Electrochemical controlling and monitoring of halogen bond formation in solution†

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Cyclic voltammetry has been used for the first time to probe and to control the formation of non-covalent halogen bonding (XB) *via* redox switching. These results strongly encourage the use of electrochemistry as an economical and precisely controllable tool for the investigation of XB in solution.

Halogen bonds[1] are non-covalent interactions in which covalently bound halogens act as electrophilic species in the presence of a Lewis base. The term "halogen bonding" (XB)[2] was introduced to stress its similarity with hydrogen bonding regarding geometry and strength (5–180 kJ mol^{-1}).[1] Halo-hydrocarbons (I, Br, Cl) are potential XB donors in the presence of a Lewis base. Halo-perfluorocarbons form particularly strong interactions owing to the electron-withdrawing fluoro substituents which are considerably increasing the so called sigma hole[3] of the halogen atom and consequently its electrophilicity. The utility and importance of XB for controlling self-assembly in the solid state[1,4] was proven in many applications in crystal engineering and materials science.[5] Until recently, it has been less clear to what extent XB is capable to influence conformation, binding or reactivity in the solution phase.[6] So far only few examples have been described and a first review[7] summarizes solution-phase thermodynamic data for XB interactions and emerging applications in molecular recognition, anion sensing, medicinal chemistry and catalysis.[8] The analytical methods[9] applied are mostly based on spectroscopic techniques such as NMR, UV, IR, Raman and EPR. In this context we are not aware of any publications based upon electrochemical methods.

The goal of the present work was to prove the concept of electrochemical controlling of XB interactions in homogeneous solution. There are only few publications reporting on the influence of redox states on XB in the solid phase[10] and so far

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no examples in solution. Tuning the strength of a redox active Lewis base *via* a reversible electrochemical reaction should change its affinity towards halogenated XB donors. Such type of redox switching is of great interest since the electrochemical probing and controlling of XB will assist to better understand supramolecular properties and reactivity of complex systems such as liquid electrolytes involving multiple competing non-covalent interactions. There is also an important potential for the development of electrochemical sensing devices and novel tools for the investigation of halogenated molecules in chemical biology and medicinal chemistry.[11]
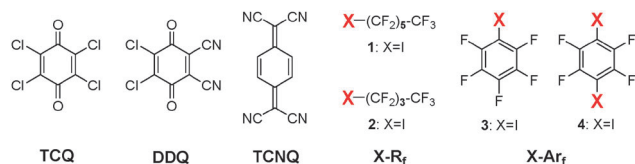
In non-aqueous solvents *p*-quinones can be reversibly reduced in two sequential one-electron transfer steps[12] generating the corresponding radical anion (semiquinone radical) and dianions, increasing considerably the respective Lewis base strength. The influence of hydrogen-bond donors and Lewis acids on the electrochemistry of quinones has been extensively studied.[13,14] The observed potential shifts in the quinone reduction potentials were attributed to the stabilization of the corresponding anions due to their association with hydrogen bond donors[13] (in the absence of proton transfer reactions) and Lewis acids[15] (alkali and earth-alkali metal cations).

For the first time we have investigated the interactions of quinone anions with XB donors by cyclic voltammetry (CV) in homogeneous solution. The relatively weak Lewis acidity of organic halo-derivatives represents an intrinsic problem for probing such interactions in a conducting liquid electrolyte involving numerous competitive interactions with the solvent molecules and the supporting electrolyte salt present in relatively high concentrations. In this study the CV experiments were conducted in a 0.1 M solution of tetra-*n*-butylammonium hexa-fluorophosphate (TBAPF$_6$) in acetonitrile, a common electrolyte with a relatively large potential window. No significant ion-pairing has been observed so far during the reduction of *p*-quinones to the corresponding dianions in contrary to supporting electrolytes containing alkaline metal cations (MPF$_6$; M = Li, Na, K).[13b,16] Furthermore Taylor and co-workers recently showed that acetonitrile is a weaker XB acceptor as it would have been expected on the

Scheme 1 Electrochemically active Lewis bases (TCQ, DDQ, TCNQ) and perfluorinated aliphatic (X-R$_f$) and aromatic (X-Ar$_f$) XB donors used in this study (X = I, Br, Cl).

Fig. 2 Dependence of the potential shift ($\Delta E^{\circ\prime}$) corresponding to the second reduction step of TCQ (0.5 mM) on the concentration of the XB-donors **1** (red dots, including standard deviations) and **3** (black squares) at 298 K.

basis of electrostatic interactions only.[17] It is important to note that all voltammetric experiments have been conducted under anhydrous conditions in the absence of oxygen (see Experimental section). Acetyl-ferrocene and [Os(bpy)$_3$](PF$_6$)$_2$ were used as internal standards in control experiments confirming the accuracy of the saturated calomel electrode. The added XB donor solutions systematically contained the supporting electrolyte salt and the quinone in order to keep both concentrations constant during the entire period of each experiment.

For this work we have chosen tetrachloro-p-quinone (TCQ), a common oxidizing agent, also known as p-chloranil (Scheme 1). The interaction of its reduced species with various aliphatic and aromatic XB donors (Scheme 1) was investigated. Typical cyclic voltammograms of TCQ in the absence and the presence of 1-iodo-perfluorohexane (**1**) are illustrated in Fig. 1.

In acetonitrile TCQ shows two monoelectronic cathodic waves which correspond to the formation of the anion radical TCQ$^{\bullet-}$ and the dianion TCQ^{2-}, respectively. In these reductions the first step is fully reversible and the second step quasi-reversible at customary scan rates (compare Table S1 in ESI†).

Upon the addition of **1** the formal standard potential of the second reduction wave was shifted significantly (up to 140 mV) to the positive direction towards more anodic potentials with no essential loss of reversibility whereas the position of the first wave remained unchanged. This observation is consistent with the previously observed weak binding of oxo anions such as nitrate or tosylate to XB donors[18] suggesting that only the highly Lewis basic dianion is able to undergo strong XB in the presence of competing interactions with the electrolyte but not
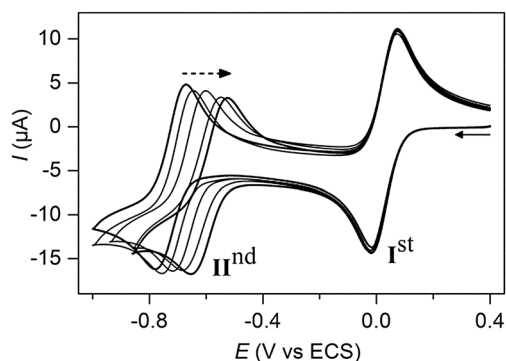
the radical anion. This behavior can be attributed to a substantial stabilization of TCQ^{2-} as it has been previously described for hydrogen bond donors in the absence of proton transfer reactions.[12] Upon the addition of a 100 fold excess of iodo-perfluorohexane (**1**) or iodo-perfluorobenzene (**3**) potential shifts of around 140 mV and 108 mV, respectively, have been observed (Table S1, ESI† and Fig. 3). The dependence of the potential shifts on the concentration of both XB donors **1** and **3** is shown in the titration curves of Fig. 2. The corresponding equilibria concerning the formation of XB complexes depending on the TCQ redox state are detailed in Scheme 2. The irreversible reduction of the XB donors was observed outside the applied potential window at more negative potentials around −1.50 V (compound **1**) and −1.65 V (compound **3**).

In order to discard any ion-pairing effects we also performed the same experiments at lower supporting electrolyte concentrations (0.02 M TBAPF$_6$) and different cations (0.1 M tetramethyl ammonium hexafluorophosphate). In both cases the standard potential shifts upon the addition of 100 equivalents of XB-donor **1** were observed to be very similar (140 and 120 mV, respectively) confirming that ion-pairing effects can be neglected under these conditions (see Fig. S5 and S6, ESI†).[16]

Besides TCQ two other electrochemically active Lewis bases dichloro-dicyano-p-quinone (DDQ) and tetracyano-quinodimethane (TCNQ) were studied (Scheme 1). Like TCQ both compounds can be reversibly reduced in two steps to the respective dianions. In TCQ^{2-} the negative charges are mainly localized on the two oxygen atoms.[19] Due to the nitrile groups the charge of DDQ^{2-} is more delocalized leading to a weaker Lewis basicity (weaker XB acceptor) than TCQ^{2-} explaining the smaller potential shift of only 53 mV

Fig. 1 Cyclic voltammograms of TCQ (0.5 mM) on a glassy carbon electrode in a solution of TBAPF$_6$ (0.1 M) in acetonitrile in the absence and in the presence of increasing concentrations of iodo-perfluorohexane (**1**) (from left to right: 0, 0.5, 5, 25 and 50 mM). Scan rate 0.1 V s^{-1}.
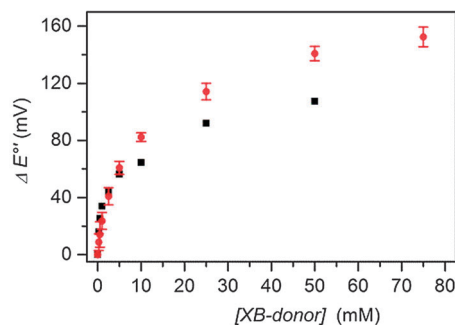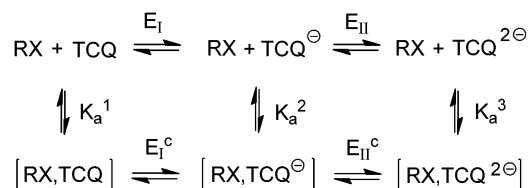

Scheme 2 Square scheme illustration the equilibria of electrochemical reactions and halogen bonding between TCQ and a XB donor (RX).

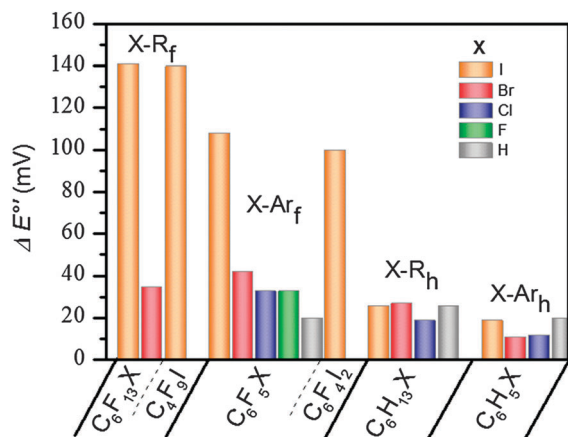Fig. 3 Formal potential shifts $\Delta E^{\circ\prime}$ of the redox couple TCQ$^{\bullet-}$/TCQ^{2-} ([TCQ] = 0.5 mM) in the presence of 100 equivalents (50 mM) of perfluorinated and non-fluorinated XB donors in 0.1 M TBAPF$_6$–acetonitrile: X-R$_f$ (1-halo-perfluoro-n-hexane), X-R$_h$ (1-halo-n-hexane), X-Ar$_f$ (halopentafluoro-benzene), X-Ar$_h$ (halo-benzene).

Fig. 4 Job's continuous variation plots ($|\chi\Delta E^{\circ\prime}|$ vs. χ, χ = [TCQ]/[TCQ] + [XB donor], [TCQ] + [XB donor] = 1 mM) for TCQ and the XB donors 1 (red dots) and 3 (black squares) based on the potential shifts of the TCQ$^-$/TCQ^{2-} redox couple in 0.1 M TBAPF$_6$ acetonitrile at 298 K.

observed upon the addition of 100 equivalents of 1 under the same conditions as described above. This explanation was supported by the absence of significant potential shifts ($\Delta E^{\circ\prime}$ = 8 mV) for the even more delocalized TCNQ^{2-}. In the latter case the corresponding di-anions can certainly not compete with the solvent molecules or the PF$_6^-$ anions being present in much higher concentrations.

Fig. 3 shows the measured formal potential shifts of the TCQ$^{\bullet-}$/TCQ^{2-} couple after the addition of 100 equivalents of several aliphatic (X-R$_f$) and aromatic (X-Ar$_f$) halo-perfluorocarbons and their non-fluorinated homologues (X-R$_h$ and X-Ar$_h$) (see also ESI†). The highest shift values of 100–141 mV have been recorded for all studied iodo-perfluorocarbons, the aliphatic derivatives I-R$_f$ 1 and iodo-perfluorobutane 2 displaying higher values than the aromatic compounds I-Ar$_f$ 3 and 1,4-diiodo-perfluorobenzene 4. Compared to these strong XB donors the other halo-perfluorocarbons (X = Br, Cl, F) induce much smaller potential shifts of 32–43 mV which is consistent with their weaker XB-donor strength. There is a tendency of the shift values corresponding to the usually observed trend[1] in XB donor strength: I > Br > Cl. However the differences are too small for being significant. The studied non-fluorinated halo-hydrocarbons are very weak XB donors and as it could be predicted they fairly shift the reduction potential of TCQ ($\Delta E^{\circ\prime}$ = 11–20 mV for X-Ar$_h$ and 19–26 mV for X-R$_h$). The similar shift values of pentafluorobenzene and benzene as well as the particularly high shifts for the aliphatic iodo-perfluorocarbons compared to their aromatic homologues exclude the hypothesis of a predominant contribution of π–π or σ–π interactions.

For the hydrogen bond donor ethanol (100 equiv.) a $\Delta E^{\circ\prime}$ of only 53 mV has been measured for the TCQ$^{\bullet-}$/TCQ^{2-} couple which is only 50% or less of the values determined for the strongest XB donors in this study. Although surprising this is not the first example of XB overcoming comparable hydrogen bonding.[20] A perturbation of the experiments by the presence of water traces could be excluded. In agreement with the literature[21] the presence of water in low concentrations (<0.1 M)
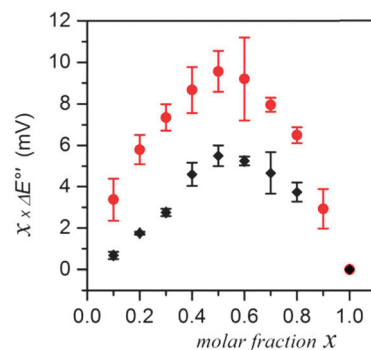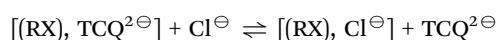
affected not only the second ($\Delta E^{\circ\prime}$ only 50 mV at 50 mM of water) but also the first reduction step significantly. Such behaviour was not observed in any of the above reported examples performed under anhydrous conditions.

The stoichiometry of XB-complexes was determined by Job's continuous variation method[22] based on the measured potential shifts (Fig. 4). For both donors 1 and 3 symmetric curves with maxima at 0.5 molar ratio indicate the formation of 1:1 complexes. Consequently the simulations of the cyclic voltammograms were based on the square scheme represented above (Scheme 2) and did not take into account the formation of complexes with higher stoichiometries than 1:1. The ratios of formal affinity constants K_a^3/K_a^2 of the strong XB-donors corresponding to the binding enhancement during the reduction of TCQ$^-$ to the dianion TCQ^{2-} were estimated by fitting the simulated cyclic voltammograms to the experimental data (see ESI†). Since the first reduction potential was not influenced by the presence of XB donors the simulations could be limited to the second reduction step. K_a^3/K_a^2 ratios of 1000 (TCQ^{2-}, compound 1) and 350 (TCQ^{2-}, compound 3) were calculated. A significantly smaller value of 50 (DDQ^{2-}, compound 1) was found for the weaker Lewis base DDQ. Previously published affinity constants of [Cl$^-$,I-C$_8$F$_{17}$] (1.3×10^2 M^{-1}, in acetonitrile and 2.2×10^3 M^{-1} in acetone)[23] and [Cl$^-$,I-C$_6$F$_5$] (1.4×10^2 M^{-1} in acetone)[18] had been determined by ^{19}F NMR titrations in pure solvents. One has to take into consideration the fact that solvent polarity and the concentration of supporting electrolyte salts strongly influence the measured affinity constants.

In order to demonstrate the reversible XB complex formation, the Lewis base competition between TCQ^{2-} and Cl$^-$ anions has been investigated. A voltammetric titration curve of TCQ with successive and alternating additions of the XB donor 1 and tetra-n-butylammonium chloride (TBACl) has been recorded (Fig. S4 in ESI†). The potential shift of 65 mV reached after the XB donor addition (10 equiv.), decreased significantly to the value of 53 mV when TBACl (20 equiv.) was added. This procedure could be repeated several times proving the competition of a strong (TCQ^{2-}) and a weaker (Cl$^-$) Lewis base in reversible XB:

$$[(RX), TCQ^{2\ominus}] + Cl^{\ominus} \rightleftharpoons [(RX), Cl^{\ominus}] + TCQ^{2\ominus}$$

In conclusion we have proven the concept of electrochemical XB switching in homogeneous solution. The XB acceptor strength of *p*-quinones such as TCQ or DDQ can be controlled by the modulation of their redox state. In the presence of iodoperfluorocarbons, binding is "on" in the reduced dianionic state of the Lewis basic quinone and "off" in the anion radical and neutral states. An electrochemical technique, cyclic voltammetry, was used for the first time to monitor these dynamic interactions in solution. XB was found to prevail among the numerous competing intermolecular interactions between the XB donors as well as the quinone dianions with the polar solvent molecules and supporting electrolyte ions present in high concentrations. The main contribution to the observed potential shifts was attributed to the stabilization of the quinone dianion *via* XB. Reversible XB acceptor competition was demonstrated between TCQ^{2-} and chloride anions. Currently work is in progress to develop a redox switch based on a halogenated electrochemically active XB donor molecule. Beyond potential applications in molecular recognition (sensing devices, molecular redox switches), these results strongly encourage the use of electrochemistry as an economical and precisely controllable tool for the investigation of the impact of XB on chemical reactivity in solution.

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