COMMUNICATION

A mild and selective route to *p*-quinomethanes using dianisyltellurium oxide

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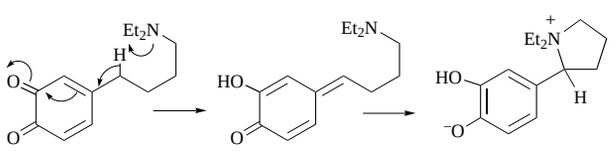
The *o*-quinones formed by chemical or enzymatic oxidation of 4-cyanomethylcatechols rapidly rearrange to isomeric *p*-quinomethanes which can be trapped: the structures of previously described 4-cyanomethyl-1,2-naphthoquinones are revised.

We describe here examples of the rapid and quantitative rearrangement of *o*-quinones to *p*-quinomethanes using the mild and highly selective oxidation of catechols by dianisyltellurium oxide (DAT).[1] We also show that *o*-quinones formed either by pulse radiolysis generation of the corresponding semiquinone and subsequent disproportionation or by tyrosinase oxidation of catechols lead to the same products.

Recently, we have used DAT to oxidise a series of catecholic tertiary amines and have characterised novel heterocyclic betaines formed in high yield by cyclisation of the intermediate *o*-quinones.[2] These results and our related biological studies[3] have led to significant conclusions concerning the mechanism of tyrosinase oxidation of phenols. When 4-(4-diethylaminobutyl)catechol was oxidised by DAT the product was formed by cyclisation of the corresponding *p*-quinomethane **2** and not from the initially formed *o*-quinone **1**. We concluded that intramolecular deprotonation leads to rearrangement to the quinomethane (**1**→**2**) which then gives the observed product **3** by a 5-*exo*-*trig* cyclisation (Scheme 1). The observation of this

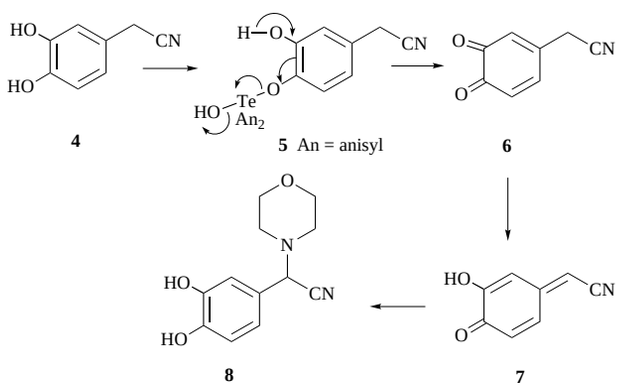


1 **2** **3**

Scheme 1

isomerisation (**1**→**2**) led us to consider that if the α-proton of the 4-substituent of an *o*-quinone is sufficiently acidic then the quinone-to-quinomethane isomerisation may occur without the need for intramolecular proton abstraction. The 4-cyanomethyl substituent was selected for investigation: the catechol precursor **4** is readily available[4] and AM1 semi-empirical MO calculations suggested that the *p*-quinomethane **7** [ΔH_f(calc.) = 0.40 kcal mol^{-1}] is more stable than the isomeric *o*-quinone **6** [ΔH_f(calc.) = 3.84 kcal mol^{-1}].

Treatment of 4-cyanomethylcatechol **4** with DAT (1 equiv.) in the presence of morpholine (1 equiv.) gave the 2-amino nitrile **8** in quantitative yield when monitored by ^{1}H NMR spectroscopy (Scheme 2). The product was isolated and fully characterised [mp 138–140 °C (decomp.) (83%)]. The ^{1}H NMR spectrum showed three aromatic protons, indicating that

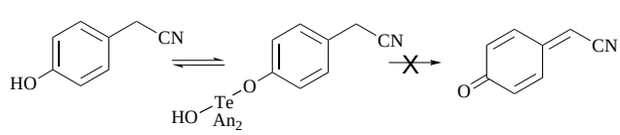


4 **5** An = anisyl **6**

8 **7**

Scheme 2

substitution of the aromatic ring had not occurred, and the proton α to the cyano and amino functions was observed as a singlet at δ 4.92. When the corresponding phenol **9** was treated with DAT under identical conditions, with or without the addition of morpholine, no quinomethane formation (*i.e.* **11**) was observed (Scheme 3). However, the ^{1}H NMR spectrum



9 **10** An = anisyl **11**

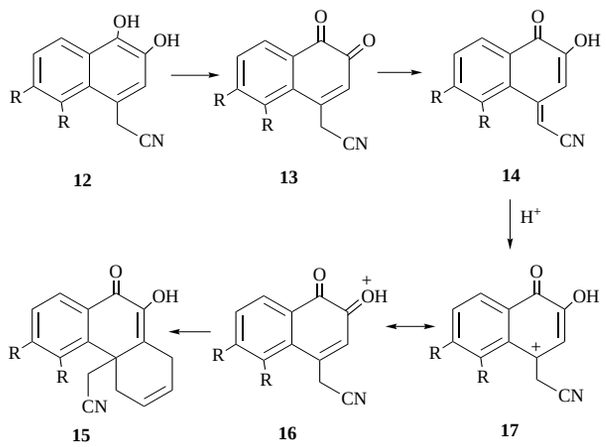
Scheme 3

showed that the phenol **9** was in equilibrium (**9**:**10** = *ca.* 3:1) with a species whose spectrum is consistent with the structure of the Te^{IV} complex **10**. We believe that the absence of quinomethane formation by the phenol **9** supports the view that the initial catechol oxidation product is the *o*-quinone **6** formed *via* the Te^{IV} intermediate **5** (Scheme 2). The reacting electrophile (An_2Te^+–OH) probably does not discriminate between the catecholic OH groups. The *o*-quinone **6**, which is associated with an acidic proton on the 4-substituent, then rapidly rearranges to the quinomethane **7** which is trapped. We do not favour a mechanism involving formation of a five-membered intermediate in which the tellurium is bonded to both catechol oxygens: the nature of the hypervalent bonding in Te^{IV} and related species [*c.f.* $PhI(OAc)_2$ and XeF_2] requires that the electronegative ligands adopt a *trans*-axial configuration as shown in structures **5** and **10**.

Further evidence for the rapid rearrangement of the intermediate *o*-quinone **6** was obtained by a pulse radiolysis study in which the catechol **4** was reacted with the one-electron oxidant $Br_2^{\bullet -}$ in N_2O-saturated phosphate buffer.[3] This led to the semiquinone which disproportionated over a few milliseconds to

form the *o*-quinone **6** (λ_{max} 380 nm at pH 5.9). In a unimolecular reaction this *o*-quinone in turn rearranged (k = 1.0 and 7.5 s^{-1} at pH 5.9 and 7.1, respectively) to a species which is assigned the quinomethane structure **7** (λ_{max} 320 and 480 nm). We have also shown that tyrosinase [EC 1.14.18.1] catalyses the oxidation of catechol **4** with an oxygen stoichiometry of 0.5 to give a product which has a UV spectrum with a peak at λ_{max} 480 nm, identical with that attributed to the quinomethane **7** in the pulse radiolysis study. The initial product of the enzymatic oxidation is almost certainly an *o*-quinone, which in this example rapidly rearranges. Further details of these studies will be described elsewhere.[5]

The instability of the *o*-quinone **6** is of interest in the context of the Gates' synthesis of morphine, in which the 4-cyanomethylnaphthoquinone **13a** undergoes a Diels–Alder cycloaddition to butadiene giving the intermediate **15a**.[6] By analogy with the monocyclic system, this *o*-quinone **13a** might be expected to rearrange to and be isolated as the quinomethane **14a** (Scheme 4). This view is supported by AM1 calc-

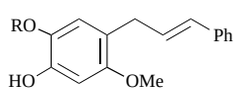


Scheme 4

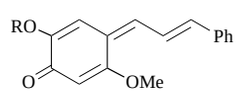
ulations which suggest that, although the energy difference is smaller than that between the monocyclic isomers, the *p*-naphthoquinomethane **14b** [ΔH_f(calc.) = 12.92 kcal mol^{-1}] is again more stable than the *o*-naphthoquinone **13b** [ΔH_f(calc.) = 14.80 kcal mol^{-1}]. The unsubstituted derivatives (**12**–**15**; R = H) were used by Gates for extensive model studies.[7] We therefore prepared the catecholic precursor **12b** and examined its oxidation. Treatment of compound **12b** with DAT (1 equiv.) was monitored by ^{1}H NMR spectroscopy and resulted in quantitative transformation to a single product that has a spectrum entirely consistent with the quinomethane structure **14b**. In particular the spectrum shows two singlets at δ 6.25 and 7.18 which can be assigned to the ring proton at position-3 and the vinylic proton (C=CHCN), respectively. There is no evidence of a cyanomethyl group (–CH_2CN) which would be expected if the structure had the isomeric *o*-quinone structure **13b**. The remainder of the spectrum is associated with the four aromatic protons of the second ring [δ 7.7 (2H, m), 7.9 (1H, d) and 8.2 (1H, d)]. The catechol **12b** was then oxidised by the method described by Gates and Newhall[7] using sodium dichromate and the product isolated as yellow needles {mp 189–192 °C (decomp.) [lit.,[7] 191–194 °C (decomp.)]}. This product has a ^{1}H NMR spectrum identical with that obtained by oxidation with DAT and we conclude that the products previously described as the naphthoquinones **13** are in fact the isomeric naphthoquinomethanes **14**.

It is interesting to consider how reaction of the tautomers **14a**,**b** with butadiene leads to the cycloadducts **15a**,**b**. It is possible that a small equilibrium concentration of the quinone isomer **13** gives the observed product, but this tautomer is not detectable in the ^{1}H NMR spectrum of compound **14b**. Alternatively, protonation of the quinomethanes **14** on the exocyclic carbon atom may give the reactive dienophiles **17**, which are resonance hybrids of the protonated quinones **16**, and the protonated species may lead to the observed adducts **15**. In this context it is significant that the calculated (AM1) HOMO of the quinomethane **14b** has a particularly large orbital coefficient (0.51) on the exocyclic carbon atom. This would be consistent with some protonation at this position. Early cycloadditions were carried out in glacial acetic acid solution, which could facilitate acid catalysis.[7] However, it was subsequently found that better yields were obtained using absolute dioxane as solvent and longer reaction times.[8] It may be that under these conditions the quinomethane is itself sufficiently acidic to autocatalyse the cycloaddition.

Although the oxidation of catechols is not a widely recognised synthetic route to quinomethanes[9] we are aware of examples of their formation in this way. For example, the natural product obtusaquinone **20** was synthesised by oxidation of the cinnamylcatechol **18** but the reaction conditions (PbO_2/benzene) also oxidised the closely related phenol **19** to the corresponding quinomethane **21**.[10] A number of examples of



18 R = H
19 R = Me



20 R = H Obtusaquinone
21 R = Me

quinomethanes formed by enzymatic oxidation of 4-alkylcatechols have also been reported recently[11] and these are relevant to the mechanism of melanin formation and the sclerotization of insect cuticles, but the synthetic potential of these transformations has not been explored.

In summary we have shown that DAT is an excellent reagent for generating quinomethanes from catechol precursors associated with an acidic 4-alkyl substituent. Reaction of DAT with catechols is clean, quantitative and highly selective,[1] thus allowing the generation of *o*-quinones in the presence of other functional groups, including phenols, that are usually sensitive to oxidising agents. This provides the opportunity of generating novel polyfunctional quinomethanes as synthetic intermediates and we are currently investigating this approach.

Experimental

The following procedures were used to prepare key compounds. Calculations were carried out using the AM1 semi-empirical method[12] and energy was minimised with respect to all geometrical variables.

2-(3,4-Dihydroxyphenyl)-2-(*N*-morpholino)acetonitrile 8

To a stirred solution of the catechol **4** (0.5 g, 3.4 mmol) and morpholine (0.29 g, 3.4 mmol) in $CHCl_3$–MeOH (9 : 1) (60 ml) under a nitrogen atmosphere was added dropwise (15 min) a solution of DAT (1.2 g, 3.4 mmol) in $CHCl_3$–MeOH (9 : 1) (20 ml). The red solution was stirred at ambient temperature (1 h) and the solvent was then removed under diminished pressure. The resulting red oil was passed down a silica column eluting first with $CHCl_3$ to remove dianisyltellurium and then with $CHCl_3$–MeOH (9 : 1) to give the crude product as a red gum (0.75 g). This material was further purified by chromatotron chromatography [eluent: light petroleum–ethyl acetate (3 : 7)] to give *compound* **8** (0.65 g, 83%) as a buff solid, mp 138–140 °C (decomp.) (Found: C, 61.5; H, 6.1; N, 11.8. $C_{12}H_{14}N_2O_3$ requires: C, 61.5; H, 6.0; N, 12.0%); ν_{max}(KBr)/cm^{-1} 3500, 3259, 2936, 2822, 2362, 2230, 1614, 1520, 1456, 1397, 1297, 1265,

1183 and 1104; $\delta_H(CD_3OD)$ 6.93 (1H, d, *J* 2,† aromatic C3-H), 6.75–6.85 (2H, m, aromatic C5-H and C6-H), 4.95 (2H, br s, OH), 4.92 (1H, s, NCHCN), 3.7 (4H, m, $2 \times CH_2$) and 2.52 (4H, m, $2 \times CH_2$); $\delta_C(CD_3OD)$ 50.9 (t), 62.5 (d), 67.7 (t), 116.2 ($2 \times$ d), 116.8 (s), 120.7 (d), 125.2 (s), 146.6 (s) and 147.1 (s); *m*/*z* 234 (M^+) (3%), 168 (14), 149 (15), 137 (33), 87 (30) and 57 (100).

4-Cyanomethylene-2-hydroxy-1,4-dihydronaphthal-1-one 14b

The procedure described by Gates and Newhall[7] using sodium dichromate oxidation of the catechol **12b** was repeated to give compound **14b** (83%), yellow needles, mp 189–192 °C (decomp.) [lit.,[7] 191–194 °C (decomp.)] (Found: C, 73.1; H, 3.3; N, 6.9. Calc. for $C_{12}H_7NO_2$: C, 73.1; H, 3.6; N, 7.1%); ν_{max}(KBr)/cm^{-1} 3349 (OH), 2203 (CN), 1649 (CO), 1599, 1417, 1270, 1220 and 757; λ_{max}(EtOH)/nm 303, 312, 361 and 480 (ε 15 075, 14 875, 10 050 and 1210); $\delta_H(CDCl_3)$ 6.25 (1H, s, C3-H), 7.18 (1H, s, CHCN), 7.70 (2H, m, C6-H or C7-H), 7.90 (1H, d, *J* 8, C5-H or C8-H) and 8.20 (1H, d, *J* 7, C8-H or C5-H); $\delta_C([^2H_6]DMSO)$ 95.9 (d), 110.2 (d), 117.9 (s), 124.0 (d), 126.4 (d), 129.5 (s), 131.2 (d), 131.6 (s), 133.2 (d), 146.4 (s), 152.2 (s) and 179.7 (s); *m*/*z* 197 (M^+) (74%), 169 (100), 140 (46), 114 (32), 74 (12), 62 (17) and 49 (13).

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† *J* Values are given in Hz.

Paper 7/09106K
Received 19*th December* 1997
Accepted 26*th January* 1998