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4-Cyanomethyl-*ortho*-quinone tautomerism and the structure of the dienophile in Gates' morphine synthesis

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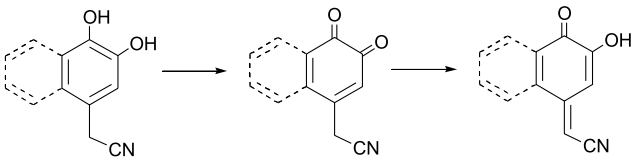
Abstract—Oxidation of (3,4-dihydroxyphenyl)acetonitrile gives (3-hydroxy-4-oxo-cyclohexa-2,5-dienylidene)acetonitrile via the isomeric *ortho*-quinone ((3,4-dioxo-cyclohexa-2,5-dienylidene)acetonitrile). This *para*-quinomethane product is formed as a mixture of diastereoisomers and with an initial composition of *Z*/*E* 4:1. Over 24 h this mixture equilibrates to a composition of *Z*/*E* 5:4. The *para*-quinomethane reacts with morpholine to give (3,4-dihydroxyphenyl)-morpholin-4-yl-acetonitrile. Similar oxidation of (3,4-dihydroxy-naphthalen-1-yl)acetonitrile also gives a *para*-quinomethane derivative and not the 1,2-naphthoquinone as previously described. The reactivity of this *para*-quinomethane derivative as a 1,3-dienophile in a key step of the Gates' morphine synthesis is attributed to formation of its conjugate acid.

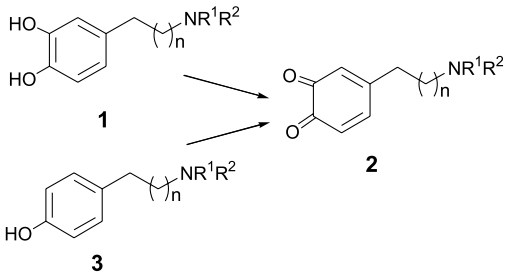
1. Introduction

In this paper, we describe our studies of the chemical oxidation of (3,4-dihydroxyphenyl)-acetonitrile and (3,4-dihydroxynaphthalen-1-yl)-acetonitrile and demonstrate that cyanomethyl derivatives of *ortho*-quinones undergo facile tautomerism to *para*-quinomethanes (Scheme 1).[1]



Scheme 1.

We have previously described studies of the oxidation of catechol amines **1** to *ortho*-quinones **2** by the enzyme tyrosinase and by chemical oxidation.[2,3] Tyrosinase also functions as a phenol oxidase and oxidizes phenol amines **3** to *ortho*-quinone amines **2**. One of the general features of the oxidation of phenols by native tyrosinase is a lag period in which the rate of oxidation, which can be monitored by measurement of oxygen uptake, slowly accelerates to the maximum rate.[4–7] This contrasts with the oxidation of catechols, which are immediately oxidised at the maximum rate. The lag period is associated with native tyrosinase occurring largely in the inactive *met* form in which the two copper atoms in the active site are in the Cu^{II} oxidation state and cannot bind dioxygen.[5] Reduction of the copper by a catechol generates the active *deoxy* form (Cu^{I}) that binds dioxygen giving *oxy*-tyrosinase. In the case of phenolic substrates indirect catechol formation necessary for enzyme activation is initially very slow and occurs via *ortho*-quinones that undergo intra- or intermolecular nucleophilic attack. As more enzyme is activated, leading to increased *ortho*-quinone formation, the reaction **3→2** accelerates and eventually reaches its maximum rate (Scheme 2).



Scheme 2.

Although the endogenous substrate for tyrosinase is tyrosine, the enzyme will oxidise a wide range of phenol derivatives. We have previously investigated a number of monosubstituted phenols[8,9] including the derivatives **4a–d** which are all readily oxidised with an oxygen uptake stoichiometry of 1.0 after the usual lag period. The observation that the cyanomethyl derivative **4e** showed a complete lack of oxygen utilization when presented as a

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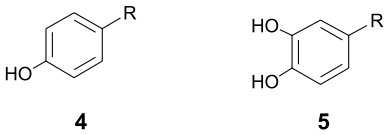
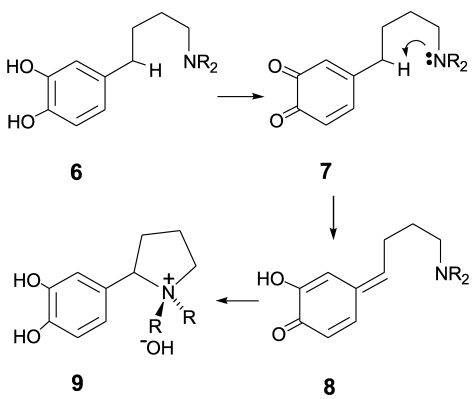
tyrosinase substrate under the same conditions was, therefore, surprising,[10] especially as the corresponding catechol **5e** was rapidly oxidised. Rationalisation of the behaviour of the phenol **4e** in terms of a steric or electronic effect of the substituent (CH_2CN) or a specific interaction of the nitrile with the active site[10] did not seem reasonable since the catechol **5e** is a good substrate. These observations were not fully explained until we investigated the oxidation of the catechol amines **6** which in contrast to lower homologues give *para*-quinomethanes upon chemical[11] and enzymatic oxidation.[12]



4 **5**

In structures **4** and **5**: **a**, R = CH_3
b, R = OCH_3
c, R = CH_2OH
d, R = CH_2CO_2H
e, R = CH_2CN

Oxidation of the catechol amines **6** gives the expected *ortho*-quinones **7** which tautomerise to the isomeric *para*-quinomethanes **8** (Scheme 3). We believe that this tautomerisation is facilitated by favourable intramolecular deprotonation. Cyclisation of the intermediates **8** then leads to the observed products **9** and details of this work have been reported elsewhere.[11,12]

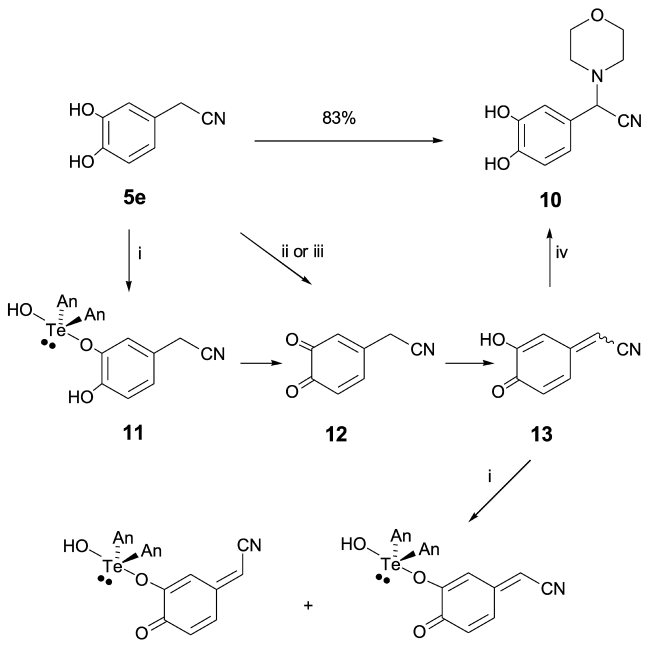


Scheme 3.

Further consideration of the reaction sequence shown in Scheme 3 led us to consider that if the α-proton of the 4-substituent of an *ortho*-quinone is sufficiently acidic then tautomerism from quinone to quinomethane (e.g. **7→8**) might occur without intramolecular assistance. Enhanced acidity could be achieved by placing a conjugated electron-withdrawing substituent on the methylene group at position 4. This possibility immediately led us to reconsider the 4-cyanomethyl derivatives **4e** and **5e** in which the cyano substituent can be expected to (i) facilitate tautomerism by increasing methylene proton acidity and (ii) stabilise the *para*-quinomethane product **13** by extending the conjugation. It seemed reasonable that such a tautomerism could be implicated in the inability of tyrosinase to oxidise phenol **4e** via an autoactivation mechanism. When the *ortho*-quinone **12**, generated by disproportionation of the semi-quinone radicals, was investigated by pulse radiolysis it was indeed found to rearrange quantitatively to the *para*-quinomethane **13** (λ_{max} 480 nm) with a rate constant of 7.5 s^{-1} (pH 7.4).[13] When the catechol **5e** was oxidised by mushroom tyrosinase the first visible product was also identified as the *para*-quinomethane **13**. The results of our pulse radiolysis and tyrosinase spectrophotometric-oximetry studies of the quinomethane **13** have been described elsewhere.[13] We now describe our studies of the chemical oxidation of the catechol **5e** and related species which provide further evidence of the facile tautomerism of cyanomethyl derivatives of *ortho*-quinones to *para*-quinomethanes (Scheme 1).

2. Results and discussion

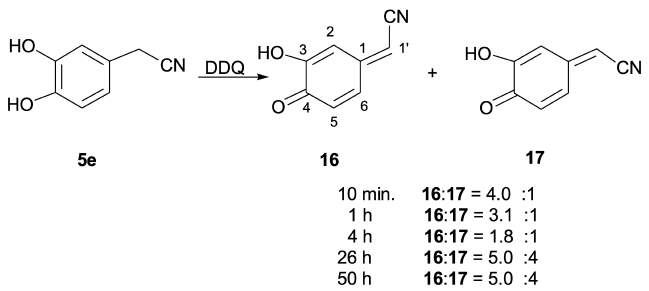
We have found dianisyltellurium oxide (DAT) ($An_2Te{=}O$)[14] to be a convenient, selective oxidizing agent for converting catechols into *ortho*-quinones. When (3,4-dihydroxyphenyl)acetonitrile **5e** was oxidized with 1 equiv. of DAT in $CHCl_3$–MeOH solution containing 1 equiv. of morpholine a product was isolated in 83% yield and identified as the morpholin-4-yl-acetonitrile derivative **10** (Scheme 4). The structure **10** is fully supported by elemental analysis and spectroscopy. Notably, in the ^1H NMR spectrum there are three aromatic protons (δ=6.75–6.95), two catecholic protons (δ=4.95) and a singlet (δ=4.92) attributable to the methine proton (NCH·CN). Product **10** must arise by nucleophilic addition of morpholine to the intermediate quinomethane. We envisage that the DAT functions initially as a base to form An_2Te^+–OH by catechol deprotonation. This electrophile then combines with the catechol anion to give the hypervalent tellurium intermediate **11**, which fragments to give an *ortho*-quinone **12**, dianisyltellurium and water. The *ortho*-quinone **12** then



Scheme 4. *Reagents*: (i) dianisyltellurium oxide (DAT)/$CHCl_3$–MeOH at 18°C; (ii) tyrosinase in 0.1 M phosphate buffer (pH 7.4); (iii) pulse radiolysis in H_2O; (iv) morpholine/$CHCl_3$–MeOH at 18°C.

rearranges to the tautomeric *para*-quinomethane **13**, which reacts with morpholine to give the product **10**. This reaction sequence is entirely in accord with our previous demonstration[13] using pulse radiolysis that the *ortho*-quinone **12** rearranges to the *para*-quinomethane **13** in aqueous media (pH 7.4) with a first order rate constant of 7.5 s^{-1}. Furthermore, when the phenol **4e** was treated with DAT under identical conditions, with or without addition of morpholine, no *para*-quinomethane formation was observed. This observation also supports the view that the *ortho*-quinone is the *para*-quinomethane precursor.

In an attempt to detect the *para*-quinomethane **13** using ^{1}H NMR spectroscopy we treated a solution of the nitrile **5e** in $CDCl_3$ solution with 1 equiv. of DAT. The spectrum clearly showed signals that could be associated with a *para*-quinomethane but, surprisingly, only half of the catechol **5e** had reacted. When the experiment was repeated using 2 equiv. of DAT all the catechol was converted to product, which appeared to be a mixture of *Z* and *E* isomers in the ratio 4:1. We now recognize that this is almost certainly a mixture of the tellurium derivatives **14** and **15**. The tautomerism **12→13** must be fast compared to the initial catechol oxidation **5e→12**. The acidic enol **13** begins to form in the presence of unreacted DAT and competes with



Scheme 5.

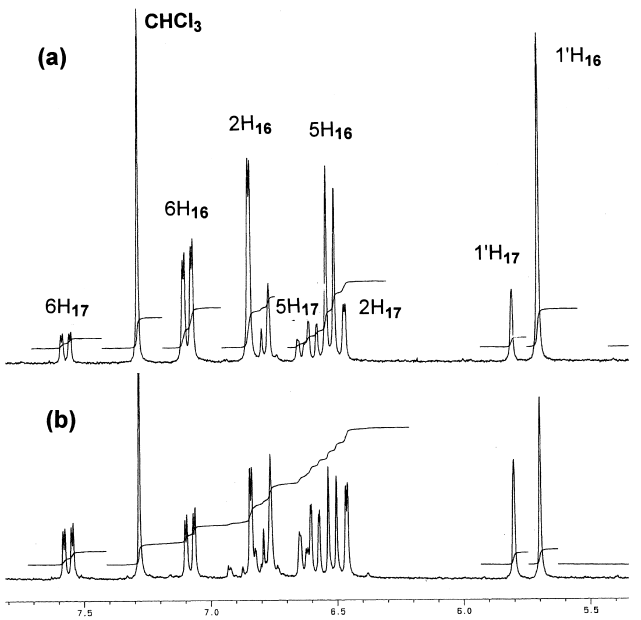


Figure 1. The ^{1}H NMR spectrum of *para*-quinomethane isomers **16** and **17** generated by oxidation of catechol **5e** (a) 10 min after oxidation and (b) 26 h after oxidation.

the catechol **5e** for the oxidising reagent resulting in formation of the derivatives **14** and **15**. As a result, half of the DAT is used to form the hypervalent tellurium products **14** and **15** and half of the nitrile **5e** remains unreacted. When 2 equiv. of DAT are used all of the nitrile is converted to the products **14** and **15**.

To circumvent this problem, we investigated the use of 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) as oxidizing agent, which also has the advantage of having no protons. When the nitrile **5e** in $CDCl_3$ solution was oxidized with 1 equiv. of DDQ complete and clean oxidation of the catechol occurred to give a spectrum consistent with the formation of the *Z* and *E* (4:1) *para*-quinomethane configurational isomers **16** and **17** (Scheme 5). The ^{1}H NMR spectrum of this mixture of configurational isomers is shown in Figure 1(a).

The ^{1}H NMR spectra of the *Z* (**16**) and *E* (**17**) isomers are characterized by significant differences in the chemical shifts of the protons at positions 2 and 6. We attribute this to the anisotropic deshielding effect of the nitrile group on the nearest ring proton as shown in Figure 2. In the *Z* isomer **16** the deshielded proton at position 2 appears at δ 6.75 whereas in the *E* isomer **17** the same proton resonates at δ 6.39. In both isomers, the proton at position 2 is coupled to the proton at position 6 (J=2.0 Hz). Similarly, the proton at position 6 of the *Z* isomer **16** appears as a doublet of doublets (J=2.0, 9.5 Hz) at δ 7.02 and in the *E* isomer **17** it is significantly deshielded due to the proximity of the nitrile function and appears at δ 7.47 (J=2.0, 9.7 Hz). The protons at position 5 and 1' show much less variation in chemical shift (Figs. 1 and 2).

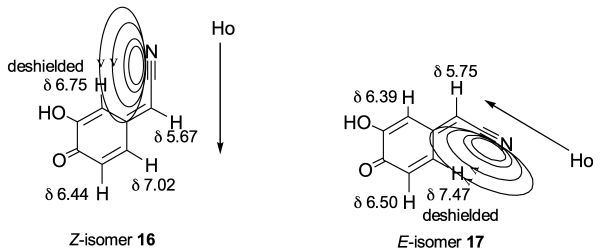
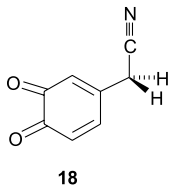


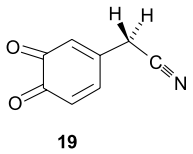
Figure 2. Deshielding of *para*-quinomethane protons attributable to diamagnetic anisotropic effects of the nitrile substituent.

When the reaction mixture was allowed to equilibrate at room temperature (50 h) the *Z*/*E* ratio slowly changed to 5:4 (Fig. 1(b)) demonstrating interconversion between the isomers. These observations raise the interesting question as to why the *Z* isomer **16** is formed preferentially during the oxidation of catechol **5e**. This does not appear to be determined by the oxidizing agent since both DAT and DDQ give essentially the same initial ratio of *Z*/*E* isomers. We conclude that the ratio of isomers is determined during the tautomerisation step (**12→13**), which is independent of the oxidizing agent. Proton rearrangement appears to occur faster via conformer **18** rather than via conformational isomer **19**.

We have calculated the relative stabilities of the tautomers **12** and **13** using AM1 semi-empirical MO calculations.[15] The results for conformer **18** and the *Z*-quinomethane **16** are



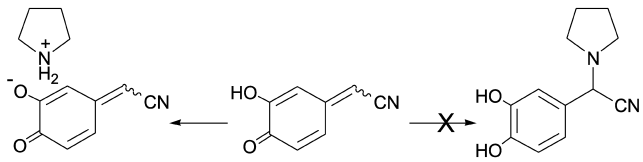
18



19

given in Table 1. In accord with the experimental results, the *para*-quinomethane is calculated to be more stable than the *ortho*-quinone (by 10.5 kJ mol^{-1}). Conformer **19** is calculated to be less stable than the stereoisomer **18** by 2.3 kJ mol^{-1} but the AM1 method is not accurate enough for this difference in calculated conformer energy to be meaningful. However, if there is a similar small difference in the energies of the corresponding transition states for proton rearrangement these subtle energy differences would account for the *Z*-quinomethane being the kinetically preferred product. In fact the *E*-quinomethane is calculated to be the thermodynamically more stable isomer (ΔH_f=1.1 kJ mol^{-1}) but again the difference (1.5 kJ mol^{-1}) is less than the accuracy of the method. We assume that in practice there are subtle differences in the activation energies for the alternative tautomerisation reactions and that these small energy differences account for the observed results.

Although the preparation of the morpholinyl derivative **10** has been repeated by several workers, preliminary attempts to use other nucleophiles have been largely unsuccessful. For example, in an identical preparation in which morpholine was replaced by pyrrolidine the corresponding pyrolidinyl derivative **21** was not obtained. We now recognize that this is attributable to the greater basicity of pyrrolidine (pK_a 11.27) over morpholine (pK_a 8.33). The



20 13 21

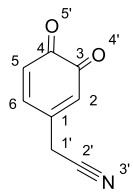
Scheme 6.

more basic nucleophile (i.e. pyrrolidine) readily deprotonates the acidic *para*-quinomethane derivative **13** to give the salt **20** which is unreactive towards nucleophiles (Scheme 6). Being a significantly weaker base, morpholine avoids this problem. The reaction of the *para*-quinomethane **13** with nucleophiles, therefore, requires careful control of conditions and reagents and merits further investigation if this aspect is to be used synthetically.

The *ortho*-quinones **12** are closely related to the *ortho*-naphthoquinones **22** (cf. Scheme 1) that were used by Gates and co-workers in the first laboratory synthesis of morphine.[16,17] In particular the *ortho*-naphthoquinone **22b** was reacted with 1,3-butadiene to give the Diels–Alder adduct **24** (Scheme 7). Subsequent catalytic hydrogenation gave the lactam **25**, which contains major skeletal elements of the morphine molecule.

Although the intermediate **24** is clearly formed by a [4+2] cycloaddition in which the nitrile derivative **22b** is the dienophile, it seemed to us, on the basis of our studies of the monocyclic nitrile **12**, that the *ortho*-quinones **22** might also be expected to tautomerise to the *para*-quinomethanes **23**, which are not obvious dienophiles. We made a preliminary

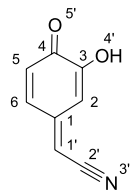
Table 1. AM1 calculated properties of *ortho*-quinone and *para*-quinomethane tautomers



	Charge (e)	HOMO	LUMO
Energy (eV)	–	−10.43	−1.86
C1	−0.04	−0.39	+0.39
C2	−0.19	−0.56	−0.39
C3	+0.21	0.00	−0.31
C4	+0.20	0.00	−0.30
C5	−0.19	+0.50	−0.36
C6	−0.09	+0.36	+0.34
C1′	−0.04	+0.11	−0.01
C2′	−0.15	−0.02	0.00
N3′	−0.02	−0.06	0.00
O4′	−0.21	+0.23	+0.36
O5′	−0.21	−0.21	+0.35

ΔHf_{calcd} 13.1 kJ mol^{-1}; μ_{calcd} 5.50 Debye

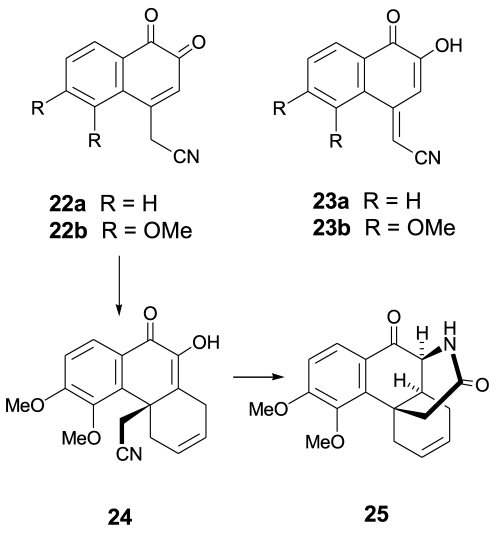
Bond length (Å): C1–C2, 1.35; C2–C3, 1.47; C3–C4, 1.52; C4–C5, 1.47; C5–C6, 1.34; C1–C6, 1.46; C1–C1′, 1.49; C1′–C2′, 1.45; C2′–N3′, 1.16; C3–O4′, 1.23; C4–O5′, 1.23



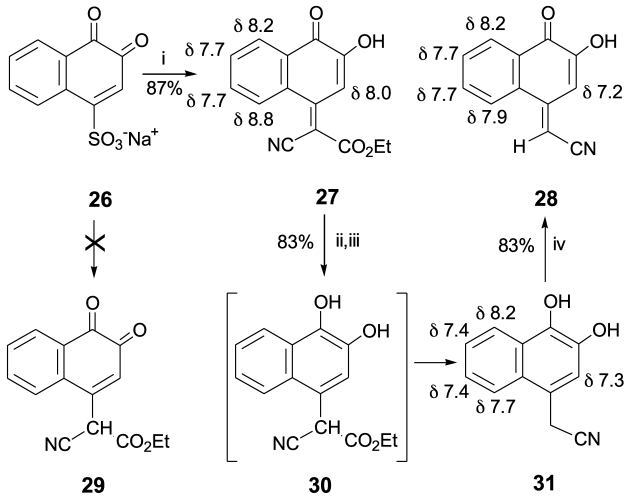
	Charge (e)	HOMO	LUMO
Energy (eV)	–	−9.45	−1.94
C1	0.00	−0.30	−0.33
C2	−0.16	+0.45	−0.24
C3	0.00	+0.42	+0.29
C4	+0.26	+0.04	+0.33
C5	−0.20	+0.21	+0.30
C6	−0.07	+0.07	−0.33
C1′	−0.05	−0.49	+0.50
C2′	−0.12	+0.06	+0.11
N3′	−0.02	+0.23	−0.23
O4′	−0.24	−0.35	−0.12
O5′	−0.28	−0.25	−0.34

ΔHf_{calcd} 2.6 kJ mol^{-1}; μ_{calcd} 3.35 Debye

Bond length (Å): C1–C2, 1.45; C2–C3, 1.35; C3–C4, 1.49; C4–C5, 1.47; C5–C6, 1.34; C1–C6, 1.46; C1–C1′, 1.35; C1′–C2′, 1.42; C2′;–N3′, 1.16; C3–O4′, 1.37; C4–O5′, 1.24



Scheme 7.



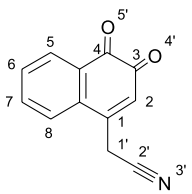
Scheme 8. *Reagents*: (i) $CH_2(CN)CO_2Et$/MeOH/aq. NAOH; (ii) aq. $Na_2S_2O_4$; (iii) hot aq. NaOH; (iv) Na_2Cr_7/AcOH.

investigation of this possibility by carrying out AM1 semi-empirical MO calculations on the pairs of bicyclic tautomers **22a** and **23a**. Gates used the unsubstituted naphthoquinone **23a** for model studies of the morphine synthesis and the Diels–Alder reaction occurs with or without the 7,8-dimethoxy substituents.[16,18]

The results of these AM1 calculations are summarized in Table 2. As in the case of the monocyclic tautomers, the *para*-quinomethane structure is calculated to be more stable than the *ortho*-quinone. The difference in energy (7.9 kJ mol^{-1}) suggests that the *ortho*-quinone **22a** might not be expected to be a stable, isolable species. When calculations were carried out on the 7,8-dimethoxy isomers **22b** and **23b** the difference in energy was slightly greater suggesting that a substituent effect does not stabilise the *ortho*-quinone tautomer. On the basis of these calculations, we decided to prepare the product described as the *ortho*-quinone **22a** and firmly establish its constitution.

Using the procedure described by Gates and Newhall,[18] the 1,2-dihydroxynaphthalene **31** was prepared (Scheme 8). Thus, treatment of the sodium salt of 1,2-naphthoquinone-4-sulfonate **26** with ethyl cyanoacetate gave the previously described product (mp 130°C) which on the basis of its ^1H NMR spectrum has the *para*-quinomethane structure **27**

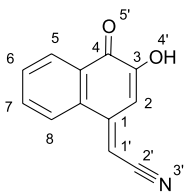
Table 2. AM1 calculated properties of *ortho*-naphthoquinone and *para*-naphthoquinomethane tautomers



	Charge (e)	HOMO	LUMO
Energy (eV)	–	−9.94	−1.71
C1	−0.01	+0.31	+0.36
C2	−0.20	+0.48	−0.35
C3	+0.21	+0.01	−0.30
C4	+0.22	−0.01	−0.29
C4a	−0.13	−0.26	−0.30
C8a	−0.02	−0.43	+0.32
C1′	−0.05	−0.05	−0.01
C2′	−0.15	0.00	0.00
N3′	−0.02	+0.02	+0.01
O4′	−0.22	−0.19	+0.34
O5′	−0.23	+0.09	+0.32

ΔHf_{calcd} 62.0 kJ mol^{-1}; μ_{calcd} 6.50 Debye

Bond length (Å): C1–C2, 1.35; C2–C3, 1.47; C3–C4, 1.51; C4–C4a, 1.48; C4a–C8a, 1.41 C1–C8a, 1.47; C1–C1′, 1.49; C1′–C2′, 1.45; C2′–N3′, 1.16; C3–O4′, 1.23; C4–O5′, 1.23



	Charge (e)	HOMO	LUMO
Energy (eV)	–	−9.28	−1.78
C1	+0.03	+0.30	+0.31
C2	−0.16	−0.40	+0.24
C3	0.00	−0.39	−0.28
C4	+0.28	−0.04	−0.33
C4a	−0.13	−0.11	−0.26
C8a	0.00	−0.16	+0.29
C1′	−0.07	+0.51	−0.46
C2′	−0.11	−0.06	−0.10
N3′	−0.03	−0.24	+0.21
O4′	−0.24	+0.31	+0.11
O5′	−0.29	+0.20	+0.32

ΔHf_{calcd} 54.1 kJ mol^{-1}; μ_{calcd} 4.56 Debye

Bond length (Å): C1–C2, 1.45; C2–C3, 1.35; C3–C4, 1.48; C4–C4a, 1.47; C4a–C8a, 1.41; C1–C8a, 1.47; C1–C1′, 1.36; C1′–C2′, 1.42; C2′–N3′, 1.16; C3–O4′, 1.37; C4–O5′, 1.24

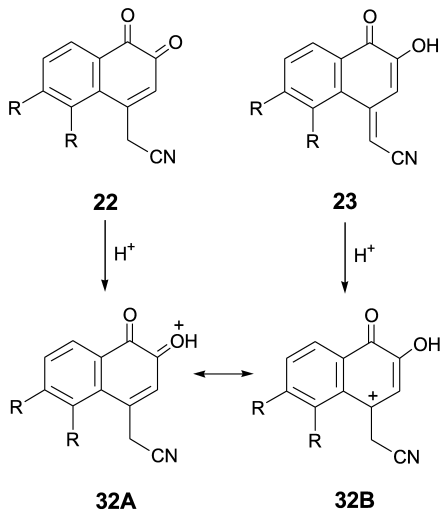
rather than the reported *ortho*-quinone structure **29**. The product shows no proton signal in the region δ 5.0 which would be characteristic of the C*H*(CN)CO_2Et function. The ^{1}H NMR spectrum suggests that only a single stereoisomer is formed to which, for reasons discussed below, we have assigned the *Z* configuration **27**. This product was reduced ($Na_2S_2O_4$) and decarboxylated (aq. NaOH) to give compound **31** via the ester **30**.

Oxidation of the catechol derivative **31** with 1 equiv. of DAT in $CDCl_3/CD_3OH$ was monitored by ^{1}H NMR spectroscopy which showed rapid and complete oxidation to form dianisyltellurium and signals consistent with formation of the *para*-quinomethane **28**. The same catechol **31** was then oxidised by sodium dichromate using the method employed by Gates[18] and the product was isolated and fully characterized. The yellow needles obtained had the same melting point and empirical formula as those reported previously.[18] However, the ^{1}H NMR spectrum, which was identical with that obtained using DAT as oxidant, confirmed the *para*-quinomethane constitution **28**. There was no evidence of 2 equiv. protons characteristic of a cyanomethyl substituent (–CH_2CN). A singlet at δ 6.25 can be assigned to the vinylic proton (C=C*H*CN) and a second singlet at δ 7.15 is attributable to the ring proton at position 2. A doublet at δ 7.9 is assigned to the proton at position 8. It is clear from both the ^{1}H and ^{13}C NMR spectra that only a single stereoisomer is formed and by comparison with the chemical shifts in the precursor **27** we have assigned the *Z* configuration to product **28**. In this configuration the ring proton at position 2 enjoys some deshielding due to the location of the nitrile (cf. Fig. 2) whereas the proton at position 8 (δ=7.9) shows no evidence of extra deshielding due to the close proximity of a substituent. In contrast, the ^{1}H NMR spectrum of the ester **27** shows considerably greater deshielding of the ring protons at position 2 (δ=8.0) and position 8 (δ=8.8). In a series of Knoevenagel condensation products, Jones and Rae[19] have shown that a nitrile substituent deshields adjacent protons by an amount in the range 0.7–0.9 ppm. This is consistent with the observed chemical shifts of the protons at position 8 in structure **28** (δ=7.9) and structure **27** (δ=8.8). Deshielding due to ester substituents is greater and this probably accounts for the shift of the proton at position 2 of structure **27** showing a significantly greater downfield shift (δ=8.0) than that in compound **28** (δ=7.2). The greater electron-withdrawing power of the cyanoester substituent may also contribute to the chemical shifts. The other three ring protons in compounds **27** and **28** have comparable chemical shifts, as might be expected.

The product of oxidation of the catechol derivative **31** is clearly the *para*-quinomethane derivative **23a** and not the *ortho*-quinone tautomer **22a**. This observation is entirely consistent with the results for oxidation of the monocyclic catechol **5e** and the calculated energies using the AM1 method. It is interesting to note that using 1 equiv. of DAT as oxidant gave quantitative formation of the *para*-quinomethane **28**. There was no formation of hypervalent tellurium derivatives analogous to those formed by a similar oxidation of catechol **5e** (Scheme 4). In this case, we presume that oxidation of the catechol **31** is much faster than tautomerism and all of the DAT is reduced before significant amounts of the final product are formed.

One final point deserves comment. If the products previously described as the *ortho*-quinones **22** are in fact the *para*-quinomethanes **23**, why do they readily participate in Diels–Alder reactions? It is possible that a small amount of the *ortho*-quinone is in equilibrium with the *para*-quinomethane, but we have not detected any by NMR spectroscopy. We believe that a more probable explanation is that the true dienophile is the protonated species **32**.

Protonation of the quinomethanes **23** on the exocyclic carbon atom gives the reactive dienophile **32B**, which is a resonance hybrid of the protonated *ortho*-quinone **32A** (Scheme 9). If the cation **32** is the true dienophile, it can be derived from either precursor (**22** or **23**). The HOMO of the quinomethane has a particularly large calculated orbital coefficient at C1′ (0.51) (Table 2) and it is reasonable to suppose that in solution the cation **32** will be in equilibrium with other species. Early cycloadditions reported by Gates and co-workers[18] were carried out in glacial acetic acid solution. Subsequent work achieved better yields using absolute dioxane as solvent and longer reaction times.[20] We suppose that under these conditions the quinomethanes **23** are sufficiently acidic (cf. Scheme 6) to autocatalyse the Diels–Alder reaction.



Scheme 9.

3. Conclusions

Our preparative and ^{1}H NMR spectroscopy studies have shown that cyanomethyl derivatives of *ortho*-quinones and *ortho*-naphthoquinones, generated by chemical oxidation of the corresponding catechols, rapidly rearrange to the corresponding *para*-quinomethanes. This isomerisation is attributable to the acidity of the cyanomethyl protons and the results are in agreement with our studies of 4-cyanomethyl-*ortho*-quinone generated by tyrosinase oxidation of the catechol or phenol and by pulse radiolysis studies of one-electron catechol oxidation.[13] Since *para*-quinomethanes are useful synthetic intermediates, their formation by rearrangement of substituted *ortho*-quinones is of potential value.

Although the synthetic potential of the *ortho*-quinone to *para*-quinomethane rearrangement has received little synthetic attention, its importance in biological systems is well established. Some of these transformations, such as the isomerisation of *N*-acyldopamine quinones leading to cuticular hardening (sclerotization) in insects and wing pigments in butterflies, are mediated by enzymes (quinone isomerase).[21–26] However, in some cases *ortho*-quinones generated by tyrosinase oxidation lead to *para*-quinomethane formation by a non-enzymatic mechanism and for some endogenous *ortho*-quinones this may be a pathway leading to toxicity.[27–30] Although fast on the NMR timescale, our studies using pulse radiolysis have shown that isomerisation is relatively slow compared to competing reactions of *ortho*-quinones with nucleophiles.[11,12] The formation of *para*-quinomethanes only occurs when alternative reactions are absent or unfavourable. To facilitate synthetic applications, structural properties favouring *para*-quinomethane formation merit further study.

4. Experimental

4.1. General

Melting points were determined using a Reichert Kofler Block apparatus and are uncorrected. Infrared spectra were recorded on a Perkin–Elmer 881 spectrophotometer with only major absorbances being quoted. Unless otherwise stated IR spectra were measured as KBr discs. ^{1}H NMR spectra were recorded at ambient temperatures using a Brucker Avance DPX 300 MHz spectrometer and were run in deuterated chloroform solution unless otherwise stated. Elemental analyses were determined using a Perkin–Elmer 240 CHN Elemental Analyser. UV-visible spectra were determined on a Carey 1C instrument. Flash chromatography was performed using silica gel (Janssen Chimica) 0.035–0.07 mm. All solvents were pre-distilled and dried appropriately prior to use. Concentration and evaporation refer to the removal of volatile materials under reduced pressure on a Büchi Rotovapor. Substances stated to be identical were so with respect to mp, mixed mp and IR spectra.

4.1.1. (3,4-Dihydroxyphenyl)-morpholin-4-yl-acetonitrile (10). A solution of (3,4-dihydroxyphenyl)acetonitrile **5e** (0.5 g, 3.4 mmol) and morpholine (0.29 g, 3.4 mmol) in $CHCl_3$–MeOH (9:1) (60 mL) was stirred under an atmosphere of nitrogen. To this mixture, a solution of dianisyltellurium oxide (1.2 g, 3.4 mmol) in $CHCl_3$–MeOH (9:1) (20 mL) was added dropwise and the resulting red solution was then stirred at room temperature (1 h). Evaporation gave a red oil that was purified by column chromatography (silica gel). Initial elution with $CHCl_3$ removed dianisyltellurium and subsequent elution with $CHCl_3$–MeOH (9:1) gave the crude product as a red gum (0.75 g). This material was further purified by chromatotron chromatography [silica gel: eluent, light petroleum-ethyl acetate (3:7)] to give (3,4-dihydroxyphenyl)-morpholin-4-yl-acetonitrile **10** (0.65 g, 83%), buff solid, mp 138–140°C (decomp.) ^{1}H NMR (300 MHz, d_4-MeOH) δ 6.93 (d, J=2.0 Hz, 1H, aromatic C2–*H*), 6.75–6.85 (m, 2H, aromatic C5–*H* and C6–*H*), 4.95 (br s, 2H, O*H*), 4.92 (s, 1H, NC*H*.CN), 3.70 (m, 4H, 2×CH_2) and 2.52 (m, 4H, 2×CH_2). ^{13}C NMR (75 MHz, d_4-MeOH) δ 50.9 (t, NCH_2), 62.5 (d, *C*H·CN), 67.7 (t, OCH_2), 116.2 (2×d, *C*2–H and *C*5–H), 116.8 (s, *C*N), 120.7 (d, *C*6–H), 125.2 (s, *C*1), 146.6 (s, *C*3) and 147.1 (s, *C*4); IR (KBr) ν_{max}/cm^{-1} 3500, 3259, 2936, 2822, 2362, 2230, 1614, 1520, 1456, 1397, 1297, 1265, 1183 and 1104; MS (EI) *m*/*z* 234 ($M^{\cdot+}$) (3%), 166 (14), 149 (15), 137 (33), 87 (30) and 57 (100). Anal. calcd for $C_{12}H_{14}N_2O_3$: C, 61.5; H, 6.0; N, 12.0. Found: C, 61.5; H, 6.1; N, 11.8.

4.1.2. Cyano-(3-hydroxy-4-oxo-4*H*-naphthalen-1-ylidene) acetic acid ethyl ester (27). A solution of ethyl cyanoacetate (8.5 g, 75 mmol) in MeOH (120 mL) was added to a stirred solution of sodium 1,2-naphthoquinone-4-sulfonate (13.0 g, 50 mmol) in H_2O (200 mL). Stirring was maintained and 25% aqueous NaOH (13 mL) was added. The solution was then acidified (dil. HCl) to give a yellow solid that was collected, dried under vacuum and identified as compound **27** (11.0 g, 87%), yellow solid, mp 130°C [Lit.,[18] 129.9–130.4°C]; ^{1}H NMR ($CDCl_3$) δ 1.40 (t, J=7.0 Hz, 3H, CH_2CH_3), 4.41 (q, J=7.0 Hz, 2H, CH_2CH_3), 7.70 (m, 2H, C6–H and C7–H), 8.02 (s, 1H, C2–H), 8.21 (d, J=8.0 Hz, 1H, C5–H) and 8.81 (d, J=8.0 Hz, 1H, C8–H). This material was used without further purification.

4.1.3. (3,4-Dihydroxynaphthalen-1-yl) acetonitrile (31). A stirred solution of compound **27** (5.0 g, 18.6 mmol) in MeOH (10 mL) was treated dropwise with a concentrated aqueous solution of sodium dithionite until the yellow colouration did not persist. To this mixture was added 25% aqueous NaOH (7.5 mL) and the solution was then heated under reflux (2 h). Acidification (dil. HCl) and cooling gave compound **31** (3.1 g, 83%), colourless needles, mp 216–220°C (with decomp.) [Lit.,[16] 220–227°C (with decomp.)] ^{1}H NMR ($CDCl_3$) δ 4.12 (s, 2H, CH_2CN), 7.28 (s, 1H, C2–H), 7.40 (m, 2H, C6–H and C7–H), 7.72 (d, J=8.0 Hz, 1H, C8–H) and 8.19 (d, J=8.0 Hz, 1H, C5–H). This material was clearly identical with the product described by Gates and Newhall[18] and was used for the preparation of compound **28** without further purification.

4.1.4. (3-Hydroxy-4-oxo-4*H*-naphthalen-1-ylidene)-acetonitrile (28). Compound **31** (2.5 g, 12.6 mmol) suspended in warm glacial acetic acid (40 mL) was treated with a solution of sodium dichromate in aqueous acetic acid. After cooling and standing, the yellow crystalline product was collected and identified as (3-hydroxy-4-oxo-4*H*-naphthalen-1-ylidene)-acetonitrile **28** (2.05 g, 83%), yellow needles, mp 189–192°C (decomp.)[Lit.[18] 191–194°C (decomp.)] ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.25 (s, 1H, C*H*–CN), 7.18 (s, 1H, C2–*H*), 7.70 (m, 2H, C6–H and C7–H), 7.90 (d, J=8.0 Hz, 1H, C8–*H*) and 8.20 (d, J=7.0 Hz, 1H, C5–*H*). ^{13}C NMR (75 MHz, d_6-DMSO) δ 95.9 (d, *C*H·CN), 110.2 (d, *C*2–H), 117.9 (s, *C*N), 124.0 (d, *C*8–H), 126.4 (d, *C*6–H), 129.5 (s, *C*4a–H), 131.2 (d, *C*5–H) 131.6 (s, *C*8a–H), 133.2 (d, *C*7–H), 146.4 (s, *C*.OH), 152.2 (s, *C*1=C) and 179.7 (s, *C*=O); IR (KBr) ν_{max}/cm^{-1} 3349 (OH), 2203 (CN), 1649 (CO), 1599, 1417, 1270, 1220 and 757; UV λ_{max} (EtOH)/nm 303, 312, 361 and 480 (ε 15,075, 14,875, 10,050 and 1210); MS (EI) *m*/*z* 197 ($M^{\cdot+}$) (74%), 169 (100), 140 (46), 114 (32), 74 (12), 62 (17) and 49 (13).

Anal. calcd for $C_{12}H_7NO_2$: C, 73.1; H, 3.6; N, 7.1. Found: C, 73.1; H, 3.3; N, 6.9.

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