Design principles for α-tocopherol analogues†

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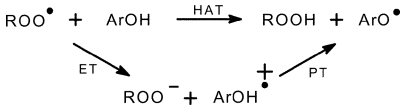
An (RO)B3LYP/LANL2DZdp//B3LYP/LANL2DZ model for the prediction of the homolytic bond dissociation enthalpy (BDE) and adiabatic ionisation potential (IP) of phenolic antioxidants containing heavy chalcogens has been developed. The model has been used to probe the relationship between geometry, chalcogen substitution and activity for a series of α-tocopherol analogues of varying ring size. From this, a series of design principles for cyclic antioxidants has emerged, embodied by the compound 4-hydroxy-2,2,3,5,6-pentamethylbenzoselenete (**4c**). This compound is predicted to have a BDE comparable to α-tocopherol, and should act in a dual chain-breaking and hydroperoxide-decomposing manner, by analogy with other selenide antioxidants. The stability of chalcogen-substituted benzoxetes was considered, and the as yet unsynthesised benzotelluretes are predicted to be stable. Finally, an attempt was made to determine antioxidant mechanism by considering calculated BDE and IP data together with experimental rate data.

Introduction

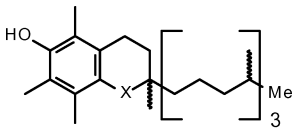
Oxygen is essential to all life, but paradoxically, it is also toxic to cells. Oxidative stress is implicated in a number of disorders, such as cancers, autoimmune and neurodegenerative diseases.[1,2] As a result, there is a constant search for new, more efficient antioxidants for application as therapeutics and protective agents.

The majority of antioxidants, both in man-made materials and in nature, are phenolic in structure. They react with peroxyl radicals to terminate autoxidation, generating a hydroperoxide and a phenoxyl radical (Scheme 1).[3]



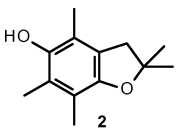
Scheme 1 Possible modes of antioxidant action.

The exact mechanism of antioxidant action is still the topic of some discussion. For example, the groups of Ingold and Burton claim that α-tocopherol (**1a**) generally reacts by direct hydrogen atom transfer (HAT),[4] whereas the group of Mukai claims the mode of action is partial electron transfer (ET) with subsequent proton tunnelling (PT) (Scheme 1).[5] The rate of HAT will be determined to a large extent by the homolytic OH bond dissociation enthalpy (BDE), whereas the rate of ET will be governed by the adiabatic ionisation potential (IP). The IP is also a reasonable indicator of how likely the antioxidant is to undergo undesirable spontaneous oxidation in air. Therefore, when considered together, the BDE and IP values are excellent indicators of antioxidant activity and mechanism.



1a X=O
b X=S
c X=Se

α-Tocopherol (**1a**), the main lipid-soluble antioxidant in humans, is one of the most active natural antioxidants known.[3] As such, it is a good starting point in the development of new compounds with improved properties. One of the most promising developments stemmed from the idea that the stereoelectronic effect of the *para*-substituent was important in stabilizing the phenoxyl radical. Hence, ring-contracted analogues of α-tocopherol, such as **2**, proved to be more efficient antioxidants, presumably due to better overlap between the lone pair on the *para*-oxygen and the phenoxyl SOMO.[4]



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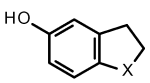

3a X=O
b X=S
c X=Se
d X=Te

Ingold *et al*. prepared the sulfur substituted α-tocopherol analogue **1b**;[6] and recently our group has synthesised the selenium analogue **1c**.[7] However, both were found to be slightly less active antioxidants than the parent tocopherol **1a**. We have prepared compounds **3a–d** and evaluated their 'antioxidant profile' in a series of models.[8] The chain-breaking capacity of the compounds in a two-phase lipid peroxidation model was found to increase with increasing size of the chalcogen. Moreover, it seems that

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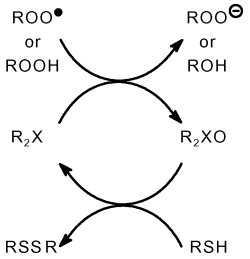
† Electronic supplementary information (ESI) available: i. Table of calculated *vs* experimental IP and BDE values for reference compounds. ii. Geometrical parameters and ΔBDE values for compounds **4–7 a–d**. iii. Absolute energies, energy corrections and cartesian coordinates for compounds **4–6**. See DOI: 10.1039/b515712a

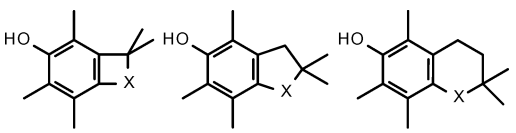
the selenium analogue can act in a catalytic fashion, the active antioxidant being regenerated by a stoichiometric co-reductant, such as a thiol or ascorbate (Scheme 2). As well as acting as chain-breaking antioxidants,[9] the tellurium analogues can also act as catalytic hydroperoxide decomposers,[10] increasing their efficacy. However, to date insufficient numbers of chalcogen-substituted analogues have been synthesized to draw any general conclusions as to their relative activity.



Scheme 2 The dual modes of chalcogenide antioxidant action (X = Se or Te).

Recently, the introduction of cheap, easily applicable DFT models for the prediction of relative BDE values and IP values by Wright *et al.* has greatly aided antioxidant design.[11] Many groups have utilized these methods for the rational design of new antioxidant scaffolds;[12] the most noteworthy being the pyridinol-based antioxidants of Pratt *et al*., which are the fastest peroxyl-radical trapping antioxidants ever reported.[13] With the availability of these methods for the investigation of previously unknown or difficult to synthesize compounds, it seemed timely to undertake an investigation into the general design principles of tocopherol analogues, with particular focus on the effects of varying the chalcogen substituent and ring size. Hopefully, the lessons learned would aid in the design of improved antioxidants and help shed light on the various modes of antioxidant action.

Thus, the primary aim of this work was to investigate the effect of chalcogen substitution on a series of α-tocopherol analogues **4-6** of varying ring size. However, Wright *et al.*'s DFT models are not directly applicable to antioxidants containing heavy chalcogens, and therefore, DFT models for the determination of BDE and IP, closely resembling those developed by Wright *et al.*, but suitable for calculations upon heavy chalcogens were developed, evaluated and used to calculate the properties of the tocopherol analogues.



4 **a** X=O
b X=S
c X=Se
d X=Te

5 **a** X=O
b X=S
c X=Se
d X=Te

6 **a** X=O
b X=S
c X=Se
d X=Te

Method of calculation

The Gaussian 98 program package was used for all calculations.[14] The LANL2DZ electron core potential (ECP) of Hay and Wadt was chosen since it is suitable for calculations on heavy chalcogens, implicitly take care of the relativistic correction, and drastically reduce the number of electrons to be calculated upon, and thus the cost of calculation.[15,16]

Geometry optimizations and frequency calculations for the parent antioxidants, phenoxyl radicals, and radical cations were performed using the unrestricted B3LYP hybrid-DFT method of Becke.[17] In analogy to the method of Wright *et al.*, single point calculations were then performed on the parent antioxidant and radical using the restricted open-shell formalism with added diffuse and polarization basis functions *i.e.* (RO)B3LYP/LANL2DZdp level.[11,18]

The homolytic OH BDE was calculated as the enthalpy difference for the reaction ArOH → ArO$^{\bullet}$ + H$^{\bullet}$ at 298 K. The enthalpy of the H atom at 298 K is corrected as −0.49764 au.[11] The enthalpies of the parent antioxidant and radical are obtained by adding the enthalpy term from the frequency calculation, scaled by a factor of 0.9806, to the obtained (RO)B3LYP/LANL2DZdp single point energy.[19]

The adiabatic IP was calculated for the reaction ArOH → ArOH$^{+\bullet}$ at 0 K. The energies of the parent antioxidant and radical cation are obtained by adding the ZPE correction, scaled by 0.9806, to the (U)B3LYP/LANL2DZ energy.

Where molecules are constrained, the reported BDE values and IP values are calculated using only the results from single point calculations, and are not corrected for enthalpy or ZPE terms.

Results and discussions

Evaluation of the models for IP and BDE determination

In order to evaluate the model for IP determination, the ionisation potentials of 38 small (⩽11 heavy atoms) chalcogen-containing compounds, mostly aromatics, were calculated and compared to the experimental IP values (Fig. 1 and electronic supplementary information (ESI)†). Experimental values are taken from the NIST WebBook.[20] Evaluated IP values are used where possible, otherwise the median value is taken. Where more than one experimental value is available, the highest and lowest experimental IP values are also listed (ESI). It can be seen that the calculated IP values are lower than the experimental IP values by 0.24 eV on average. However, the IP values relative to phenol (ΔIP) in general show good agreement between calculated and experimental results (Fig. 1). The mean absolute deviation (MAD) for the set is 0.163 eV (3.76 kcal mol^{-1}). Furthermore, all calculated ΔIP values fall within the boundaries set by the highest and lowest

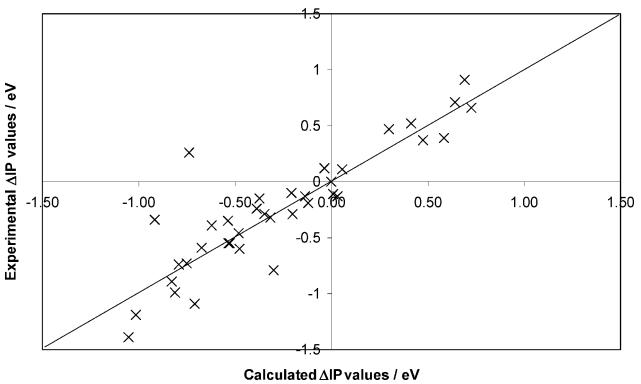


Fig. 1 Plot of relative calculated *vs* experimental ΔIP values.

experimental values, where multiple values are available. All of the five compounds that deviate from the experimental ΔIP value by more than 0.25 eV have only one single experimental value available. Values for the three compounds that have too low ΔIP come from one paper by Baker *et al.*, which reports only vertical IP values from photoelectron spectroscopy.[21] On closer inspection of the photoelectron spectra it is apparent that most of the adiabatic IP values are considerably higher than those given by the NIST WebBook, and are consistent with the calculated ΔIP. Of the values that are too high, one is in fact a vertical value, and therefore the adiabatic IP would be expected to be substantially lower.[22] The other is obtained by the electron impact technique, and as noted by the author: "electron impact values are 0.1–0.2 eV higher than the more accurate photon impact values".[23] Hence, taking account of these corrections means that all calculated ΔIP values should lie within experimental limits. Removing these outliers from the data set gives a MAD of 0.099 eV (2.28 kcal mol^{-1}) for data spanning a range of 1.8 eV.

The OH BDE values of a series of alkyl- and alkoxy-substituted phenols have been precisely determined by Pedulli and coworkers using an EPR radical equilibration technique.[24] This method gives accurate BDE values relative to a reference compound, 2,4,6-tri-*tert*-butylphenol.[25] We have utilized this experimental data to evaluate the model for BDE determination (Fig. 2, ESI†). Phenols with *ortho*-*tert*-butyl groups were left out of the comparison, as these have already proved to give inaccurate results using Wrights DFT model.[11] It can be seen that the calculated absolute BDE values lie on average 0.9 kcal mol^{-1} lower than the experimental BDE values. Keep in mind, however, that all experimental data is calculated relative to 2,4,6-tri-*tert*-butylphenol, and any error in the calorimetrically measured value for this compound will be mirrored in the whole series.[25] Relative BDE data shows good agreement with experiment. ΔBDE values relative to 2,4,6-trimethoxyphenol, the compound estimated to have least experimental error, have a MAD of 0.52 kcal mol^{-1} for data spanning a range of approximately 10 kcal mol^{-1}. Fitting by least-squares analysis gives a slope of 0.85 and $R^2 = 0.977$. We recently determined the BDE of selenotocopherol (**1c**) to be 0.95 kcal mol^{-1} higher than α-tocopherol by experiment.[7] This is in excellent agreement with the calculated difference of 0.94 kcal mol^{-1}. Thus, having established the ability of these models to predict relative OH BDE and IP values, we turned to the evaluation of chalcogen-substituted tocopherol analogues **4–6**.

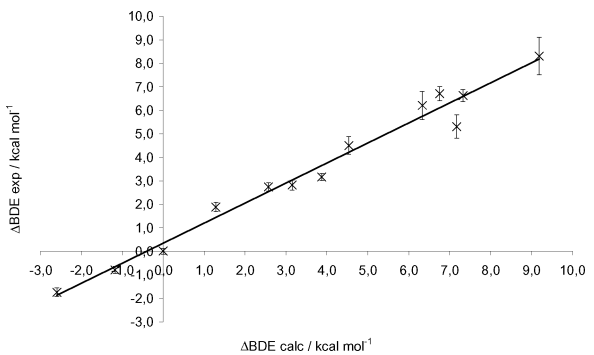


Fig. 2 Plot of relative calculated *vs* experimental ΔBDE values.

Effect of ring size and chalcogen substitution on antioxidant properties of tocopherol analogues

For tocopherol analogues **4–6** there are apparent group trends in BDE and IP (Tables 1 and 2). For any given size of the nonaromatic ring, the BDE increases as the group of chalcogens is descended. This can be attributed to progressively poorer overlap between the phenoxyl SOMO and chalcogen lone pair with increasing chalcogen size. The converse is true for the IP: *i.e.* as the group of chalcogens is descended the IP decreases, due to increasing softness of the chalcogen atom. The trends with varying ring size are not quite so clear cut. IP constantly increases as the ring is contracted for all chalcogens. In all cases, the four-membered ring analogue has the lowest BDE for any given chalcogen. As the ring is expanded in size, the oxygen and tellurium analogues show a continuous increase in BDE. However, with the compounds incorporating sulfur and selenium, the 5-membered analogues have slightly higher BDE values than the 6-membered analogues. This means that the **4a** analogue has the lowest BDE and highest IP, whilst the converse is true of analogue **6d**. Compounds **4b** and **4c** are noteworthy in that whilst both have similar BDE values to the α-tocopherol model 6-hydroxy-2,2,5,7,8-pentamethyl chromane (HPMC, **6a**), their IP values are significantly higher, meaning that they would be expected to be more air stable than α-tocopherol. Of the Te-containing analogues, **4d** is most comparable in properties to HPMC, having a BDE only 0.54 kcal mol^{-1} higher, and an IP 1.04 kcal mol^{-1} lower. At this stage it should be recalled that, once oxidized, the resulting seleno- or telluroxides are expected to be easily reduced back to the active antioxidant by a stoichiometric co-antioxidant such as ascorbate or a thiol. Thus, for antioxidants containing these elements a low IP value is potentially desireable, since this should lead to more efficient peroxidase-like activity.

Effect of bond geometry on BDE

Previously, the greater activity of **5a** compared to **6a** has been attributed to greater overlap of the phenoxyl SOMO with the fused ring oxygen lone pair due to increasing ring planarity.[4] However, it appeared to us that this difference was insufficient to account for the drastically differing activity of the two compounds.

Table 1 Calculated ΔBDE values (kcal mol^{-1}) of compounds **4–6** relative to **6a**

Compound	**4**	**5**	**6**
a	−1.79	−1.46	0.00
b	−0.18	0.81	0.71
c	0.19	1.14	0.94
d	0.54	1.37	1.67

Table 2 Calculated ΔIP values (kcal mol^{-1}) of compounds **4–6** relative to **6a**

Compound	**4**	**5**	**6**
a	5.31	1.19	0.00
b	4.68	2.22	0.72
c	2.46	0.46	−1.24
d	−1.04	−2.31	−3.06

Phenol **5a** is approximately 1.5 times more active than **6a** in the inhibition of oxidation of styrene, and is calculated to have approximately 1.5 kcal mol^{-1} lower BDE. As determined by X-ray crystallography, **5a** is 6° from planar and **6a** is 17° from planar.[4] However, Wright has calculated the cost in BDE of rotating the methyl group in *p*-methoxyphenol out of the aromatic plane, and the cost in rotating from 6° to 17° appears to be almost negligible.[11] In a similar vein, if fused ring planarity was the sole determining factor of the geomeric effect of the *para*-substituent, then the planar 4-membered fused ring compounds would be expected to have similar BDE values to the near-planar 5-membered fused ring phenols, and not the large (~1 kcal mol^{-1}) differences calculated. In order to shed some light on the origin of these differences, we decided to undertake a general study of the effect of phenol geometry on BDE, starting with varying the *para*-substituent planarity (Fig. 3, ϕ).

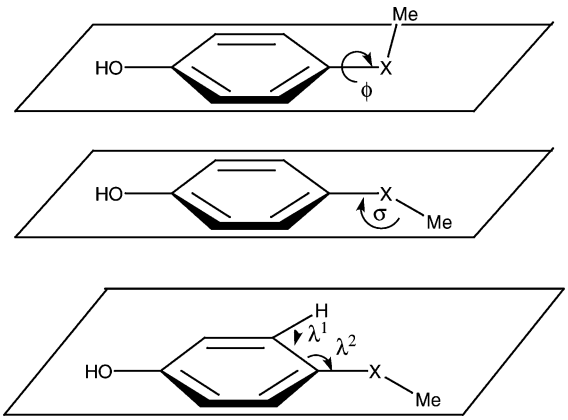


Fig. 3 The torsion angle (ϕ), bonding angle (σ) and aromatic bond angles (λ) in compounds **7a** (X = O), **7b** (X = S), **7c** (X = Se) and **7d** (X = Te).

We calculated the ΔBDE profile of *p*-methoxy-(**7a**), *p*-methylthio-(**7b**), *p*-methylselenenyl-(**7c**) and *p*-methyltellurenyl-phenol (**7d**) as the methyl group is rotated out of plane (Fig. 4). Unsurprisingly, it can be seen that for all chalcogens the maximum cost in BDE is incurred at a rotation of 90°. For compound **7a** this cost is calculated to be 3.61 kcal mol^{-1}, significantly lower than for the other chalcogens. The costs in BDE of rotating the methyl group perpendicular to the plane in **7b**, **7c** and **7d** are all very similar at 6.09 kcal mol^{-1}, 6.11 kcal mol^{-1} and 6.11 kcal mol^{-1} respectively. Interestingly, the reason that these values are all so similar is due to the existence of perpendicular rotamers of successively lower energies for the phenols **7b**, **7c** and **7d** which compensate for the observed decrease in the phenoxyl radical energies on descending the group.[21,28] As expected from Wright's results, the difference in deviation from planarity upon varying fused ring size is not sufficient to account for the differences in BDE values for any series of antioxidants. Therefore, other geometrical factors were considered.

The next geometric effect to be investigated was the chalcogen bonding angle (Fig. 3, σ). For the series of substituted phenols **7a**, **7b**, **7c** and **7d** the BDE was calculated for varying chalcogen bond angles, whilst the methyl group was constrained to the plane (Fig. 5). For analogue **7a**, upon stretching the bond angle from equilibrium (118°) to 180°, the BDE decreases by approximately 2.0 kcal mol^{-1}. Upon squeezing the bond angle from equilibrium to 70°, the BDE increases by approximately 4 kcal mol^{-1}. Similar trends are apparent for **7b**, **7c** and **7d**, although these compounds reach a minimum of BDE at between 120–130° and then level out. This effect can be conceptualized as being due to increasing SOMO–lone pair overlap as the lone pair orbital varies from sp^3 hybridized to increasing p-character upon straightening. Hence, the bond angle around the chalcogen has a significant effect on BDE, but in the opposite sense from expected; *i.e.* as the bonding angle is contracted, this effect should lead to an increase, not the expected decrease, in BDE. This means that some other, opposing effect must be of significance in fused ring systems.

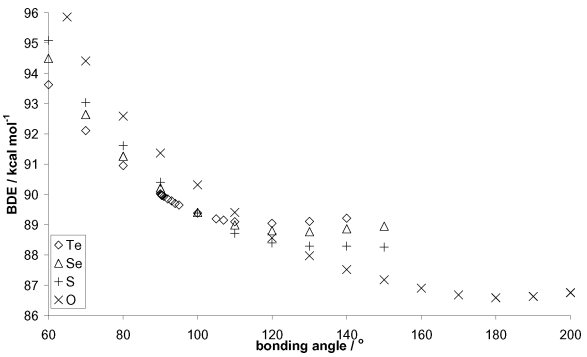


Fig. 5 Variation in BDE of compounds **7a–d** with bonding angle σ.

The remaining prominent geometric effect caused by the fused ring is a Mills–Nixon type distortion of the aromatic bond angles (Fig. 3, λ) as the ring size is decreased. For the phenols **7a–7d**, the BDE was calculated for various values of λ (where $\lambda^1 = \lambda^2$), whilst the methyl group was constrained to the plane (Fig. 6). It can be

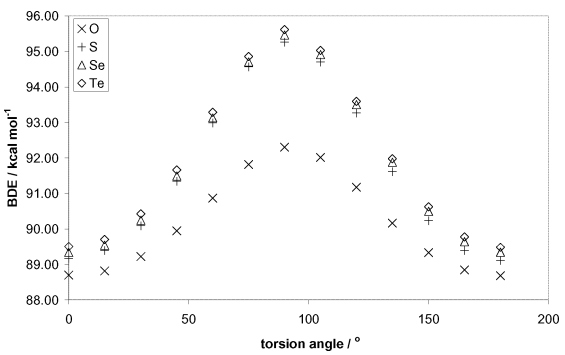


Fig. 4 Variation in BDE value of compounds **7a–d** with torsion angle ϕ.

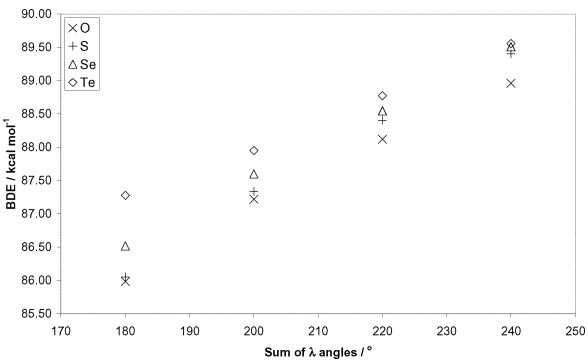


Fig. 6 Variation in BDE of compounds **7a–d** with sum of angles λ.

seen that as the sum of the angles is decreased from 240° to 180°, the BDE decreases linearly by 2.98, 2.71, 2.99 and 2.27 kcal mol^{-1} for **7a–d** respectively; quantities sufficient to account for the observed BDE values of the fused ring systems. Thus, this aromatic deformation is most likely to be the major contributing factor to the increased efficacy of smaller fused rings. It has previously been observed that deformations of this type lead to a lowering of the energy of the π system in benzene,[29] which would account for the observed stabilization of the phenoxyl radical. Recently, a paper has been published where the selectivity in oxidation of a number of tocopherol derivatives has been correlated to the sum of the angles λ.[30] It would be interesting to investigate whether this selectivity correlated with antioxidant activity in the same compounds.

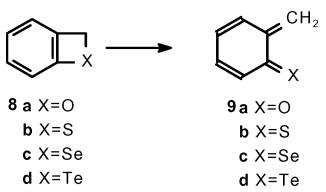
As demonstrated above, the BDE value of a fused ring antioxidant is dependant on the complex interplay of a number of geometrical effects, some cooperative and some counteractive, and therefore is difficult to predict solely on the basis on geometry. If looking for a general "rule-of-thumb", it appears that fused ring planarity is still the most reliable indicator of the relative BDE values for a related series of antioxidants with varying geometry. For the series **4–6**, only compound **6b** is an exception to this rule. This is explained by the structure having sufficient flexibility that upon hydrogen-atom abstraction, it can adopt a significantly more planar structure (the dihedral ϕ changes from 16.6° to 8.5°). More importantly, this study reveals that there are potentially large gains in activity to be made by looking "beyond planarity" and incorporating Mills–Nixon type strain into antioxidants, as for compounds **4b** and **4c**.

Stability of the 4-membered ring analogues

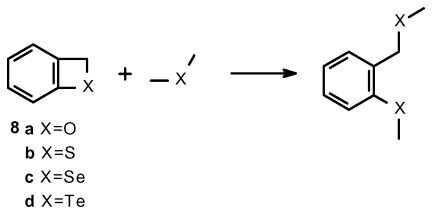
The potential the 4-membered ring analogues hold as potent antioxidants prompted us to investigate the probable stability of their parent skeletons. Benzoxetes are known to isomerise to their more stable quinone methide form even at low temperatures, and their isolation is only possible using matrix techniques.[31] Benzothietes and benzoselenetes on the other hand are stable and accessible using standard synthetic techniques.[32,33] The benzoselenete **8c** was calculated to be 13.96 kcal mol^{-1} more stable than its valence isomer **9c** at B3LYP/6-31++G(2d,p) level (Scheme 3).[23] Benzotelluretes have to the best of our knowledge never been synthesized. In order to assess the stabilities of the full series of compounds **4a–d**, the relative energies of the closed (**8**) and open (**9**) valence isomers were calculated (Scheme 3, Table 3). The homodesmotic ring strain energies of the series **8** were also calculated (Table 3), using the reaction shown in Scheme 4.[34] All calculations were performed at B3LYP/LANL2DZ level. It can be seen that the benzoxete **8a** is less stable than its quinone methide valence isomer **9a** by 11.08 kcal mol^{-1}. Conversely,

Table 3 Calculated energies of valence isomerisation and homodesmotic strain

Compound	$\Delta G^{\text{isomerisation}}$/kcal mol^{-1}	Strain/kcal mol^{-1}
8a	−11.08	38.0
8b	+11.81	21.4
8c	+14.79	19.2
8d	+18.18	15.3



Scheme 3 The valence isomerisation of compounds **8**.



Scheme 4 The reaction used for calculation of the homodesmotic strain in **8**.

benzothiete **8b** is more stable than its valence isomer by a roughly similar amount, 11.81 kcal mol^{-1}. As the period of chalcogens is further descended, the trend is towards increasing stability for the closed ring isomer. Benzoselenete **8c** and benzotellurete **8d** are respectively 14.79 kcal mol^{-1} and 18.18 kcal mol^{-1} more stable than their open ring isomers.

The homodesmotic ring strains tell a similar story, with benzoxete **8a** being 16.6 kcal mol^{-1} more strained than benzothiete **8b**, which in turn is 2.2 kcal mol^{-1} more strained than benzoselenete **8c**. The benzotellurete **8d** is the least strained of all the closed ring isomers, by 3.9 kcal mol^{-1} compared to the benzoselenete. Taken together, these measurements of relative stability suggest that whilst benzoxetes are highly strained and prone to isomerisation, benzothietes, benzoselenetes and benzotelluretes should all be stable. As the group of chalcogens is descended, the stability increases. For known species (all except benzotelluretes), these conjectures are borne out by experiment, and therefore it is predicted that benzotelluretes should also form stable, isolable compounds.

Mechanism of antioxidant action

As previously mentioned, the exact mechanism of antioxidant action for phenolic antioxidants is still somewhat of a contentious issue. Progress in distinguishing the different modes of mechanism has been hampered by the fact that for most phenolic antioxidants, the BDE and IP are strongly correlated. However, as Table 2 demonstrates, this is not the case when the phenols are substituted by heavy chalcogens. Thus, by varying the antioxidant chalcogen and ring size it should be possible to probe where the boundary between the HAT and ET mechanisms lies. As a first approach at elucidating the mechanism of a series of such antioxidants, the BDE values and IP values for the compounds **3** were calculated, and compared to experimental rate data for a two-phase peroxidation inhibition model (Table 4).[8] It can be seen that the tellurium-substituted compound **3d** is the best antioxidant, whereas the oxygen analogue **3a** is the poorest inhibitor. This correlates with the IP values and suggests that the antioxidant **3d** is operating by an electron-transfer mechanism that is not so

Table 4 Calculated BDE and IP values, and experimental rate values for compounds **3a–d**

Compound	BDE/kcal mol^{-1}	IP/kcal mol^{-1}	Inhibited rate/μM h^{-1}
3a	78.92	169.13	79
3b	80.43	167.91	64
3c	80.8	165.09	64
3d	81.2	160.96	30

readily accessible to **3a**. It should be emphasized that the BDE values of these compounds are far higher than those of commonly utilized antioxidants, and therefore any conclusions drawn for this set cannot necessarily be extended to other sets with lower BDE values. Any general conclusions regarding mechanism, or attempts to evaluate mechanism on a more qualitative basis must await further experimental rate data.

Conclusions

Alongside issues of dynamics and localisation,[35] it is the radical trapping ability of antioxidants which determines their activity. A method suitable for the prediction of IP and BDE values of chalcogen-substituted phenolic antioxidants, and thus their ability to trap radicals, was developed. When applied to a series of 4–6 membered fused ring analogues of α-tocopherol, substituted with O, S, Se and Te, it was found that in general the 4-membered analogues would make the most potent antioxidants. In particular, **4b** and **4c** were found to have BDE values lower than α-tocopherol. Furthermore, **4c** should have hydroperoxide decomposing activity, in analogy with other antioxidant selenides. A simple rule-of-thumb was observed where BDE was correlated to planarity of the exocyclic ring. More importantly, it was shown that it was possible to increase antioxidant activity "beyond planarity" by incorporating Mills–Nixon type strain into the molecule. The stability of the benzoxete analogues was considered, and the as yet unsynthesised benzotelluretes were predicted to be stable. Finally, an initial attempt to use the experimental rate data of heavy-chalcogen containing antioxidants combined with calculated IP and BDE values to investigate antioxidant mechanism was undertaken. It was suggested that the telluride antioxidant **3d** was reacting by an electron-transfer mechanism, but further studies must await the synthesis and evaluation of new heavy-chalcogen antioxidants. Such work is currently underway in our laboratory, guided by the principles outlined in this paper.

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