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Three-electron two-centred bonds and the stabilisation of cationic sulfur radicals

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Electronic communication in biological systems is fundamental to understanding protein signalling and electron hopping pathways. Frequently studied examples are cationic radical methionine and its functional derivatives. These systems are understood to be stabilised by a *direct* 'three-electron two-centred' bond. We demonstrate for methionine and a series of cationic radical methionine analogues that long-range multi-centred *indirect* stabilisation occurs, which cannot be attributed to three-electron two-centred interactions. A revised description of the radical stabilisation process is presented, which includes contributions from all atoms with accessible p-orbitals, independent of the distance to the sulfur radical.

1 The 'three-electron two-centred' bond: radical stabilisation over two motifs

The 'three-electron' bond has a rich history. Molecules with odd numbers of valence electrons proved challenging for early phenomenological descriptions of the chemical bond.[1] The existence of free-radicals could be explained with the advent of quantum chemistry. Pauling developed the valence-bond theory of 'three-electron two-centred' bonds with reference to simple chemical systems like He_2^+ and NO,[2,3] shown in Fig. 1a and c.[4] The contemporary understanding of this phenomenon remains through the combination of orbital symmetry, resonance structures and molecular orbital theory.[5] One of the more complex examples is that of 1,5-dithiocane, Fig. 1b, where a single electron is delocalised between two equivalent sulfur p-orbitals.

The three-electron bond classification has been expanded and applied to many-nuclei systems, particularly involving aromatic radicals.[6] However, there is a disparity between the description of centrosymmetric and non-centrosymmetric three-electron two-centred systems involving aromatics: defining the centre of an asymmetric molecule becomes arbitrary. aromatic three···aromatic three-electron two-centred systems may be a special case of the Pauling description, if the system is centrosymmetric. Otherwise, the bond may not be considered two-centred, but may still be composed of three electrons. Thus, the current definition of the 'three-electron two-centred' bond is the stabilisation of three electrons over two centres (nuclei or symmetric aromatic).[7] The result is the formation of an unconventional chemical bond.[8,9]

The three-electron bond discussion has also been extended to complex cationic organic radicals, where the unpaired electron is stabilised by neighbouring electron-rich motifs (*e.g.*

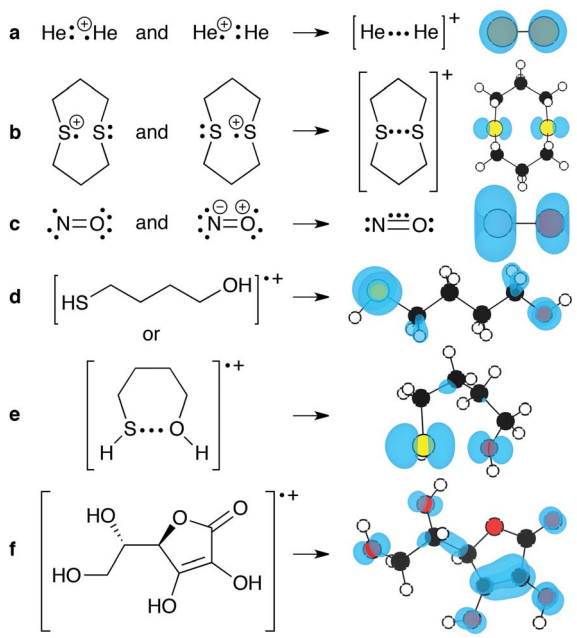

Fig. 1 Examples of three-electron two-centred systems: (a) He_2^+; (b) 1,5-dithiocane cationic radical; (c) NO neutral radical. The hydroxy-thiol cationic radical shown in (d)/(e) can exist in multiple conformations, the straight-chain (d) and the pseudo-cyclic (e). As the system complexity increases, so does the description of the radical localisation; an example is the cationic ascorbic acid radical, (f). Calculated spin density ($\rho^{\uparrow} - \rho^{\downarrow}$) for each radical state is shown on the right.

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carbonyls, aromatics, amides). The properties of such radicals have been explained by the formation of a chemical bond; an interaction dependent on the distance (orbital overlap) between the radical and the electron-rich motif.[10] Quantifying the existence and strength of these bonds can be challenging. One example is the thiol-alcohol shown in Fig. 1d and e, where one-electron ionisation can result in two states, (d) the 'one-electron' cation and (e) the 'three-electron two-centred' cation.[11] The radical is stabilised by oxygen in both cases, independent of the interatomic distance, *d*(S–O).[12]

A more complex case is the cationic ascorbic acid radical, Fig. 1f. It is possible to consider the formation of a three-electron two-centred bond between one of the aliphatic hydroxyl groups and the enolic –OH motifs from geometrical considerations. However, upon ionisation, the unpaired electron is stabilised over all electron-rich motifs with accessible p-orbitals. Here the '*x*-electron *y*-centred bond' nomenclature is inappropriate.

2 Sulfur radicals as biological electronic communicators

The formation of radical cationic thioethers sited at protein methionine residues underpins processes as diverse as electron transport[13–18] and Alzheimer's disease.[19] The one-electron oxidation of methionine residues has been extensively studied,[20–29] reflecting the biochemical significance of this process. In contrast to the second sulfur-containing amino acid, cysteine, which has a wide range of functional roles in proteins, methionine is poorly understood, with clearly defined mechanistic roles often lacking.

In a protein function study, Sachs and co-workers substituted non-active-site surface methionines in two receptor complexes, TRAIL-DR5 and LTα-TNFR1; these substitutions resulted in an inactive protein.[30] This suggests that (a) the methionine plays an important structural role, (b) the methionine S was accessible from the surface, where it could be ionised and thus communicate to the active site of the protein or (c) the combination of the former. The ionisation potential (IP) of the methionine S is sensitive to its local environment; the distance and relative conformation from S to the surrounding functionality is expected to influence the transfer of an electron to an electron acceptor.[31–33] In contrast, quantum mechanical calculations of the single methionine and cysteine cationic radicals indicate multi-centred stabilisation of the cationic radical states, Fig. 2.

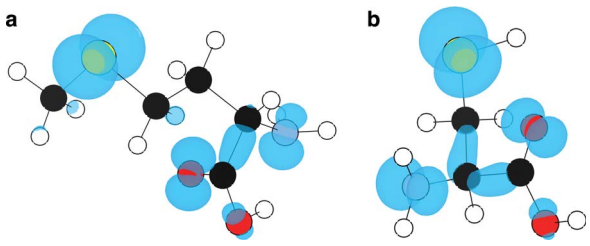

Fig. 2 Calculated spin density of cationic radical methionine (a) and cysteine (b). The electron is delocalised over the spin-stabilising nuclei.

In assessing the influence of structural effects, Glass reported a series of conformationally restricted methionine models for S-radical precursors.[34–36] These studies demonstrated that pendant aromatic moieties, or pyrrolidine amides, could significantly lower the IP as gauged by direct ionisation measurements or indirectly *via* electrochemical oxidation. The positioning of the IP-lowering motifs in both studies was at a single site relative to the thioether. Glass and co-workers discussed their results in the context of orbital interactions occurring *through space* (direct orbital overlap) or *through bond* (remote indirect stabilisation) following the terminology of Hoffmann, Gleiter and others.[6,37–39]

3 Destabilisation of the sulfur ground state or stabilisation of the cationic radical

The ionisation potential of a molecule may be considered as a process where the products are the molecular cation and a free-electron, *i.e.*

$$Q \rightarrow Q^{+} + e^{-}. \quad (1)$$

The reaction energy (IP) is determined by the relative stability of the neutral and charged states. A low IP can be caused by (i) a less-stable neutral state (Q) or (ii) a more-stable charged state (Q^{+}).[40] While photoelectron spectroscopy can provide a measurement of the IP, computational chemistry can be used to quantify the underlying contributions. We employ a combination of density-functional and many-body perturbation (*GW*) theory to explore the nature of these ionisations.

The methylthioether compounds in Fig. 3 have been selected to probe the various interactions present in these systems. Like Fig. 1d–e, systems **8a–d** have been selected to probe the *through bond* and *through space* interactions, whilst the other compounds explore the characteristics described in the former

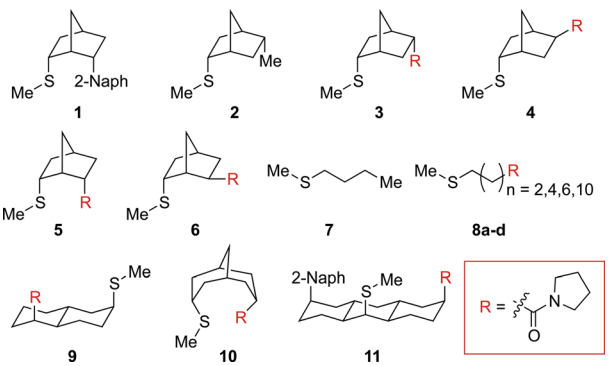

Fig. 3 Methylthioether compounds studied here. **1**–**6** are structurally restricted, limiting the distance between S and O. Compound **8** permits a broad range of *d*(S–O). **9** and **10** are unusual because they are structurally restricted with long and short *d*(S–O), respectively. **11** is a model biological system, combining structural elements from **1** and **9**.

paragraph. As a quantitative standard, the IP of **1** calculated from the *GW* quasiparticle energy was found to be within 3.5% of experiment.[34]

In the first class of methylthioethers (compounds **1–6**), the largest IP is observed where no electron-rich motif is present (**2**; 7.67 eV), Table 1. The smallest IP is found for nearest-neighbour naphthalene (**1**; 7.35 eV), illustrating a net stabilisation of 0.32 eV. The dependence on the structural configuration is illustrated by the pyrrolidine amide substituents. Similar IPs are obtained where the R group is orientated *trans* to S (**4** and **6**). A stabilisation of *ca.* 0.3 eV is found only for *cis* substitutions (**3** and **5**). The presence of an electron-rich motif close to a neutral S is unequivocally repulsive (*e.g.* **3** is more stable than **5** by 9.7 kJ mol^{-1}).

Glass and co-workers[35] measured the same difference in IP between a *cis* and *trans* configuration (**5** and **6**), which suggested a dependence on *d*(S–O). However, **3** shows a smaller IP than **5** even though *d*(S–O) is 0.6 Å longer. The neutral state (Q) of **3** is 7.1 kJ mol^{-1} less stable than **4**; a combination of both S repulsion and the preference of –R for the equatorial position. The ionised state (Q^+) of **3** is 28.1 kJ mol^{-1} more stable than **4** due to chemical stabilisation from the O and N electron-rich neighbours. Multiple fused cyclohexane rings and the inclusions of large substituents (like that of naphthalene in **1**) also decreases the IP, and this is emphasised by the similarities in IP for **1**, **3** and **9**.

Compound **7** represents an aliphatic primary methylthiolether analogue with no electron-rich cation stabilising motif. The IP is significantly larger than for the secondary cyclic systems (7.86 eV). A terminal pyrrolidine amide substituent is found to produce only a weak perturbation in the IP (Δ0.06 eV) with no significant dependence on *d*(S–O) (**8a–d**).

Following ionisation, upon relaxation to the local minimum structure, there is a contraction of *d*(S–O) in all instances. Indeed the difference in IP and the subsequent electron affinity (EA) of the relaxed structure is indicative of the adiabatic stabilisation provided by the neighbouring electron-rich motifs. Compound **9** has a low IP similar to **3** despite the much longer *d*(S–O). Due to the structural restriction, the EA is only smaller by 0.22 eV. In contrast, the structural flexibility associated with **10** results in a 1.56 eV shift in the EA with a final *d*(S–O) of 2.52 Å.

Configuration-coordinate diagrams for four representative systems with variable *d*(S–O) are shown in Fig. 4. The highest occupied molecular orbital (HOMO) for the ground-state and the resulting spin-density ($\rho^{\uparrow} - \rho^{\downarrow}$) for the spin-doublet charged-state are also drawn. Notably, the HOMO is primarily composed of a S p-orbital, which is subsequently ionised, following the Franck–Condon principle. Moreover, the spin-density shows that while having a majority S p component in all cases, the unpaired electron is stabilised across almost all unsaturated atoms (*e.g.* C in **1**, **2** and **7**; S, O and N in **3–6** and **8–11**). Accordingly, there is no evidence of three-electron two-centre bonds in the presence of more than one spin-stabilising nucleus.

The linear, primary methylthioether, compound **8** (Fig. 4b) shows no distance dependence on the spin density distribution and a very weak dependence on the IP, as previously discussed. By forcing the molecule to coil such that $d(\text{S–O})_{GS}$ is comparable to **3**, lower IPs are achieved, primarily from the destabilisation of the neutral state. Once ionised, there is competition between the stabilisation energy of minimising $d(\text{S–O})_{IS}$ and the energetic cost of contorting the molecule.

The combination of methylthioether, naphthalene and pyrrolidine amide motifs in compound **11** is analogous to systems frequently found in enzymes. The system results in the lowest IP (7.23 eV), which demonstrates a cooperative effect from the presence of multiple electron-rich groups in the same molecule. This result further emphasises that *three-electron two-centred* bonds are unlikely to be the primary mechanism for S stabilisation in biological systems.

Table 1 Ground-state (GS) and ionised-state (IS) S–O distances, vertical ionisation potential (IP_{GS}) and electron affinity (EA_{IS}) for systems **1–10**. Compound **7** does not have *d*(S–O) or EA, as there is no oxygen present, and upon geometric relaxation of the ionised state, the compound decomposed as described by Jursic[41]

	$d(\text{S–O})_{GS}$ (Å)	$d(\text{S–O})_{IS}$ (Å)	IP (eV)	EA (eV)
1[a]	3.24	2.97	7.35	6.69
2[b]	4.29	4.14	7.67	7.37
3	3.84	2.61	7.36	6.14
4	6.14	6.04	7.67	7.51
5	3.28	2.40	7.45	5.50
6	5.54	4.38	7.68	7.51
7	—	—	7.86	—
8a	5.38	5.31	7.80	7.73
8b	7.89	7.85	7.81	7.74
8c	10.45	10.42	7.82	7.75
8d	15.55	15.54	7.83	7.76
9	4.49	4.00	7.37	7.15
10	3.63	2.52	7.26	5.70
11[c]	4.52	4.20	7.23	7.07

[a] Distance measured from S to 2-naph-C. [b] Distance is measured from S to C. [c] Shortest distance measured from S to O.

4 Implications of multi-centred cationic radical stabilisation

The stabilisation mechanism is key to understanding radical molecules and reaction pathways. For instance, if the hole is partially delocalised over many spin-stabilising centres, S becomes relatively positive, subsequently increasing the acidity of the α-C–H protons. Conversely, systems which localise the radical on a single atom will be more reactive at the radical site. In a biological context, the methionine motif is common but will *always* be neighboured by peptide linkages, *i.e.* spin-stabilising atoms, thus delocalising the electron spin density. As a compliment to this spin stabilisation mechanism, electron-rich motifs, for example, the indole residue of tryptophan, are regularly found within close proximity of methionine residues. This point has been confirmed in a recent bioinformatics study by Sachs and co-workers, which shows that 33% of all known protein structures contain at least one methionine-aromatic

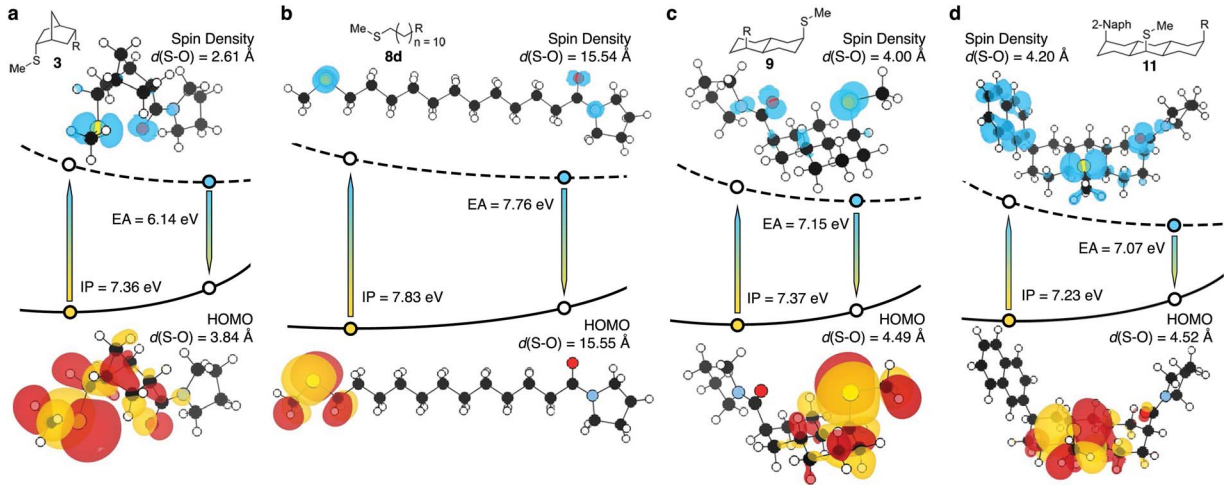

Fig. 4 Vertical ionisation potential (IP) and electron affinity (EA) diagrams. The (two electron) HOMO images correspond to the equilibrium ground-state structure (gold point), whilst the (single electron) spin-density images correspond to the ionised equilibrium structure (blue point). In all systems studied, sulfur p-orbitals are the major contributor to the HOMO and hence the centre of ionisation. (a, b and c) **3**, **8d** and **9**: spin density is partially delocalised over S, O and N. (d) **11**: the radical is distributed over all spin stabilising atoms. Isovalue = 0.04 e Å^{-3}. Visualisations were made using *VESTA*.[42]

motif.[30] Accordingly, biological systems are exceptional at destabilising the ground state, stabilising the radical state and transferring electrons over long distances *via* many atoms.

The non-locality of the unpaired electron (hole), whether in a protein or small molecule environment, is subtle but important.[43] The mechanisms detailed in our study provide initial insight into the function of the non-active site methionine residues in TRAIL-DR5 and LTα-TNRF1, and may extend to other complex radical systems. It is a step towards a quantitative understanding of single electron transfer events (*e.g.* electron hoping and active site mechanisms) and interpretation of single-electron phenomena in proteins.

A spectroscopic study by Forbes and co-workers suggested that upon ionisation *N*-Ac-methionine, at pH 2.0, forms a five membered ring, attributed to an intramolecular S–N three-electron bond.[44] Electron-spin resonance showed N hyperfine coupling; however, the coupling constants are consistent with *through-bond* interactions, that is, a straight-chain system, not a five-membered ring. This interaction is comparable to that of the systems shown in Fig. 4. N is non-nucleophilic in amides, hence it would be the least cation-stabilising heteroatom in *N*-Ac-methionine. Their findings are consistent with spin-stabilisation by N, and infer contributions from O.[45] Direct calculations confirm both O and N are spin-stabilising, in contrast to conventional understanding of chemical bonding in radical methionines.

The mechanisms described here are not limited to S radicals;[46–48] organic radicals will distribute their spin over stabilising atoms. We have shown that the ionisation of a molecule can be influenced by both the chemical composition and conformation through multi-centre interactions that do not conform to a three-electron bond. Furthermore, we have demonstrated that electron-rich motifs can destabilise the ground-state and stabilise the charged states; both contribute to changes in the observed ionisation potentials.

5 Computational details

All quantum-chemical calculations were performed using the *FHI-aims* package.[49] Within this all-electron approach the electronic wavefunctions are constructed using numeric atom-centred basis functions. A converged 'tight' basis set was employed, which includes d, f and g functions on the S atoms, and scalar relativistic effects were treated.

Local structure optimisations were performed using the forces from density functional theory (DFT) using the PBE exchange–correlation potential (V_{xc}^{KS}).[50] The quasi-particle electron addition ($N+1$) and removal ($N-1$) energies were assessed within the framework of *GW* many-body perturbation theory, originally developed by Hedin[51] and recently implemented into *FHI-aims* using a resolution-of-identity procedure to efficiently calculate the two-electron Coulomb integrals.[52] Here, G relates to the Green's function of the Kohn–Sham (PBE) Hamiltonian, which is perturbed by W, the screened Coulomb potential described within the random-phase approximation. The result is a correction of the Kohn–Sham single-particle eigenvalues (ε_n^{KS}) to the quasi-particle ($N-1/N+1$) electron energies ε_n^{GW}:

$$\varepsilon_n^{GW} = \varepsilon_n^{KS} + \langle \Phi_n^{KS} | GW(\varepsilon_n^{KS}) - V_{xc}^{KS} | \Phi_n^{KS} \rangle. \quad (2)$$

While traditionally developed within the condensed-matter physics community, the application of perturbative G_0W_0 theory based on an underlying PBE-DFT electronic structure has been extended to molecular systems with great success in describing electron removal energies.[53] Additional tests were performed using the hybrid PBE0 and B3LYP exchange–correlation functionals,[54] which were found not to change either the localisation of the radical spin or the trends in the resulting quasi-particle ionisation potentials.

The ionisation potentials are computed relative to the vacuum level. The inclusion of a polarisable continuum would

not change the qualitative trends reported here. Indeed the current model has been shown to reproduce experiment to within 3.5% of the measured IP. Whilst solvation of radicals in aqueous media has been observed,[55] our model can be considered representative of certain complex biological systems. The internal chemistry of a protein, the site of electron hoping, is defined by motifs similar to what is studied here: hydrocarbons with ubiquitous heteroatoms, sparsely hydrated.

Acknowledgements

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