Studies Using Hypervalent Reagents of Te, I and Xe: A Heterocyclic Betaine Saga

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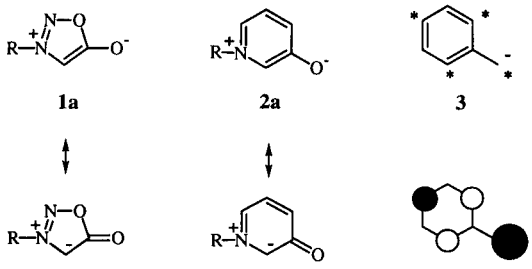
Betaines and Three-Centre, Four-Electron Bonds.

Our work with hypervalent reagents of the elements Te, I and Xe has developed from a long-standing interest in the chemistry and bonding of heterocyclic mesomeric betaines. This interest began with work on meso-ionic compounds, such as the sydnones **1** whose representation as resonance hybrids of a number of dipolar structures (*e.g.* **1a** ↔ **1b**) was first recognised by Baker and Ollis [1,2,3]. Other examples of heterocyclic mesomeric betaines include the six-membered pyridinium-3-olates **2a** ↔ **2b**.



1a **2a** **3**

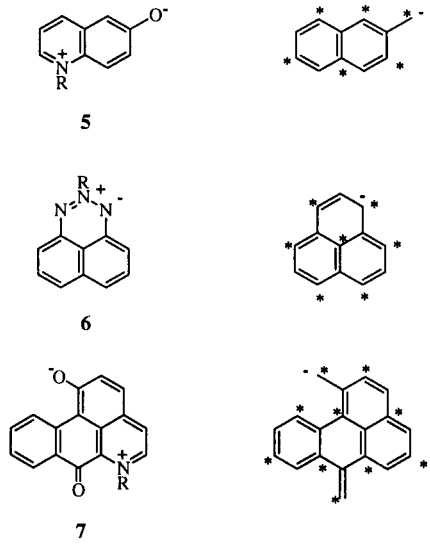
1b sydnones meso-ionic

2b mesomeric betaines

4 NBMO

The molecules **2** can be recognised as belonging to a large family of heterocyclic betaines that are isoconjugate with odd alternant hydrocarbon (AH) anions (*e.g.* **3**) in which the heteroatom that formally donates two electrons to the π-system is located at an unstarred position [4]. It is well known that odd AH have special properties including a non-bonding molecular orbital (NBMO) [5]. Because of their isoconjugate relationship, the betaines **2** are also associated with the highest occupied molecular orbitals (HOMO) that have the characteristics of a NBMO (*e.g.* **4**) and this influences their properties. Other examples of this large class of heterocyclic molecule [4,6,7] and their isoconjugate odd AH anions are shown in structures **5**-**7**. We have previously described a perturbation molecular orbital (PMO) model of these molecules and have demonstrated good structure-property relationships [4]. In this PMO model all the π-electrons are delocalised throughout the conjugated system.

Another way of viewing the heterocyclic mesomeric betaines discussed above, *e.g.* **2**, is that they are associated with localised three-centre, four-electron [3*c*-4*e*]



5

6

7

bonds [8] that are part of a larger π-system of localised two-centre, two-electron [2*c*-2*e*] bonds. The localised [2*c*-2*e*] bond model works very successfully in organic chemistry for the discussion of properties that depend on all the electrons (collective properties) [5], even though electrons are not localised between pairs of atoms. The extension of this localised bond concept to [3*c*-4*e*] bonds is equally valid and useful. Figure 1 shows schematic representations of the formation of [2*c*-2*e*] and [3*c*-4*e*] bonds from two and three atomic orbitals respectively. It can be seen that a NBMO is a fundamental property of [3*c*-4*e*] bonding and in this respect the localised bond model is entirely consistent with the delocalised PMO model of these betaines.

In heterocyclic mesomeric betaines such as the pyridinium-3-olates **2** the localised [3*c*-4*e*] bond is a 1,3-dipole, *e.g.* **2b**. 1,3-Dipoles are examples of [3*c*-4*e*] bonding in which three $2p_z$ orbitals overlap linearly as shown in Figure 2. It is important to note that the central atom contributes two electrons to the three-centre bond. Betaines such as **2**, **5**, **6** and **7** can therefore be regarded as containing a localised 1,3-dipolar [3*c*-4*e*] bond as part of a larger π-system and this localised bond description satisfactorily rationalises some of their properties. However, the delocalised PMO model gives greater insight into aspects such as regio- and periselectivity of cycloadditions and must be used to analyse one-electron properties such as ultraviolet spectra and ionisation potentials [4].

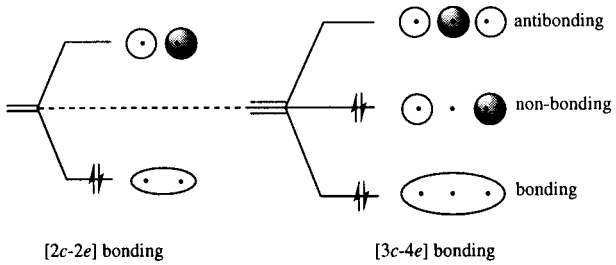


Figure 1. Schematic representation of [2*c*-2*e*] and [3*c*-4*e*] bonding.

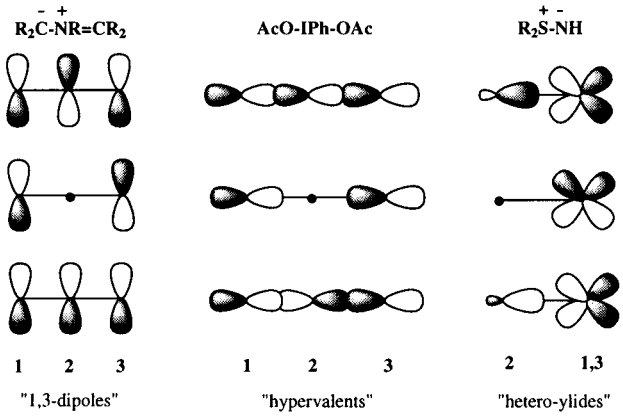


Figure 2. Three types of [3*c*-4*e*] bonding.

1,3-Dipoles, Hypervalent Molecules and Hetero-ylides.

Three-centre, four-electron bonding is not limited to overlap of $2p_z$ orbitals [8,9]. Figure 2 shows two other ways in which overlap of atomic orbitals can lead to an analogous bonding situation. The second example illustrates a simple view of the bonding in hypervalent molecules such as diacetoxyiodobenzene [DAIB: $PhI(OAc)_2$] [10]. The third example shows a bonding model of molecules such as sulfoxides and sulfimides in which two orthogonal atomic orbitals participating in the [3*c*-4*e*] bond are on the same atom. Viewed in this way a large and diverse number of organic molecules that cannot be represented by simple two-centre bonds between atoms in their normal valence state can be recognised as being closely related by the similarity in their bonding. We find it convenient to describe the three major types of molecule having this bonding as 1,3-dipoles, hypervalents and hetero-ylides (Figure 2). The common type of bonding in these molecules leads to similarities in their modes of reaction, some of which we have discussed elsewhere [9]. Surprisingly, and in contrast to [2*c*-2*e*] bonded molecules, the mechanisms of organic reaction of many [3*c*-4*e*] bonded species are often poorly understood and this is an area that merits further experimental study.

The bonding relationships described above have led us to extend our research interests from heterocyclic mesomeric betaines to new reactions of hypervalent reagents and the chemistry of hetero-ylides, such as sulfimides [11]. The main objective of these studies is to discover new and useful reactions that are a result of the type of bonding. A second objective is to learn more about the modes and mechanisms of reaction of these types of molecules. We are currently interested in hypervalent reagents of the Periodic Table triad Te, I and Xe and in particular we are investigating new reactions of the reagents shown in Figure 3. All these reagents are readily available, stable and crystalline, and some interesting trends and similarities in their chemistry are beginning to evolve.

Hypervalent Reagents of Te, I and Xe.

These hypervalent reagents **8**-**10** appear to have two main mechanisms of reaction with organic substrates and which mechanism occurs depends upon a number of factors. As shown in Scheme 1, one of the mechanisms of reaction is single electron transfer (SET), giving products *via* a radical cation intermediate ($M^{\cdot+}$). The other mech-

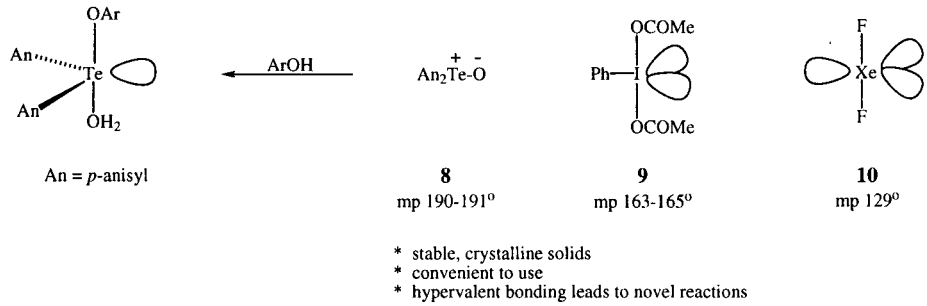
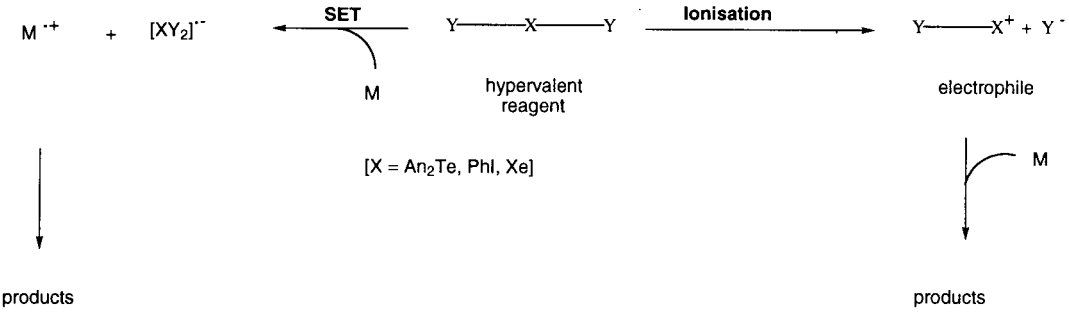


Figure 3. Three readily available hypervalent reagents of Te, I and Xe.

anism is ionisation to give a cation which can react first as an electrophile and then as a good leaving group (*i.e.* An_2Te, PhI or Xe). For xenon difluoride we have found that the mechanism of reaction that dominates can be influenced by the choice of solvent and the nature of the reaction vessel [12]. For hypervalent iodine reactions (*i.e.* $PhIX_2$), SET seems to be more favoured when the ligands Y (Scheme 1) are particularly electron-withdrawing (*e.g.* Y = F or CF_3CO_2) [13] and the diacetate DAIB (Y = $MeCO_2$) appears to react mainly, but not always [14], by the ionic mechanism [15]. The electronegativity of the hypervalent element (Te, I or Xe) also influences the mechanism of reaction and reagents derived from the less electronegative element Te appear to react solely by ionisation.

Scheme 1
Two Mechanisms of Reaction of Hypervalent Reagents



Our studies with XeF_2 have focused on new fluorination methodology of potential value to medicinal chemists and for the rapid introduction of ^{18}F ($t_{1/2}$ 110 minutes) into molecules for positron emission tomography (PET) studies [12,16,17,18]. Using the hypervalent iodine reagent DAIB **9**, we have made a study of reactions with amidines and this has led to a rearrangement route to 2-aminofuran derivatives [15]. Our work with hypervalent tellurium reagents has been associated with an interest in the mechanism of the enzyme *tyrosinase* [19]. The remainder of this review describes the heterocyclic chemistry associated with these studies and the use of dianisyltellurium oxide **8** (DAT) as a selective reagent for oxidation of catechols.

Tyrosinase and Indolium-5-olates.

Tyrosinase [EC 1.14.18.1] is a copper containing enzyme that is widely distributed in nature and which utilises dioxygen to oxidise L-tyrosine **11** or L-DOPA **14** to melanin pigment *via* initial formation of an *ortho*-quinone (DOPA-quinone **12**) [20]. It is usually claimed that L-tyrosine **11** is converted to the DOPA-quinone **12** in two steps *via* formation of L-DOPA (*i.e.* **11**→**14**→**12**) [21]. We have recently reported evidence that this is not the case and that L-tyrosine **11**, and other monohydric phenols, are converted directly by *tyrosinase* to the *ortho*-quinone, *e.g.* **12**, directly in one step as shown in Scheme 2 [19,22]. In this revised mechanism the DOPA-quinone **12** cyclises to give the catechol **13** and a disproportionation then leads indirectly to L-DOPA formation together with dopachrome **15** which is a melanin precursor. This indirect formation of a catechol, *e.g.* L-DOPA **14**, satisfactorily accounts for the induction (or lag) period observed during *tyrosinase* oxidation of monohydric phenols, *e.g.* L-tyrosine **11**, in the following way.

Tyrosinase occurs in the *met* form in which the two copper atoms at the active site are in the Cu(II) oxidation state and in this form the active site cannot bind oxygen [20]. It is necessary that the *met* form is reduced to the *deoxy* form by a catechol to produce Cu(I) at the active site which can then bind O_2 (Equation 1).

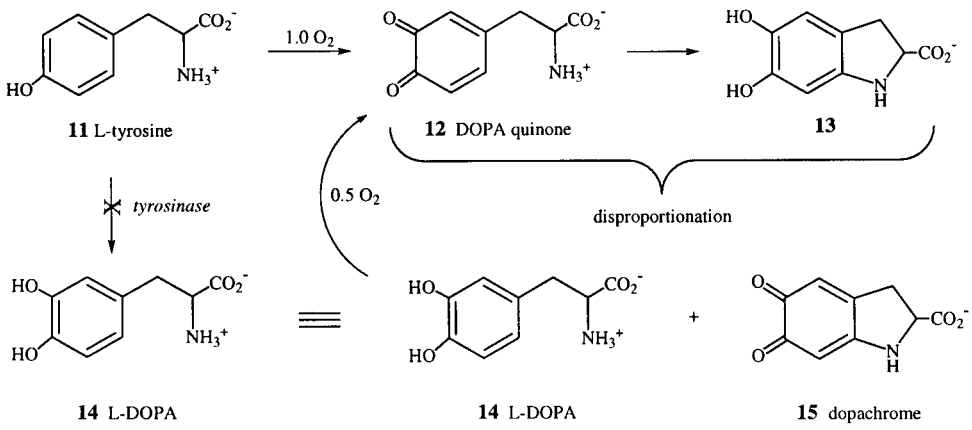
$$2Cu^{2+} + \text{catechol} \longrightarrow 2Cu^{+} + \textit{ortho}\text{-quinone} + 2H^{+}$$

Equation 1.

In the absence of a catechol to activate the enzyme, *tyrosinase* oxidation of phenols is initially extremely slow due to the very small amount in the *deoxy* form. However, a small amount of catechol is slowly produced by the indirect disproportionation mechanism shown in Scheme 2 and this leads to activation of more enzyme (Equation 1) and acceleration of the rate. The lag period is therefore a result of the initially slow activation of the *met* enzyme by indirect catechol formation. Our evidence for this revised mechanism (Scheme 2) is based on an examination of substrates that cannot lead to catechols *via* this indirect mechanism [19,22]. This includes the following studies using tertiary amine substrates.

When our collaborator Prof. Patrick Riley (University College London, Medical School) investigated the tertiary amine derivatives **16** as *tyrosinase* substrates he found that no reaction occurred using unactivated enzyme, even after long periods. However, if the enzyme was

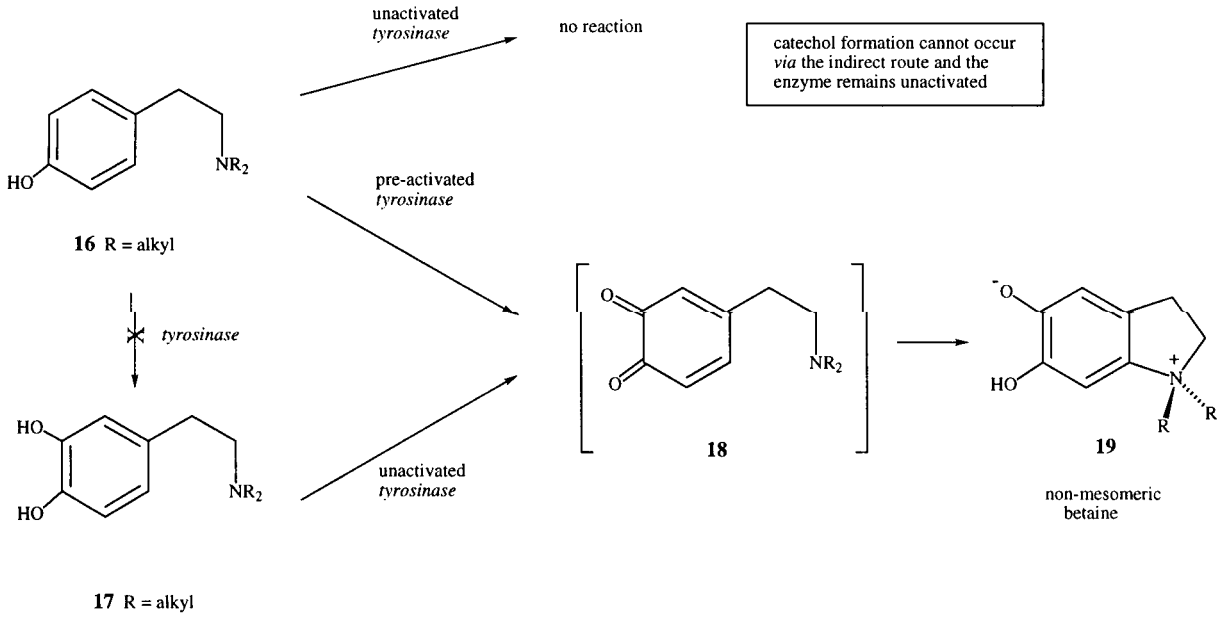
Scheme 2
Tyrosinase - A Revised Mechanism



pre-activated, using a trace of DOPA **14**, oxygen uptake readily occurred and a product (λ_{max} 290 nm), which was not a quinone, was detected [19]. In contrast, when the catechol precursors **17** were used, even with unactivated enzyme, rapid oxidation took place to give the same products (λ_{max} 290 nm). In this case the catechol precursor **17** rapidly reduces the enzyme to the active form. In the case of the phenol precursors **16** treated with unactivated *tyrosinase* it is clear that catechol formation does not occur either by a direct or by an indirect mechanism and this provides good evidence that *tyrosinase* does not enzymatically oxidise phenols directly to catechols. If it did there would be no difference between oxidation of primary (Scheme 2) and tertiary (Scheme 3) amines. We speculated that the products of enzymatic oxidation of the phenols **16** and the catechols **17** must be the betaines **19** formed by rapid cyclisation of the *ortho*-quinones **18**. The betaines **19** are not catechols and their formation precludes catechol formation and enzyme activation.

A priori it was not obvious that the tertiary amine derivatives **18** would cyclise but the ^1H nmr spectra of crude material isolated from the reaction medium were consistent with the betaine structure **19**. At this stage we required authentic synthetic samples of the novel betaines **19** prepared by chemical oxidation of the catechols **17**.

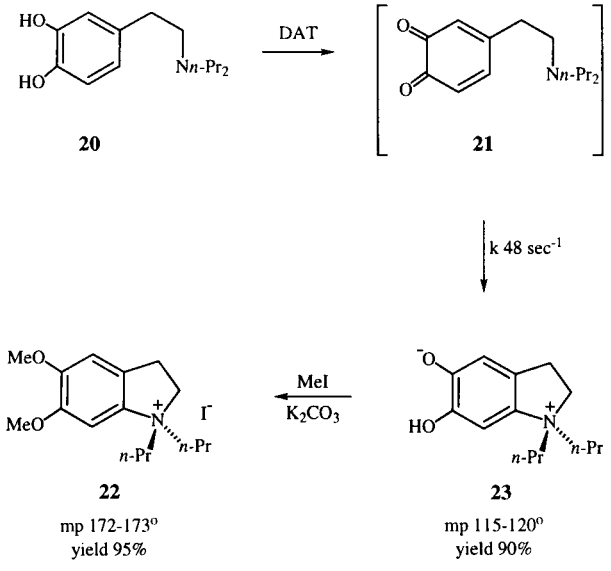
Scheme 3



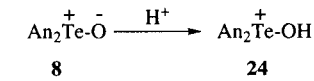
Synthesis and Mechanisms of Formation of Novel Betaines.

Although there are a number of reagents that can be used to oxidise catechols to *ortho*-quinones, our interest in hypervalent tellurium compounds led us to investigate dianisyltellurium oxide **8** (DAT) (Figure 3). This has previously been reported to be a highly selective reagent for catechols in the presence of other oxidisable functional groups [23] and, for our purposes, this was an attractive feature. Initially we monitored oxidation by ^{1}H nmr spectroscopy. Reaction of the catechol **20** with one equivalent of DAT resulted in a quantitative transformation and production of a clean spectrum that was consistent in all its features with the betaine structure **23**. When the reaction was repeated on a preparative scale the betaine **23** was isolated in 90% yield and the structure fully confirmed (Scheme 4) [24]. Treatment with iodomethane/potassium carbonate (MeI/K_2CO_3) gave the iodide **22** and in a similar way other derivatives were prepared.

Scheme 4

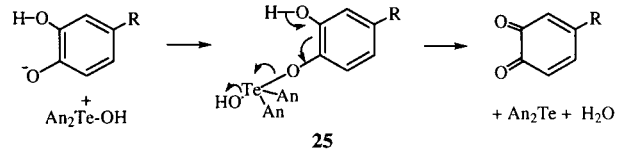


The reagent DAT **8** is a hetero-ylide (Figure 2) and we believe that its selectivity for catechol oxidation is due to its reaction initially as a base [25] to form the cation **24** (Equation 2). This requires the substrate to be acidic. The cation **24** belongs to the class of electrophiles Y-X$^+$ shown in Scheme 1 and can react with the catechol anion to form the hypervalent tellurium molecules **25** (Scheme 5). This hypervalent intermediate **25** may then fragment in the manner shown in Scheme 5 to give An_2Te (good leaving group) and the *ortho*-quinone [26]. This mode of reaction is analogous to mechanisms that we have proposed for hypervalent I and Xe intermediates in which the good leaving groups are PhI and Xe respectively [15,16,17].



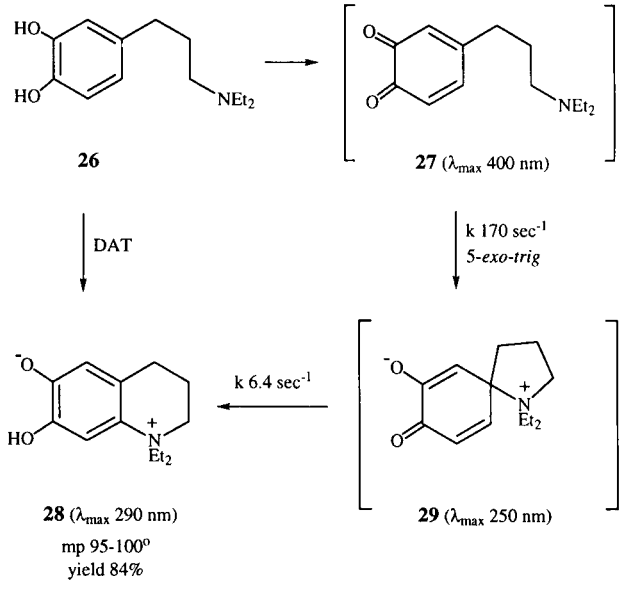
Equation 2.

Scheme 5



The betaine **23** was found to be identical to the material formed by *tyrosinase* oxidation (Scheme 3; R = *n*-Pr) [24]. The intermediate *ortho*-quinone cyclises too rapidly for it to be detected by nmr spectroscopy. However, our colleague Dr. Ted Land (Paterson Research Institute, Manchester) has generated and detected the *ortho*-quinone **21** (λ_{max} 400 nm) using pulse radiolysis and has demonstrated that it undergoes a fast unimolecular decay to the betaine **23** with a rate constant of 48 sec^{-1} [19].

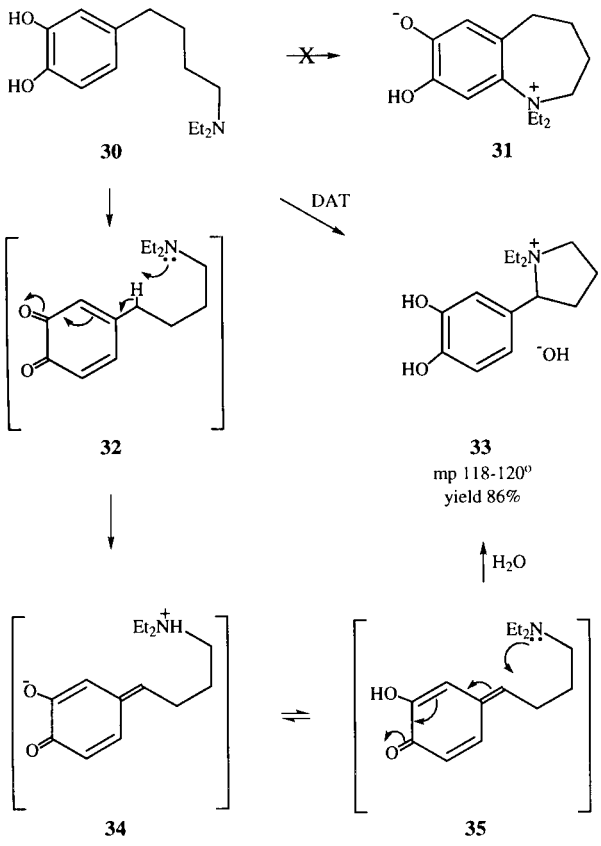
Scheme 6



We next investigated the higher homologue **26** and observed similar behaviour upon oxidation with DAT **8**. The quinolinium-8-olate **28** was isolated in 84% yield and fully characterised [24]. However, when the kinetics of this reaction were investigated using pulse radiolysis [27] an interesting difference from the behaviour of the dopamine derivatives, *e.g.* **20**, was observed (Scheme 6). In this case the short-lived *ortho*-quinone (λ_{max} 400 nm) was found to react to give an intermediate (λ_{max} 250 nm)

that is not the betaine **28**. We propose that this intermediate is the spiro-derivative **29** that is formed by a favourable 5-*exo-trig* cyclisation of the quinone. This intermediate is then observed to rapidly rearrange to the thermodynamically more stable betaine **28** (λ_{max} 290 nm).

Scheme 7



Curiosity then led us to investigate oxidation of the next higher homologue **30**. We did not expect the seven-membered betaine **31** to form under these conditions and this expection was confirmed. However, the product that did form was unexpected and introduced us to a new facet of catechol oxidation. When the catechol **30** was treated with one equivalent of DAT in CH_2Cl_2/MeOH the salt **33** was obtained [24]. We rationalise the formation of this product (Scheme 7) by proposing an intramolecular deprotonation of the initially formed *ortho*-quinone **32** to give the betaine **34** which then equilibrates with the *para*-quinomethane **35**. A favourable 5-*exo-trig* cyclisation to a betaine and subsequent hydration then leads to the observed product **33**.

Conclusions.

The concept of the [3*c*-4*e*] bond allows a wide variety of molecules that cannot be represented by uncharged covalent structures with atoms in their normal valence state to be recognised as belonging to a large class of related molecules with common properties. These molecules include not only meso-ionic compounds and other heterocyclic mesomeric betaines (1,3-dipoles) but also molecules such as diacetoxyiodobenzene (hypervalents) and sulfimides (hetero-ylides). Similarities in the bonding of these diverse types of molecules, which superficially appear to be unrelated, lead to common modes of reaction.

Surprisingly, and in contrast to classical molecules containing only [2*c*-2*e*] bonds, the mechanisms of many reactions of these non-classical molecules are not well defined. We believe that a better understanding of the reactions of these molecules and a systematic study of their chemistry will lead to new and useful transformations. Our own interest in the bonding and chemistry of heterocyclic mesomeric betaines (heterocyclic 1,3-dipoles) has led us to investigate new chemistry of hypervalent reagents of Te, I and Xe and, by chance, the discovery of a new class of heterocyclic betaine related to the oxidation mechanism of the enzyme *tyrosinase*. It is important to emphasise that these betaines (*e.g.* **23** and **28**) are not mesomeric betaines since the positive charge is associated with a saturated atom. They are probably best classified as zwitterions. We are now investigating extensions of this work to heterocyclic synthesis [28].

Acknowledgements.

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