Intramolecular dissociative electron transfer

Sabrina Antonello and Flavio Maran*

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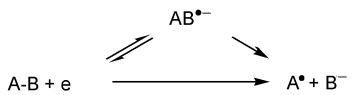
Dissociative electron transfers (ET) are reactions in which the ET is associated with the cleavage of a sigma bond. Although a rather satisfactory amount of information is currently available on the intermolecular and heterogeneous dissociative ET reactions, less is known for the corresponding intramolecular processes, despite the relevance of these reactions in both chemistry and biochemistry. This *tutorial review* focuses on the most recent developments in this area, with particular emphasis on the reactions occurring in well-defined Donor–Spacer–Acceptor molecular systems. The goal is to provide the reader with the essential background to understand and possibly predict the feasibility and rates of these reactions, as well as to stimulate the application of the intramolecular dissociative ET concepts and related issues to still unexplored molecular systems.

1 Dissociative electron transfer: concepts and mechanisms

Understanding and predicting the rate of electron transfer (ET) reactions is one of the most significant and fascinating achievements of modern physical chemistry. Thanks to the Marcus theory of ET[1] and subsequent refinements,[2] the ET rates can be estimated using rather simple concepts, such as reaction driving force, reorganization energy, and electronic coupling between reactant and product states. In several chemical systems, the ET causes the cleavage of a σ-bond, therefore leading to a dissociative ET (DET). Generally speaking, DETs are useful reactions in that they provide an elegant and chemically clean way to generate reactive species such as radicals and, depending on whether we deal with a reductive or oxidative process, bases or acids, and nucleophiles or electrophiles. In the following, we will focus mostly on reductive DET processes, for which the majority of the mechanistic studies have been carried out; some dissociative oxidations will be considered occasionally. DETs may occur by different mechanisms, among which the two limiting cases are the stepwise mechanism, in which a labile, though discrete, radical-ion intermediate forms, and the concerted DET, in which the dissociation of the σ-bond is concerted to the ET itself. Scheme 1 illustrates the two processes for the common case of reduction of a neutral molecule, AB.



Scheme 1 Stepwise and concerted DET reactions.

*f.maran@chfi.unipd.it

Sabrina Antonello

Sabrina Antonello was born in Italy in 1970. She was educated at the University of Padova, where she received her Laurea degree in Chemistry in 1996. She obtained her PhD in Chemistry in 2000 with a Thesis entitled ''Dissociative Electron Transfers'', which was awarded in 2001 as the best PhD thesis by the Electrochemistry Division of the Italian Chemical Society. She currently holds a Research Associate Fellowship at the University of Padova. Her current research interests include electron transfer across interfaces, nanoparticles, and electrochemical microscopy techniques.

Flavio Maran

Flavio Maran obtained his Laurea Degree in Chemistry from the University of Padova in 1980. He took a faculty position in the same university in 1983. He has been a Visiting Scientist in Canada, USA, and Japan. He is currently Professor of Physical Chemistry at the University of Padova, where he leads the Electrochemistry Group and teaches physical chemistry, electrochemistry, and electron transfer reactions to undergraduate and graduate chemistry students. Besides dissociative electron-transfer reactions, his current research focuses on molecular electrochemistry, electron transfers through biologically relevant bridges, and monolayer-protected clusters.

Whereas many examples of stepwise DETs can be found in the literature, less common are cases of unequivocal concerted DETs. In the eighties, compelling evidence had accumulated indicating that the rate constants of some dissociative reductions were characterized by very weak driving-force dependence,[3] implying a particularly large nuclear reorganization of the reacting system on its way to the transition state. In this context, Savéant proposed a model to describe concerted DETs and to mark the distinction with the corresponding stepwise processes.[4] The original model is based on a Morse-type description of the reactant and product curves and leads to a quadratic relationship between the activation free energy ($\Delta G^{\ddagger}$) and the reaction free energy (ΔG°) that is formally identical to the well-known Marcus equation (Scheme 2).[1] The original treatment was later modified to take into account nonadiabaticity[5] and entropy effects associated with the formation of the fragmentation products inside the solvent cage.[6,7]

From a kinetic viewpoint, the main difference between the outer-sphere ET initiating a stepwise process and the single step of the concerted DET is the value of the intrinsic barrier ($\Delta G_0^{\ddagger}$). The latter is the activation free energy at $\Delta G^{\circ} = 0$ and, therefore, is the most important parameter characterizing the kinetic facility of the given reaction. $\Delta G_0^{\ddagger}$ contains free-energy contributions from both the solvent reorganization energy (λ_s) and the inner reorganization energy (λ_i). Whereas the outer-sphere ET step of common stepwise DETs is ruled mostly by λ_s, $\Delta G_0^{\ddagger}$ is particularly large for concerted DETs. For the latter reaction, $\Delta G_0^{\ddagger}$ is proportional to one quarter of the bond dissociation energy (BDE).[4] Scheme 2 summarizes these basic concepts. λ_i' is the inner reorganization term corresponding to λ_i except for the absence of the mode corresponding to the cleaving bond. The rate constant for DET (k) may be described as shown in Scheme 2. Z is the nuclear frequency factor and κ is the electronic transmission coefficient: while for adiabatic processes (sufficiently strong electronic coupling at the transition state) $\kappa = 1$, for nonadiabatic ETs (weak electronic coupling regime) the rate is controlled by the electron-hopping frequency at the transition state and $\kappa \ll 1$. Since the width of the $\Delta G^{\ddagger}$–ΔG° parabola and thus of the log k–ΔG° curve is inversely proportional to $\Delta G_0^{\ddagger}$ (curvature $= \partial^2 \Delta G^{\ddagger}/\partial(\Delta G^{\circ})^2 = 1/8\Delta G_0^{\ddagger}$), it follows that the rate–ΔG° relationship of concerted DETs is, for the same ΔG° range, closer to linear (or farther from parabolic) than that of an outer-sphere ET reaction.

The ΔG°s of the two possible ET pathways (thermally-activated ETs) are calculated using the formal potential (E°) values of reductant (generically indicated in Scheme 1 as "e") and acceptor. Whereas the E° of the ET step of the sequential mechanism is obtained straightforwardly, the E° of the concerted mechanism is conveniently expressed, through a thermochemical cycle, as a function of the A–B bond dissociation free energy (BDFE) and the E° of the leaving group,[8] as shown in Scheme 2. $E_{D/D^{\bullet-}}$ represents the E° of the electron donor, such as that for the formation of an aromatic radical anion (homogeneous DET). For heterogeneous reductions, it is simply replaced by the applied electrode potential (E).

The occurrence of the stepwise or concerted DET mechanisms is ruled by a delicate balance of factors such as, particularly, driving force and temperature.[9] The picture so far described, however, is complicated by the possible occurrence of borderline mechanisms, making the distinction between the two limiting DET reactions as less sharp. Let us consider the stepwise process first. Generally, the kinetics of both the initial electron uptake and subsequent bond-cleavage reaction of the stepwise DET mechanism is function of the specific molecular properties of the acceptor molecule. The initially formed radical anion may be particularly stiff (little molecular deformation occurs) and thus the ET step is characterized by a small intrinsic barrier. This is the case of, *e.g.*, ethers and aryl halides.[8,10] The SOMO (singly occupied molecular orbital) is very weakly coupled to the σ* orbital of the frangible bond and the bond cleavage step entails an exergonic intramolecular DET from the moiety initially hosting the unpaired electron to the A–B σ* orbital. This step is accompanied by stretching of the A–B bond and significant solvent reorganization. For other classes of compounds, on the other hand, the SOMO involves more or less significantly the frangible bond and λ_i (most often associated with stretching of the A–B bond) increases accordingly. λ_i can now be even larger than λ_s, as found for sulfide reduction.[11] Finally, there are compounds for which the SOMO is significantly localized onto the bond undergoing the cleavage or may even correspond to the σ* orbital. The reduction intermediates are defined as loose radical anions, as opposed to the stiff ones (π* radical anions) described above. Since in σ* radical anions the bond weakens and elongates (because of decreased bond order), λ_i is particularly large. The cleavage step is now an endergonic reaction associated with stretching of the frangible bond and little solvent reorganization, the charge being already localized essentially in the same region in which it will be after the cleavage. A typical example of this mechanism is provided by the reduction of disulfides.[12]

The second possibility arises when a favorable ion-dipole interaction between the caged fragmentation products takes place. This effect increases the rate of concerted DETs: by enhancing the polar character of the radical A$^{\bullet}$, the interaction

$$\Delta G^{\neq} = \Delta G_0^{\neq}\left(1 + \frac{\Delta G^{\circ}}{4\Delta G_0^{\neq}}\right)^2 \qquad \Delta G_0^{\neq} = \frac{\lambda_s + \lambda_i}{4} \qquad \Delta G_0^{\neq} = \frac{\lambda_s + \lambda_i' + \mathrm{BDE}}{4} \qquad k = \kappa Z \exp(-\Delta G^{\neq}/RT)$$

$$\Delta G^{\circ}_{\text{outer-sphere ET}} = -F(E^{\circ}_{\mathrm{AB/(AB)^{\bullet-}}} - E^{\circ}_{\mathrm{D/D^{\bullet-}}})$$

$$\Delta G^{\circ}_{\text{concerted DET}} = -F(E^{\circ}_{\mathrm{AB/A^{\bullet},B^-}} - E^{\circ}_{\mathrm{D/D^{\bullet-}}}) = -F(E^{\circ}_{\mathrm{B^{\bullet}/B^-}} - E^{\circ}_{\mathrm{D/D^{\bullet-}}}) + \mathrm{BDFE}$$

Scheme 2 Main equations relevant to DET mechanisms.

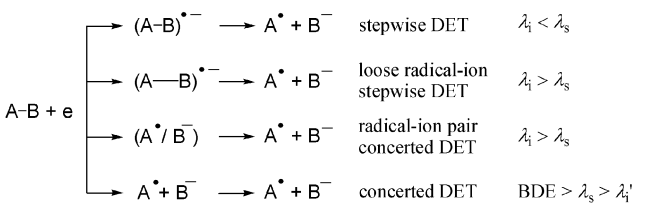
with the anion B^- becomes stronger, the transition state becomes more reactant-like, and the activation energy decreases accordingly. Striking examples of this borderline DET mechanism have been found in studies of the dissociative homogeneous (by using freely-diffusing electron donors, such as aromatic radical anions) or electrode reduction of ring-substituted benzyl halides[13] and the electrode reduction of haloacetonitriles.[14] The strength of the interaction is essentially determined by the nature of the substituents on the radical $A^{\bullet}$ and the polarity of the solvent. Because of this interaction, the separation of the caged product is a thermally-activated endergonic process. Interestingly, since the intrinsic barrier of this kind of concerted DET can be rather significantly smaller than that of purely dissociative processes, it may turn out to be similar to that of the stepwise DET mechanism proceeding through formation of loose radical anions.

This scenario would point to a rather progressive variation of the characteristics of the stepwise and concerted DETs. The actual DET mechanism is thus related to specific features of the acceptor molecule, such as the importance of the SOMO–σ* coupling, the strength of the frangible bond, the nature of the A and B groups and of the two atoms forming the bond, the presence of a dipole moment in the radical fragment, as well as the dielectric and molecular properties of the solvent. Scheme 3 summarizes the above possible mechanistic paths and the relative relevance of the terms determining the value of $\Delta G_0^{\ddagger}$.

2 Intramolecular DET

At present, we have reached a valuable understanding of how the rate of heterogeneous and intermolecular DETs changes as a function of driving force ($\equiv -\Delta G^{\circ}$). In particular, it has been shown with peroxides, which are compounds having particularly small BDEs and thus $\Delta G_0^{\ddagger}$ values, that the predicted[4] quadratic rate–driving force relationship nicely accounts for the experimental trend, whether obtained at the electrode[15] or by using solution electron donors (Fig. 1).[16] For a more comprehensive account on this and related issues, the reader may refer to very recent reviews.[8,10] On the other hand, much less is known for intramolecular DETs, although many examples of radical anions decaying by fragmentation of a σ-bond can be found in the electrochemical and photochemical literature.[8,10,17]

By definition, the intramolecular DET concept concerns the second step of common stepwise DET processes, *i.e.*, the thermally-activated σ-bond cleavage step.[18] Because of the nature of the antibonding orbital initially hosting the unpaired electron, the BDE of radical anions is significantly smaller



Scheme 3 Summary of the possible DET reaction pathways and associated relative reorganization energy relevance.

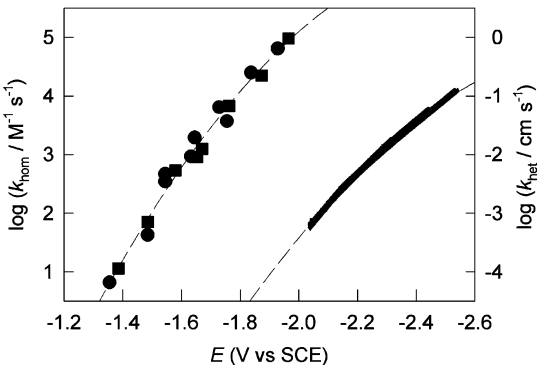
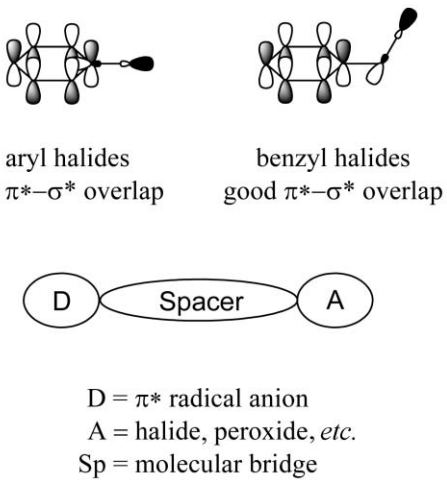


Fig. 1 Driving force dependence of the logarithm of the rate constant for the dissociative reduction of $(PhMe_2CO)_2$ at the electrode (right scale, DMF)[15] and by aromatic radical-anion donors (left scale; ●, DMF; ■, MeCN).[16] The dashed lines have been drawn by using the DET quadratic equation. Adapted from ref. 8.

than that of the neutral molecule. Although this facilitates the cleavage reaction, not all radical-ion bond cleavage reactions should be considered as being the result of an intramolecular DET. Instead, an intramolecular DET should be viewed as the ET reaction occurring in a system in which the orbital initially hosting the electron (most often a π* orbital) is weakly coupled, while in the equilibrium configuration of the reactant system, to the σ* orbital of the cleaving bond. Sometimes, in fact, the π*–σ* coupling is so large to make the description of the overall process in terms of electron uptake followed by intramolecular π* → σ* ET as not quite realistic. This is, *e.g.* (Scheme 4), the case of benzyl halides, in which the overlap between the π* system and the C–halogen σ* orbital is good; on the other hand, there is virtually no overlapping between the π* orbital and the orthogonal C–halogen σ* orbital of aromatic halides, which requires out of plane vibrations of the C–halogen bond during the activated cleavage step.[19]

Because of these and further considerations, to obtain unequivocal information on the factors determining the efficiency of intramolecular DETs the electron exchanging centers must be clearly identified and characterized and so



Scheme 4 Models of poor and good π*–σ* orbital overlap and schematic representation of a D–Sp–A system.

must be their thermodynamics. This situation is conveniently achieved by chemically connecting a donor (D) and an acceptor (A) by means of a molecular spacer (Sp) (Scheme 4). It is well-known that this type of strategy has led to fascinating results in the area of intramolecular nondissociative ETs, leading to a deep knowledge of how electrons are transferred through bonds and space.[20] In the case of DETs, rather surprisingly, this approach has been employed only occasionally. For the sake of clarity and also to obtain a better-defined understanding of the most relevant features of the intramolecular DETs, we will consider primarily examples of systems based on the D–Sp–A strategy or otherwise meeting the weak D/A electronic coupling criterion.

One of the purposes of this article is to assess to which extent the knowledge so far accumulated on the corresponding intermolecular processes can be extended to intramolecular DETs. More generally, the goal is to provide the reader of the essential background to understand these reactions and possibly to stimulate the application of the intramolecular DET concepts to still poorly understood or unexplored molecular systems.

3 Experimental methodologies

To study intramolecular DETs in D–Sp–A systems, several issues must be taken into account. First, the formal potentials of both A and D must be obtained independently, possibly by using model molecules having either the Sp–A or the D–Sp structure. Second, the competitive second-order intermolecular reaction, in which the D end of a molecule reduces the A side of another one, must be characterized so that the intramolecular reactivity can be decoupled from the observed rate. Third, a reliable way to measure the intramolecular rates and test the goodness of the complementary information related to the previous issues (*e.g.*, the actual E° values in the D–Sp–A molecules) is needed. Fourth, the structure and dynamics of the molecular bridge must be known quite well, which often requires specific experimental and/or theoretical conformational studies. To provide the reader of a quick reference on how to approach the study of these reactions, some of the most commonly employed experimental (electrochemical) methodologies now are briefly described. More information can be found in, *e.g.*, ref. 8.

Determining the E° of D, which is chosen from moieties suitable to yield stable radical anions, is easily accomplished experimentally, for example by cyclic voltammetry. Care must be exercised to assess whether the E° of the model donor (D–Sp) will be unaffected by the presence of the A group in the D–Sp–A molecule. The E° of the dissociative-type acceptor A, on the other hand, cannot be determined directly. In fact, the direct dissociative reduction of A is observed at potentials much more negative of the E° value (often, by $\sim$1 V). The latter, however, may be estimated from the irreversible voltammetric curves by using the convolution analysis approach[15] and the DET theory.[4] The convolution analysis is a very powerful electrochemical approach to study the fine details of heterogeneous ETs. Unlike conventional electrochemical methods, all of the experimental *i*–*E* data composing a single voltammetric wave are used in the kinetic analysis and, in addition, the kinetic data can be analyzed without the need of defining *a priori* the ET rate law. In practice, the heterogeneous rate constant k_{het} is obtained as a function of E. These experimental $k_{het}(E)$ data are the equivalent of a series of rate constant values obtained by using a huge number of solution electron donors with E° values in the same E range. By using this method, the quadratic rate–free energy relationship (Scheme 2) could be established for the reduction of several classes of compound.[8] The final step of the convolution analysis is the determination of the transfer coefficient α, which describes how driving force variations affect $\Delta G^\ddagger$ ($\alpha = \partial\Delta G^\ddagger/\partial\Delta G^\circ$). Since $\Delta G^\circ = -F(E^\circ - E)$, the apparent value of α can be obtained from the convolution data as $\alpha = -(RT/F)\partial \ln k_{het}/\partial E$. Therefore, for an uncomplicated DET mechanism, α is a linear function of E, being $\alpha = 0.5 + F(E - E^\circ)/8\Delta G_0^\ddagger$. For $\alpha = 0.5$, an estimate of E° is thus obtained.

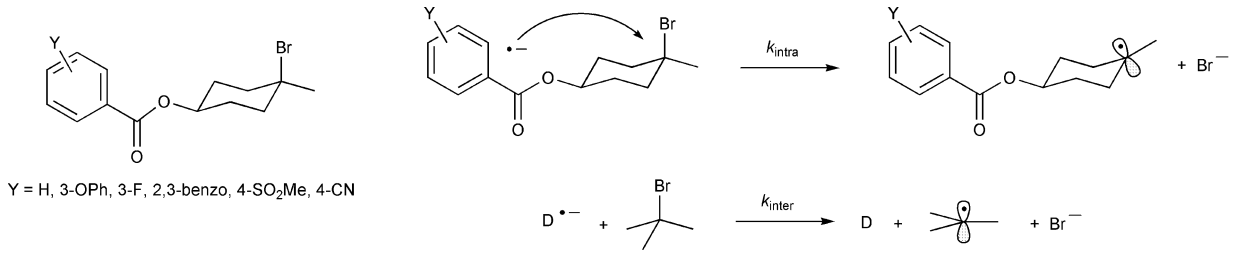
The relevance of the competitive intermolecular reaction in affecting the overall kinetics is determined by studying the homogeneous reduction of the model acceptor molecule (Sp–A) by a series of radical anion donors, possibly chosen among molecules of the D–Sp type. This is conveniently accomplished by using, in particular, the homogeneous redox catalysis approach,[8] which is a powerful methodology developed by Savéant and his co-workers to allow determining the intermolecular rate constants, k_{inter}. Finally, the intramolecular rates are calculated by voltammetric analysis and/or digital simulation of the experimental curves obtained with the D–Sp–A compounds in a wide range of concentrations and voltammetric scan rates. The independent knowledge of the various E° and k_{inter} values is particularly useful in this part of the analysis.

Sometimes, the kinetic data can be determined by using other experimental approaches, such as pulse radiolysis, laser flash photolysis, or other photochemical methods. The necessary thermodynamic data can be obtained through thermochemical cycles, specific electrochemical experiments, or photoacustic calorimetry.[8] In the context of DET studies, the emerging role of specific *ab initio* molecular orbital (MO) calculations must be emphasized. Calculations can be very useful to highlight molecular and solvent effects on the structure of reactants, products, and transition states, or to understand the role played by the molecular bridge connecting D and A as well as to characterize its conformational preferences. In fact, the best way to tackle DET problems is to couple well-devised experimental studies with specifically focused theoretical analyses. It appears that this tendency will develop further in the years to come.

4 Driving-force dependence of the intramolecular DET rates

The first steps in the direction of studying the driving-force dependence of the DET rate in well-defined D–Sp–A models were made by using a series of molecules in which a tertiary bromide was the acceptor, ring-substituted benzoates were the donors, and cyclohexyl was the spacer (Scheme 5).[21]

The acceptor was selected to compare the intramolecular results with the large amount of data available for the



Scheme 5 Reactions and model systems employed to study the free-energy dependence of the intramolecular DET.

intermolecular reduction of *tert*-butyl bromide, which is by far the most studied molecule undergoing a DET.[22] As a matter of fact, for this experimental system data are available (homogeneous reduction in amide solvents) for an overall variation of the intermolecular rate constant by 13 orders of magnitude. In this reaction (and also in the ET to other alkyl halides), the experimental data seems to fit a parabola, as predicted by the theory, or a straight line almost equally well. This is primarily because these reactions have particularly large $\Delta G_0^{\ddagger}$ values (besides the BDE values, also because of the hybridization change accompanying the formation of the carbon radical (Scheme 5)) and of additional effects that may contribute to straighten the curve, particularly at low driving forces.[22–24]

By using the experimental methodologies described in the previous section, we found that the intramolecular DET rate constant (k_{intra}) is more sensitive to variation of ΔG° than observed for the corresponding intermolecular reaction. Fig. 2 shows the comparison between the intramolecular and the intermolecular data. It should be noted that whereas for the intermolecular DETs α is distinctly smaller than 0.5 (*ca.* 0.38–0.41), as expected for such exergonic processes, the value of α for the intramolecular ETs is 0.51, *i.e.*, a value that would be expected only for $\Delta G^{\circ} \approx 0$. A similar outcome has now been observed with the corresponding series of *trans*-1-methyl-4-benzoyloxycyclohexyl bromides.

This experimental outcome was explained by considering the effect of the ring substituent. In fact, introduction of a more electron-withdrawing substituent (such as when H is replaced with CN) produces both a decrease of the reaction driving force (less negative donor E°) and a shift of the centroid of the donor π^* orbital, in which the unpaired electron is initially located, the SOMO, away from the acceptor. Because of this shift and thus increase of the effective D/A distance, the D/A electronic coupling decreases as the driving force decreases.

This hypothesis, however, called for further experimental tests. A similar series of D–Sp–A compounds was thus synthesized. In these molecules, a peroxide was the acceptor and substituted phthaloyl groups provided the D moieties, while cyclohexyl was again chosen as the spacer (Scheme 6).[25] By changing the aryl substituents of the phthalimide moiety, the driving force could be varied by 0.74 eV. X-Ray diffraction crystallography and *ab initio* conformational calculations pointed to D–Sp–A molecules having the same conformation and D/A orientation. Moreover, *ab initio* MO calculations indicated that, except for the nitro substituted compounds, the location of the centroid of the donor SOMO does not vary appreciably along the series. In addition, they confirmed the electrochemical data, which gave clear indication of having a concerted DET to the peroxide moiety. As in the study on the DET to bromides, the intramolecular DET was studied in DMF by electrochemical means, in comparison with the thermodynamic and kinetic information obtained with models of the acceptor and the donor.

The rate constants of the intramolecular reaction were compared with the corresponding intermolecular values (Scheme 7). Unlike the bromides previously described, for the peroxides, in which the relative D/A distance could be controlled, the intramolecular slope now was found to be

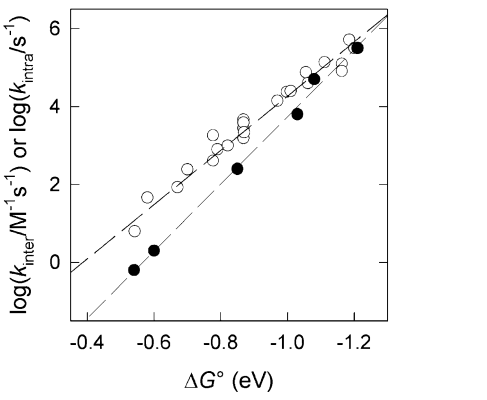
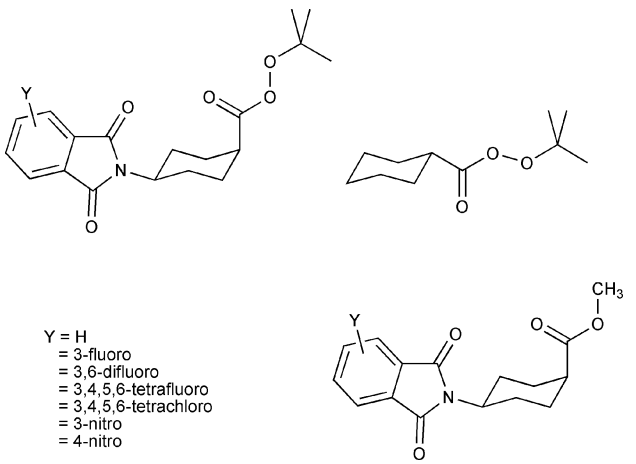
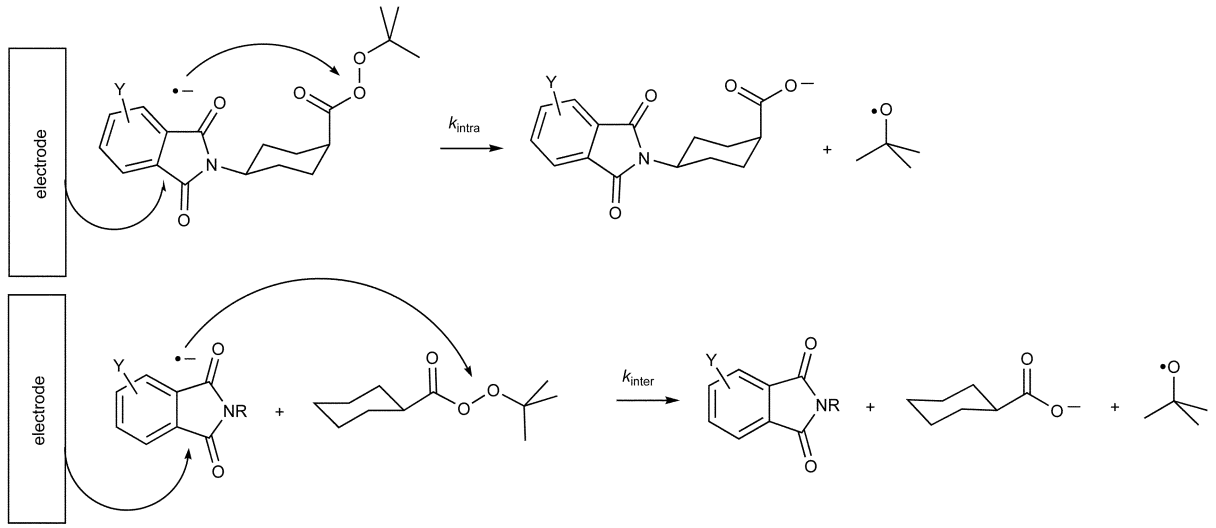


Fig. 2 Free-energy dependence of the logarithm of the intramolecular (●) and intermolecular (○) ET rate constants for reduction of tertiary bromides in DMF. The dashed lines are the fit to the two series of data. Adapted from ref. 21.



Scheme 6 Second generation dissociative-type D–Sp–A molecules and corresponding models of the donors and peroxide acceptor.



Scheme 7 Electro-initiated intra- and intermolecular DET to the perester acceptor.

slightly smaller than the intermolecular one (Fig. 3). This outcome was in line with the expectations. Concerning the slight difference of the two slopes, it is accounted for by considering that a particularly large solvent reorganization energy (and thus $\Delta G_0^{\ddagger}$) accompanies the ET in the D–Sp–A systems.

On the other hand, introducing strong electron-withdrawing groups on the donor moiety modifies the rate significantly: with the two nitro-phthaloyl derivatives we found, both experimentally and by theoretical calculations, that the effective D/A distance increases, causing the intramolecular rate constant to be smaller than expected by as much as 1.6 orders of magnitude. The localization of the SOMO is pictorially highlighted in Scheme 8.

On the contrary, the intermolecular rates, measured with the corresponding D–Sp molecules (Scheme 7), are perfectly in line with the results obtained with the other donors. This is because the intermolecular rate is a consequence of random distance and orientation distributions in the encounter complex. The main outcome of these studies is thus that once a larger solvent reorganization than for the intermolecular DETs and the effective D/A distance (and thus electronic coupling: see below) are taken into account, quantitative predictions of intramolecular DET rates can be straightforward. As for other intramolecular ETs, a larger solvent reorganization is required by the additional D/A separation caused by the spacer. In fact, according to the Marcus model,[1] λ_s is proportional to the term $(2r_D)^{-1} + (2r_A)^{-1} - (R_{DA})^{-1}$, where r_D and r_A are the donor and acceptor radii and R_{DA} is the D/A distance, which can be taken as equal to $r_D + r_A + d_{Sp}$, where d_{Sp} is the edge-to-edge distance increase brought about by the spacer.

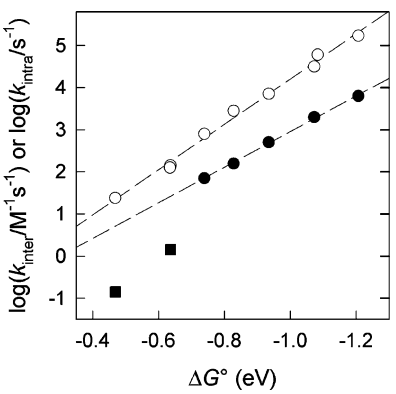
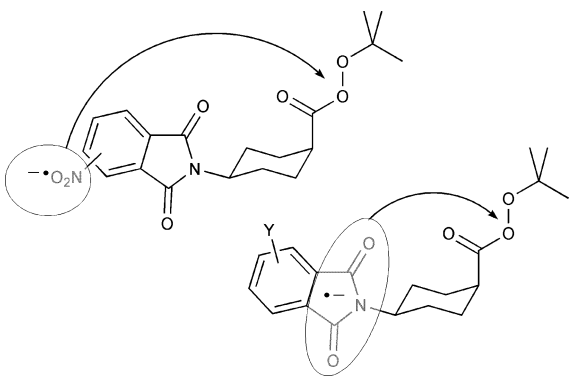


Fig. 3 Free-energy dependence of the logarithm of the intramolecular (●, and, for the nitro-substituted compounds, ■) and intermolecular (△) ET rate constants for the reduction of the perester acceptor in DMF. Adapted from ref. 25.

5 Homolytic and heterolytic cleavages

The mechanism of radical-anion bond cleavage strongly depends on the specific molecular framework. As a consequence, the pertinent intrinsic barrier and the $\Delta G^{\ddagger}$–ΔG° relationship also depend on it. For the sake of clearness, it now is convenient to introduce a slightly different terminology. While D and Sp will retain their previous meaning, the acceptor moiety will be renamed A–B, to stress that the fragmentation pertains that specific bond and that the negative

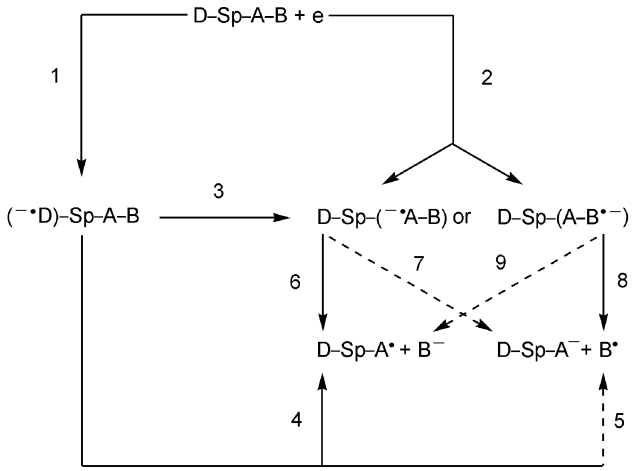


Scheme 8 Schematic representation of the localization of charge in the SOMOs of the nitro derivatives as opposed to the halide-substituted phthaloyl donors.

charge is eventually located in either the A or B group. At this point, various reaction paths are possible, as illustrated in Scheme 9.

The electron can be injected either into the molecule on the D side (reaction 1) or directly into the acceptor group, A–B, leading to a transient radical anion (reaction 2). The latter species, which may slightly differ depending on whether the charge is located mostly on the A or B side (this dualism vanishes if a σ* radical anion forms, such as, *e.g.*, with disulfides[12]), can be formed also indirectly, through reaction 1 followed by the intramolecular ET reaction 3. Reactions 4 and 5 represent the heterolytic and homolytic cleavage reaction mechanisms. While the first mode of cleavage occurs when the charge crosses the scissile A–B bond (thereby leaving the spin density in A), the second one refers to when the charge remains on the same side of the molecule in which it was initially located (although not the same moiety). Of course, the same two-fold possibility can be defined for the cleavage of the transient anions formed in reactions 2 or 3. In the past, a simpler version of Scheme 9 was adopted because the presence of an actual spacer was not explicitly considered: the heterolytic and homolytic cleavages were thus depicted as shown for the A–B side alone (reactions 6 or 8 and 7 or 9).

The intramolecular DET depends on the nature of the spacer, which may consist of a single methylene group, a (partially) π-conjugated molecular backbone, or an unconjugated molecular bridge. For the latter systems, provided the bridge is sufficiently rigid and at least two or three σ-bonds long, the donor and acceptor E°s are essentially the same as those of the model molecules D–Sp and Sp–A–B, respectively. This means that the spacer can efficiently isolate the redox properties of the D end from those of the A end. Therefore, the ΔG° of both the homolytic and heterolytic cleavage reactions 4 and 5, which are particularly clear-cut cases of intramolecular DETs, can be expressed as already described for intermolecular DETs in Scheme 2. The equation for ΔG° was successfully employed for the intramolecular reactions shown in Scheme 5 and 7, which correspond to reactions 4[21] and 5,[25] respectively. It is likewise simple to define the ΔG° of the



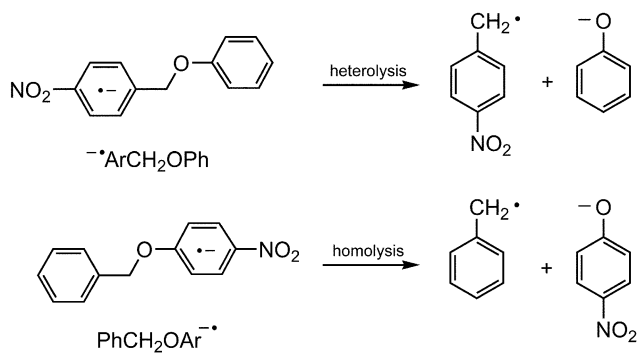
Scheme 9 Possible radical-anion fragmentation pathways. Where pertinent, the solid and dashed lines represent the heterolytic and homolytic cleavages, respectively.

nondissociative intramolecular ET, reaction 3. Again, for sufficiently long bridges the separation of the two redox sites can be such to warrant that the E°s of D and A–B are the same as in the D–Sp and Sp–A–B molecules and that the BDFE of the initially-formed radical anion is the same of that of the neutral molecule.

Reactions 3–5 are the intramolecular equivalent of the bimolecular reaction employed in the redox catalysis experiments (compare, *e.g.*, the two reactions of Scheme 7). Of course, the similarity ends here because the intramolecular mediator can exchange only one electron (or two: the intramolecular reduction of the carbon radical of Scheme 5 occurs in a similar manner as the reduction of the C–Br bond[21]) with the acceptor. For thermally-induced intramolecular ET reactions 3–5, the D end of the molecule acts as an electron antenna, whose function is to shuttle the electron onto the actual DET acceptor. Interestingly, this role of D can be valid even though the direct reduction of A–B is thermodynamically easier. In fact, whereas the reduction of D is governed mostly by solvent reorganization (D is usually a delocalized aromatic moiety), the direct reduction of A–B is kinetically slow because of the large intrinsic barrier of dissociative-type acceptors or acceptors forming σ* radical anions (*cf.* Scheme 3). This is a very peculiar and also useful aspect of intramolecular DETs as they are, in fact, irreversible processes which because of their large intrinsic barrier can be studied at rather negative ΔG° values without the complication of back ET.

A more complex situation arises for those classes of radical anion in which the spacer is either absent or allows for substantial communication between the redox centers. For these species, which by far have been the most investigated cases, the BDE of the A–B bond of the radical anion is substantially smaller than that of the neutral species. In other words, injection of an electron into an antibonding orbital weakens the A–B bond, an effect that is particularly important when the SOMO significantly involves the scissile bond. Therefore, a different story holds for the thermodynamics of reactions 6–9.[8,10,18] Concerning the activation–driving force relationships ruling these intramolecular transfers, quadratic equations (similar to the one valid for intermolecular processes, as shown in Scheme 2) have been derived and applied to most of the reactions of Scheme 9, including the situation in which ion–dipole interactions stick the fragments in the solvent cage;[10,14,18,26] for the formation of σ* radical anions, in which λ_i is particularly large, a different approach is more suitable.[27]

The problem of homolytic versus heterolytic bond cleavage in radical anions has been discussed in several occasions.[8] The fragmentation of the C–O bond in ether radical anions liable to produce either $^{-\bullet}ArCH_2OPh$ or $PhCH_2OAr^{-\bullet}$ (Scheme 10) was studied in detail.[28] In both cases, fragmentation leads to the pertinent phenoxide ion and benzylic radical. While there is a thermodynamic advantage for the fragmentation of $PhCH_2OAr^{-\bullet}$, the fragmentation of $^{-\bullet}ArCH_2OPh$ is faster by orders of magnitude. The difference may be related either to differences in the intrinsic barriers or in the electronic coupling between the reactant and product surfaces, or both. Originally, the difference was assigned entirely to differences in the



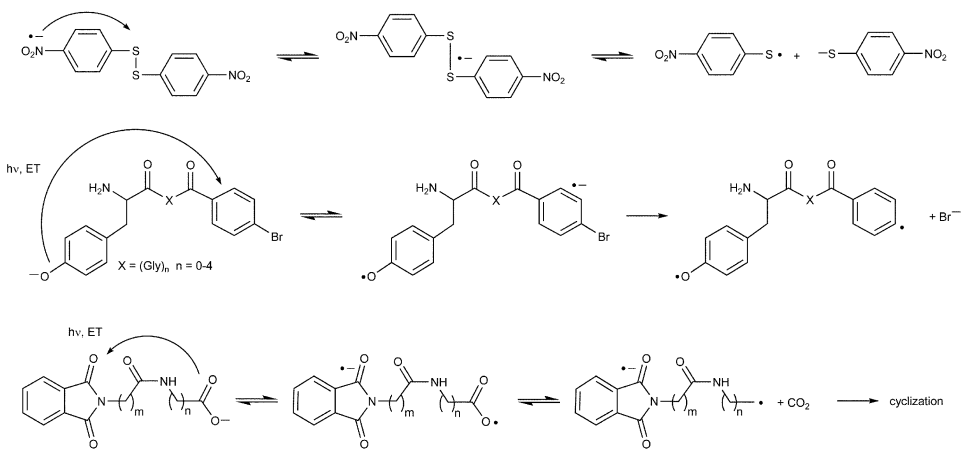
Scheme 10 Heterolytic *vs.* homolytic cleavage in ether radical anions.

intrinsic barriers. The homolysis and heterolysis pathways were discussed in terms of the valence bond configuration mixing model.[29]

In the intramolecular DET model, the fragmentation is seen as coupled to the stretch of the A–B bond (and, in condensed phase, accompanied by solvent reorganization);[18,30] while this decreases the σ* energy rapidly, the π* energy increases only slightly. This system has been nicely described in terms of potential energy curves in a study of dissociative electron attachment to some alkyl chlorides.[30] When these energy curves match, the intramolecular DET can occur. Consideration of this view of the mechanism of fragmentation led to an alternate explanation for the apparently lower intrinsic barrier of heterolytic cleavages.[31] The difference may be attributed to differences in the electronic coupling at the avoided crossing; it has been suggested that there is greater delocalization of charge across the scissile bond in the heterolytic cleavage compared to the homolytic cleavage.[31] The problem of homolytic *versus* heterolytic fragmentation has been discussed in some detail also for the reduction of α-nitrocumenes.[32] It was found that proper substitution, while affecting the cleavage driving force, may change the mechanism of the cleavage of radical anions within the same family of compounds.

In the general context of radical ion fragmentation, it also is worth mentioning that in some instances the bond breaking leads to formation of a distonic radical ion, *i.e.*, a species in which the specific molecular framework does not allow for bimolecular separation of the radical from the ion. Upon rearrangment, however, the two reactive centers are located in different portion of such secondary radical-ion intermediate. These reactions can be very important for both synthetic and mechanistic purposes. The latter aspect is often related to the use of such species to monitor ET events, *i.e.*, as radical clocks. The reaction may or may not involve a formal intramolecular DET and thus may be the equivalent of either reactions 3–5 or 6–9, respectively (*cf.* Scheme 9). Representative examples can be found in studies concerning the opening of cyclopropylcarbinyl-type rings, in which it was shown how delocalizations of both charge and spin are important ingredients governing radical-ion reactivity,[33] and of the DET to endoperoxides,[34] pointing to the relevance of the λ_i' term (*cf.* Scheme 2). For some compounds, the dissociative process may also be inverted. It has been recently reported that electrochemical associative oxidation of rhodium complexes, to form a metal–ligand bond, may be followed by dissociative reduction of the same bond.[35] Both intramolecular processes are endowed by a large change in both the length of the forming or breaking bond and the pertinent torsion angle.

While the occurrence of intramolecular DET reactions 4 and 5 of Scheme 9 is relatively well documented, less frequent are reported cases of reaction 3. For this reaction to occur, the secondary formed intermediate has to be a true although labile species (whether of the π* or σ* type). Three examples will be mentioned (Scheme 11). The reduction of a nitro disubstituted diaryl disulfide was studied, together with other disulfides, by electrochemistry and *ab initio* MO calculations.[12] For this disulfide, the unpaired electron is first accommodated into a π* antibonding orbital entirely localized onto one of the two nitrophenyl groups. Upon stretching of the S–S bond (main contribution to the reaction coordinate), the relative orbital energies change to the point at which the electron may tunnel into the σ* S–S orbital to form a different radical anion. Finally, an endergonic S–S bond cleavage takes place. A similar mechanism could be responsible for the the cleavage of radical anions of aromatic halides.[36,37]



Scheme 11 Examples of intramolecular DETs going through the formation of a secondary ET intermediate.

The two other examples are taken from ET reactions in biologically-interesting systems. In the first, photoinduced ET leads to formation of a transient intermediate in which the aryl bromide acceptor is transformed into its radical anion.[38] The ET reaction fits nicely with reaction 3 of Scheme 9 and with the known reductive behavior of aryl bromides.[10] C–Br bond cleavage eventually yields the aryl radical together with bromide ion. This process is a nice approach to the transient generation of neutral biradicals in liquid solution. The final example, is taken from an interesting photochemical approach to cyclopeptide formation.[39] The reaction entails photoexcitation of the phthalimido moiety, intramolecular ET to form the very unstable $RCO_2^{\bullet}$ radical intermediate (cleavage rate constants in the range 10^9–10^{11} s^{-1}), C–C bond cleavage to form a carbon radical, and subsequent cyclization *via* radical-radical coupling. This reaction, which features a case of oxidative DET, is indeed an elegant synthetic process fully exploiting the potentialities of DETs. Besides methylene spacers (as shown in Scheme 11), oligopeptides were successfully tested.

6 Electronic coupling and DET rates

The preexponential factor of the DET rate-constant expression may be affected by the efficiency of the reactant-to-product transition at the avoided-crossing region of the energy *vs* reaction coordinate profile. Among them, we here consider the following ones: intrinsic nonadiabaticity, orbital symmetry restrictions, and distance effect on the DET rate.

Usually, ET reactions proceed adiabatically unless the D/A separation increases to such an extent that the rate falls off more or less rapidly with distance; the rate-constant prefactor, which for adiabatic processes is determined by a nuclear vibration frequency, is now an electron-hopping frequency. In fact, outer-sphere ETs and most DET reactions takes place adiabatically at van der Waals D–A separation (*cf.* Scheme 2, $\kappa = 1$). In these processes, the electronic coupling between the reactant and product states (H_{RP}) is on the order of the RT term; while resonance at the transition state slightly decreases the activation barrier, H_{RP} has no effect on the dynamics of barrier crossing. Concerning typical DET acceptors such as alkyl halides, the reaction is in agreement with the adiabatic DET theory,[23] as also verified[16,24] by applying the nonadiabatic DET theory.[5] A new situation, however, was encountered by studying the DET to peroxides, which also are well-defined dissociative-type acceptors. In fact, by studying the kinetics of the reduction of dialkyl peroxides,[16] endoperoxides,[34] and peresters,[9,24] the prefactors were found to be smaller than predicted by the adiabatic DET theory even by orders of magnitude. Noteworthy, the same nonadiabaticity outcome could be observed by using electrode, solution, or intramolecular donors, which points to the DET to peroxides as an inherently nonadiabatic process. This peculiar observation was attributed to the failure of the Born–Oppenheimer approximation near the transition state,[24] by analogy with the outcome of other dissociation reactions.[40] It appears that for some bond-breaking reactions the electronic wavefunction may not instantaneously adjust along the reaction coordinate near the transition state. If the dynamics of the electronic rearrangement is sufficiently slow, the crossing between the reactant and product curves is only narrowly avoided (very small H_{RP}), causing the reaction rate to drop significantly. At difference with common nondissociative-type ETs, DETs should be considered as very slow reactions not only because of the much larger intrinsic barrier but also because they appear to be particularly prone to proceed nonadiabatically.

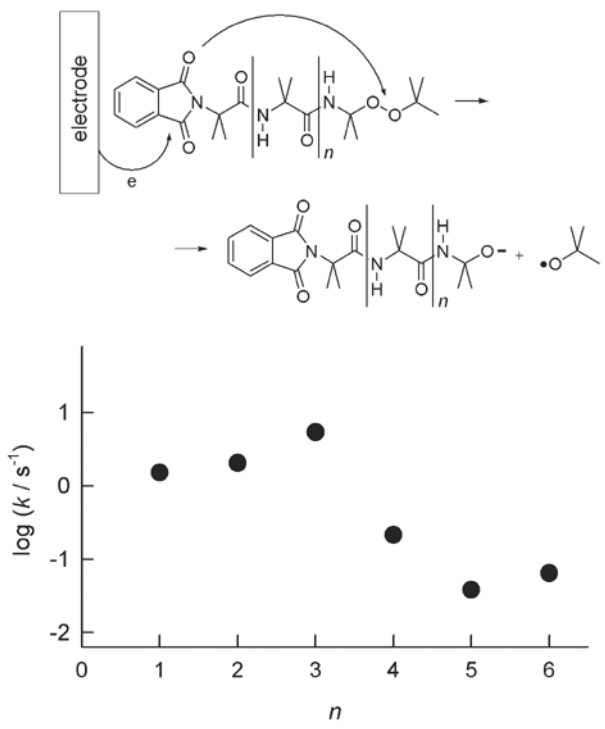
As for any other ET process, the intramolecular DET rates also are affected by the relative orientation of the exchanging orbitals, the distance between the D and A redox centers, and the nature of the molecular bridge. DETs differ from nondissociative-type ETs also because the acceptor orbital is a σ* orbital. This is an important issue when considering rigid molecular framework. In fact, we have already mentioned that overlapping between the π* orbital and the orthogonal C–halogen σ* orbital of aromatic halides, which allows for electron tunneling at the transition state, requires out of plane vibrations of the C–halogen bond; the latter and the C–halogen bond elongation are, in fact, the main inner reorganization requirements of the system. Other examples have been reported in which rigid molecular frameworks affect the intramolecular DET reaction rate significantly. It appears that the ET rate can be sustained by vibronic coupling at the transition state. The role of symmetry restrictions on the efficiency of π*–σ* coupling has been particularly stressed for intramolecular DETs to halide acceptors, either in the gas[30] or solution phase.[41] For example, by comparing the intramolecular DET rate of a radical anion subject to symmetry restriction to that of a nonrestricted but otherwise identical compound, it was shown that because of symmetry constrains the rate drop observed on going from the former to the latter amounts to a few orders of magnitude.[41]

As for nondissociative ETs, intramolecular DET processes are also affected by both the distance between the D and AB redox centers and the nature of the spacer or bridge. However, despite the relevance of DETs in complex molecular systems and biologically-relevant environments, the research in this area is still, rather surprisingly, in its infancy. Nevertheless, a few significant results in this area were obtained by varying the lengths of rigid, flexible, and also peptide bridges.

We have already described two cases of photoinduced DETs in which the spacer length was varied (Scheme 11). In both reactions, either the efficiency of exchange interactions within the biradical, as studied by time resolved electron paramagnatic resonance,[38] or the cyclization yield[39] were found to be functions of the chain length. In both cases, the spacers were rather flexible. Some interesting results concerning the distance effects in gas-phase dissociative electron attachments also have been published. In one of them, in which rigid norbornyl systems were used to separate a π* donor and a C–Cl acceptor, the importance of the distance dependence of the coupling between the π* and σ* orbitals and the competition between direct electron attachment to the acceptor and indirect reduction *via* intramolecular DET were stressed.[30] The fragmentation of the C–Cl bond in compounds such as $Ph(CH_2)_nCl$, with n = 1–4, was studied in comparison with the behavior displayed by similar compounds in which the (flexible) spacer was partially modified introducing third-row heteroatoms (S, Si).[42] One electron was first injected into the

phenyl π* orbital and then transferred dissociatively to the C–Cl bond. This study revealed how important is the bridge in modulating the through-bond electronic coupling between the π* and σ*(C–Cl) orbitals; in fact, the decrease of the fragmentation rate brought about by an increase of the donor/acceptor distance is significantly attenuated upon introduction of Si or S. In the latter case, however, C–S bond cleavage competes with the C–Cl cleavage pathway.

Long range DET in biologically-relevant bridges is still an almost unexplored area. Very recently, we studied the intramolecular DET from an electrogenerated phthalimide radical-anion donor to a peroxide acceptor.[43] The phthalimide and peroxide electrophores were attached at the two ends of α-aminoisobutyric acid (Aib) homo-oligomers in which the number of residues was varied substantially (Scheme 12). These peptides were chosen for their propensity to form rigid 3_{10}-helices because of steric hindrance at the α-carbon and resulting reduced torsional freedom. As illustrated in Scheme 12, we found that the intramolecular rate constant depends very mildly upon the number of Aib units (or the edge-to-edge D–A distance). As a matter of fact, we were surprised to find that the ET rate was even increasing when *n* was varied from 1 to 3. These results were attributed to an active role played by intramolecular hydrogen bonds, which would support the electron tunneling by providing efficient shortcuts to the actual DET (thereby increasing the electronic coupling). The exponential decrease of the rate observed with most bridges[20] could not be observed because adding a new α-amino acid unit does not simply produce a distance increase but also modifies significantly the energy of the peptide backbone through the secondary structure and, probably, conformational effects. Significant progress is expected to be made in this area in the next few years.



Scheme 12 Intramolecular DET in peptide systems.

7 Concluding remarks

Although still actively underway, the research in the area of intramolecular DET reactions has already produced sufficient information on the basic concepts. On the other hand, more experimental data on carefully selected donor–spacer–acceptor molecules and specific theoretical calculations are still needed to better understand the dynamics of these reactions, which are inherently very slow. Similarly, more information is needed about the corresponding photoinitiated intramolecular DET processes, which have obvious and not so obvious features that distinguish them from the corresponding thermal ones.[10]

We also should stress that the relevance of intramolecular DET in many areas is only now being realized. Various expected developments could be mentioned. Among them, for example, the possibility of using suitable frangible bonds to switch on and off molecular devices through reductive cleavage and then oxidative radical coupling. Significant progresses also are expected to be made in the area of DET in biologically-relevant systems, particularly in view of the important role of the disulfide bridges in peptides and proteins or the interest of triggering intramolecular reactions by dissociative oxidation of carboxylates. Several applications in the area of synthetic chemistry are likewise possible, as these reactions may yield powerful nucleophiles or reactive radicals, even within the same molecular framework.

The research is thus looking for new experimental systems, challenges, and other areas in which the DET concepts may make an impact. Expedient to achieve these goals is that our arsenal of experimental methods and analysis tools to investigate these processes is sufficiently well developed.

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Sabrina Antonello and Flavio Maran*
Department of Chemical Sciences, University of Padova, via Marzolo 1, 35131 Padova, Italy. E-mail: f.maran@chfi.unipd.it

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