likely that the mechanism will be ECE or DISP [3]

$$TosOR + 1e \longrightarrow TosOR^{\cdot\ominus} \quad (1)$$
$$TosOR^{\cdot\ominus} \longrightarrow Tos^{\ominus} + {}^{\cdot}OR \quad (2)$$
$${}^{\cdot}OR + 1e \longrightarrow {}^{\ominus}OR \quad (3)$$
$${}^{\cdot}OR + TosOR^{\cdot\ominus} \longrightarrow {}^{\ominus}OR + TosOR \quad (4)$$

However, the peak characteristics of the voltammograms in the sweep range studied were: $\partial E_p/\partial \log v = -30$ mv; peak width $\Delta E_p = 50$ mv. This clearly indicates a first order reaction with respect to the radical anion formed.

The competition between reactions (3) and (4) is defined in terms of a factor p [2]

$$p = K_D\, c\, (Fv/RT)^{1/2} / K^{3/2}$$

Where K_D is the diffusion constant and c the concentration

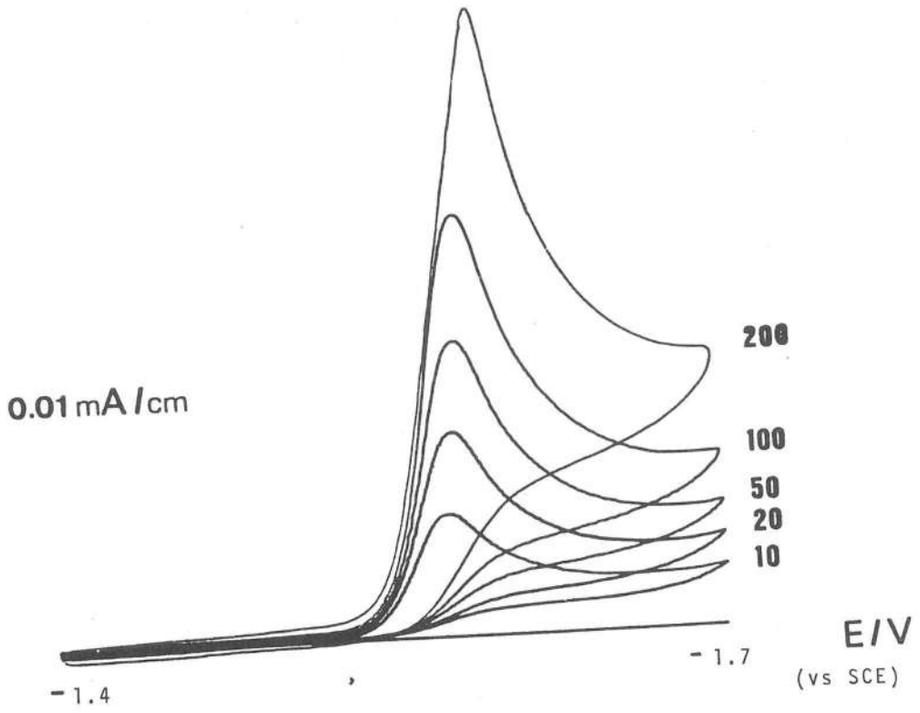

Figure 1 - Cyclic voltammograms for $TosOC_2H_5$, 5×10^{-3} M in DMF/Bu_4NBF_4 at a vitreous carbon electrode and at the sweep rates in mV/s as indicated.

of ester. Only when p is close to one should both mechanisms be considered; if $p \ll 1$ then the ECE mechanism dominates. This last situation should occur for large values of K which is the present case considering the results obtained with the cyclic voltammetric studies.

The mechanism and kinetics of the reduction of the tosyl esters in DMF were determined by the homogeneous redox catalysis method developed by Savéant et al.[4]. The basis of this method is the replacement of the electron transfer at the electrode by the electron transfer in solution as exemplified for the EC mechanism:

ELECTRODE PROCESS

$$A + 1e \rightleftharpoons B \quad (1\ el)$$

CATALYTIC PROCESS

$$P + 1e \rightleftharpoons Q \quad (0)$$

$$Q + A \underset{K2}{\overset{K1}{\rightleftharpoons}} P + B \quad (1\ sol)$$

$$B \xrightarrow{K} C \quad (2)$$

The catalyst redox couple P/Q is selected so as to fulfill the following conditions: (i) the standard potential E_{PQ} is positive to the reduction potential of the substrate A (ii) electron transfer between electrode and P or Q is fast, and (iii) except for electron transfer P and Q are chemically stable towards A and B. Under this conditions, addition of A will result in an increase of the peak current of P due to its regeneration through reaction (1 sol) ; the kinetics of this regeneration is expressed in terms of the ratio $i_p/\gamma i_{pd}$, where i_p is the catalytic peak current, i.e. the current for reduction of P in the presence of A, i_{pd} is the peak current of the

reversible P wave in the absence of A and γ is the excess factor, i.e., the ratio between the substrate and catalyst concentrations ($\gamma = C_A^o / C_P^o$). The principle of the application of this method is based upon the observation of these kinetic parameters as a function of operational parameters such as C_A^o, C_P^o and v.

Considering the following dimensionless parameters,

$$\lambda_1 = (K_1 C_P^o / v)(RT/F)$$

$$\lambda_2 = (K_2 C_P^o / v)(RT/F)$$

$$\lambda = (K/v)(RT/F)$$

Two limiting situations can be observed in pratice:
a) If $K >> K C_P^o$ the kinetic control is by the electron transfer process, forward reaction (1 sol). The system then depends upon the parameters λ_1 and γ; $i_p/\gamma i_{pd}$ is given as a function of λ_1 by a set of working curves, one for each value of γ. A diagnostic criterion that the kinetic control is actually by forward reaction (1 sol) derives from the effect of the catalyst concentration keeping γ constant. If K_1 is constant over a C_P^o range this provides evidence that the control is by reaction (1 sol). In this limiting situation information about the stability of B cannot be obtained; hence, in this study conditions were selected so that this limiting situation does not occur. (b) If $K << K_2 C_P^o$ the kinetic control is by reaction 2 and the system depends upon γ and $\lambda\lambda_1/\lambda_2 = KK_1/K_2 \cdot (RT/Fv)$; $i_p/\gamma i_{pd}$ is given as a function of $\lambda\lambda_1/\lambda_2$ by a set of working curves. If KK_1/K_2 is constant over a C_P^o range it means that the kinetic control is by reaction 2.

The cleavage reactions studied were assumed to follow a SET mechanism [5]:

$$P + 1e \rightleftharpoons Q$$

$$Q + TosOR \longrightarrow P + TosOR^{\cdot\ominus}$$

$$TosOR^{\cdot\ominus} \xrightarrow{K} Tos^{\ominus} + {}^{\cdot}OR$$

$${}^{\cdot}OR + Q \longrightarrow {}^{\ominus}OR + P$$

The catalyst used for study was anthracene and figure 2 shows cyclic voltammograms for the catalyst alone and for the catalyst and substrate at a vitreous carbon electrode in DMF/Bu_4NBF_4. Table 1 presents the results obtained for $TosOC_2H_5$ which indicate control by reaction 2.

The values of KK_1/K_2 show no trend over the concentration range studied (and show an average value of 0.2) but K_1 decreases stongly with increasing C_P^o.

Substitution of our experimental data, for example, for the compound $TosOC_2H_5$ and the catalyst anthracene, $KK_1/K_2 = 0.2$, $E_{PQ}^o = -1.90$ V and $E_p + \frac{RT}{2F} \ln v = -2{,}12 \pm 0.01$ V (for $v = 0.2 - 2\ V s^{-1}$) into the two equations, one for the catalysed reaction

$$\frac{RT}{F} \ln \left(\frac{KK1}{K2}\right) = E_{AB}^o - E_{PQ}^o + \frac{RT}{F} \ln K$$

and the other for the non-catalysed one,

$$E_p = \frac{RT}{F}\left(\ln \frac{RT}{F} - 0.78\right) + E_{AB}^o + \frac{RT}{2F} \ln \frac{K}{v},$$

leads to the simultaneous equations

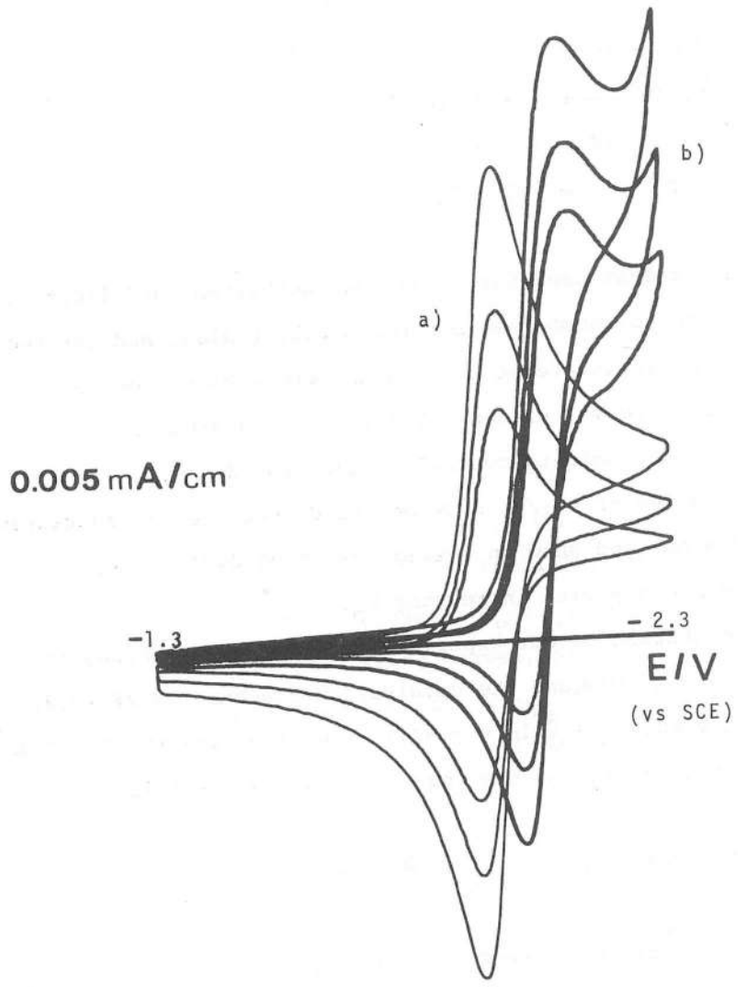

Figure 2 - a) Cyclic voltammograms for anthracene 4×10^{-3}M in DMF/Bu_4NBF_4 at a vitreous carbon electrode. b) the same as a) but with $TosOC_2H_5$, 4×10^{-3}M.

$$E^{\circ}_{AB} + \frac{RT}{2F} \ln K = -2.11 \text{ V}$$

$$E^{\circ}_{AB} + \frac{RT}{F} \ln K = -1.83 \text{ V}$$

which may be solved to give

$$K = 4.7 \times 10^{5} \text{ s}^{-1}$$

$$E_{AB} = -2.28 \text{ V.}$$

The knowledge of K also allows the determination of the competition factor.Table 2 presents these values for the three compounds studied.

T A B L E 2

Values of E_{AB}, K and p for different tosyl esters

	E°_{AB} (V)	K (s^{-1})	p
$TosOCH_3$	-2.36	1.0×10^{7}	9×10^{-4}
$TosOC_2H_5$	-2.28	4.7×10^{5}	9×10^{-2}
$TosOCH(CH_3)_2$	-2.33	9×10^{5}	3×10^{-2}

The observation of these values indicates that the structure of the tosylate does not seem to affect the mechanism or kinetics strongly.

The p values clearly show the domination of the ECE mechanism while the E°_{AB} and K values are similar.

T A B L E 1

Study of the kinetics of $TosOC_2H_5$

$C_A^o=C_P^o$	2×10^{-3} M			4×10^{-3} M			6×10^{-3} M		
(Vs^{-1})	0.2	0.1	0.05	0.2	0.1	0.05	0.2	0.1	0.05
$\frac{i_p}{\gamma_1 pd}$	0.671	0.769	0.905	0.695	0.816	0.949	0.575	0.674	0.833
λ_1	0.157	0.280	0.478	0.181	0.349	0.578	0.064	0.160	0.367
K_1	603.8	538.5	459.6	348.1	335.6	277.9	82.1	102.6	120.5
$\frac{\lambda\lambda_1}{\lambda_2}$	0.028	0.045	0.087	0.032	0.057	0.100	0.015	0.028	0.083
$\frac{KK_1}{K_2}$	0.215	0.173	0.167	0.246	0.219	0.192	0.115	0.108	0.121

The ethyl derivative differs most and it is interesting to note that this behaviour was also noted by Mann and coworkers [6].

However, larger molecules should be tried, e.g. the tosylate esters of phenols, benzyl and natural products alcohols and this will be the subject of further studies.

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