Thermal Cycloaddition of Alkenes to Phenols: a Theoretical Approach

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A theoretical approach to mechanistic and structural aspects of the thermal 2,5-cycloaddition of alkenes to phenols is described. Our calculations show that this reaction can only occur when strained cyclic alkenes are employed.

The thermal 2,5-cycloaddition of *N*-phenylmaleimide to phenol has recently been reported.[1] The reaction has been extended to other systems, notably the addition of maleic anhydride to phenol and the addition of *N*-phenylmaleimides to various *p*-substituted phenols,[2] the reactivity of which was found to increase with increasing donor character of the phenol *p*-substituent.

These reactions can be thought of in terms of an extension of the Diels–Alder reaction, the rates of which are normally governed by the donor–acceptor character of alkene and diene. Diels–Alder reactions normally occur with donor dienes and acceptor alkenes although many examples where the inverse is the case are known.[3] In the title reaction, the alkene is a powerful dienophile, *i.e.* the carbon–carbon double bond is 'poor' in electrons. However, somewhat surprisingly, this 2,5-cycloaddition process does not occur with the electron-poor alkenes fumaronitrile and tetracyanoethene.[3]

Apart from their considerable potential synthetic utility,[4,5] thermal 2,5-cycloadditions to phenol are of considerable interest from an academic point of view. Benzenic compounds do not normally undergo addition reactions, their chemistry being dominated by substitutions. Addition causes loss of aromaticity, which we have calculated to be 96.2 kJ mol^{-1} for phenol.

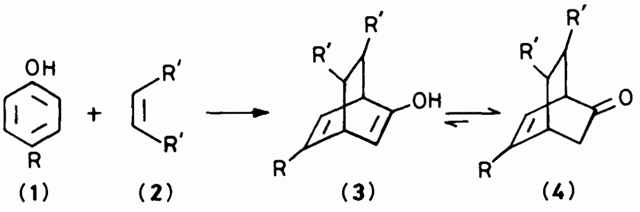
The 2,5-cycloaddition of an alkene to phenol can be envisaged to occur *via* two different reaction pathways; the formation of the *endo*-isomers *via* these two possible mechanisms is shown in Schemes 1 and 2.

Mechanism 1 (Scheme 1) involves direct addition of a powerful dienophile to the phenol aromatic system (**1**). The first-formed product is an enol (**3**), which would be expected quickly to rearrange to the final product (**4**). This enolisation effectively prevents the reverse reaction, which might otherwise be expected to occur under the rather severe reaction conditions.[1] Reaction *via* mechanism 1 resembles the known thermal 1,4-cycloaddition of maleic anhydride to naphthalene.[5]

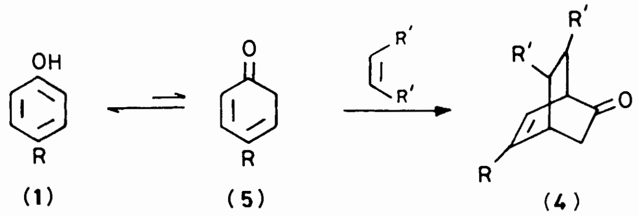
Mechanism 2 (Scheme 2) involves prior rearrangement of phenol to cyclohexa-2,4-dienone (**5**), which subsequently reacts *via* a classic Diels–Alder reaction to form directly the final product (**4**).

The two possible mechanisms are quite different, but experimental attempts to ascertain which pathway is followed have largely failed.[2]

The experimental observation that electron-donor groups on the phenol *p*-position facilitate the reaction can be interpreted in terms of either mechanism. The cycloaddition step in both mechanisms should occur more readily when the two reactants form an electron-donor–electron-acceptor pair. The fact that the powerfully dienophilic alkenes fumaronitrile and tetracyanoethene do not undergo the cycloaddition reaction with phenol, whereas maleic anhydride and some maleimides do, is more difficult to explain; it does not, however, imply a preference for either mechanism.



Scheme 1.



Scheme 2.

With the foregoing experimental data as a background, a theoretical approach to the reaction was undertaken in an attempt to decide between mechanisms 1 and 2, and to predict other alkene–phenol systems which should undergo this unusual cycloaddition process.

Methods

Relative perturbation energies can give, as a first approximation, a reasonable indication of relative activation energies for the cycloaddition steps of mechanisms 1 and 2.[6] These steps are similar in the two proposed mechanisms, and we can justifiably compare perturbational energies on approach of an alkene to a cyclohexadienone or a phenol. We have used the classical model proposed by Sustmann[7] with the Trong approximation.[8] No attempt was made to calculate the activation energy barrier of any monomolecular step of either proposed mechanism. These steps are the enolisation of the first-formed adduct in mechanism 1 and the tautomerisation of the phenol in mechanism 2. Both processes are 'forbidden,' and are known to occur readily in solution. It has therefore been assumed that the activation energies of both processes in solution are zero, *i.e.* both are governed solely by thermodynamics.

The molecular orbital energies and heats of formation of the species discussed here were calculated using the MNDO method.[9] Most of the geometrical structures which we have calculated were unknown and we have therefore minimised geometrical parameters in the theoretical calculations. These MNDO-optimised geometries, as well as those of other related derivatives, are not extensively discussed here but are available on request.

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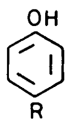
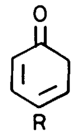
Results and Discussion

Throughout this work, only the 2,5-addition of alkenes to phenols has been considered. The HOMO coefficients of phenol and cyclohexa-2,5-dienone (see Table 1) suggest that the preferred mode of addition of an electrophilic dienophile to phenol (or a derivative of phenol carrying an electron-releasing *para*-substituent) would be the 1,4-orientation. Addition to cyclohexadienone is expected to occur always in the 2,5-orientation.

The fact that only 2,5-addition products are observed experimentally can therefore be taken as conclusive evidence that the reaction occurs *via* mechanism 2 (*i.e. via* the cyclohexadienone). The HOMO coefficients do not suggest a preference for either reaction mechanism for the following reasons. (1) Products from 2,5-addition of alkene to phenol are essentially 'trapped' by the ketonisation of the first-formed adduct [(**3**) in Scheme 1]. This makes the reverse reaction difficult. The product from 1,4-cycloaddition cannot be trapped by this process. Under the rather severe reaction conditions[2] the reverse reaction is expected to occur readily; therefore, only 2,5-addition products are observed. (2) There are steric constraints for the 1,4-addition of an alkene (particularly with bulky substituents) to phenol or a *p*-substituted derivative.

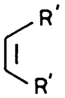


(1)



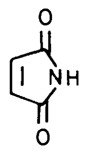
(5)

R
a; OMe
b; H
c; CN



(2)

R'
a; OMe
b; Me
c; H
d; CN



(2e)

(2f)

Table 1. HOMO coefficients of phenol and cyclohexadienone calculated by the MNDO method

Position	Phenol coefficient	Cyclohexadienone coefficient
Oxygen	−0.3703	−0.2331
1	0.4807	0.0042
2	0.3285	0.5401
3	−0.2523	0.3669
4	−0.5343	−0.4415
5	−0.1814	−0.5340
6	0.3765	0.0793

Table 2. Perturbational second-order energies (kJ mol^{-1}) for the approach of olefins to phenols and tautomeric cyclohexadienones (values are negative)

	Diene					
Olefin	(**1a**)	(**5a**)	(**1b**)	(**5b**)	(**1c**)	(**5c**)
(**2a**)	20.88	21.25	20.37	21.08	21.08	21.54
(**2b**)	19.91	20.00	19.41	19.83	19.83	20.00
(**2c**)	19.25	19.29	18.74	19.04	19.12	19.25
(**2d**)	21.46	20.88	20.79	20.58	20.79	20.58
(**2e**)	21.76	21.08	21.08	20.79	20.96	20.67
(**2f**)	22.13	21.25	21.34	20.88	21.08	20.67

Kinetic Aspects.—The second-order perturbational calculations were carried out on tautomeric pairs of a range of *para*-substituted phenols (**1a**—**c**)/(**5a**—**c**), and a range of ethenes (**2a**—**f**). Table 2 shows that for a given phenol or cyclohexadienone the perturbation energy is high with the strong electron-donor dimethoxyethene (**2a**), then reduces with electron-donor character before increasing again for the very strong acceptor alkenes (**2d**—**f**). This is due to the fact that both HOMO olefin–LUMO diene and HOMO diene–LUMO olefin interactions are considered: with a powerful electron-donor alkene (**2a** or **b**), the HOMO olefin–LUMO diene interaction is strong and the resulting energy contribution large, whereas the HOMO diene–LUMO olefin contribution to the total perturbation energy will be small. On the other hand, with a powerful electron-acceptor alkene (**2a**—**f**) the HOMO diene–LUMO olefin contribution is large and the HOMO olefin–LUMO diene contribution small. The latter situation is, of course, normal for the Diels–Alder reaction.

In order to try to distinguish between mechanisms 1 and 2, it is necessary to consider the tautomeric pairs (**1**) $\rightleftharpoons$ (**5**). There is only a small activation energy difference between approach of a given alkene to a phenol (**1**) and approach to its cyclohexadienone tautomer (**5**). However, for donor alkenes, approach to the cyclohexadienone tautomer is slightly favoured and for acceptor alkenes, approach to the phenolic tautomers is slightly favoured (*i.e.* there is a lower activation energy barrier). These results reflect the fact that, with respect to their phenolic tautomers, cyclohexadienones are electron-poor systems, carbonyl being a powerful electron-withdrawing group. All the reactions discussed earlier involve strongly electron-acceptor alkenes. From a kinetic point of view, direct addition (mechanism 1) is marginally favoured for this system. On the other hand, perturbation energy differences are not large for the tautomeric pairs studied and thus the reactions are expected to be governed by thermodynamic factors.

Thermodynamic Aspects.—We first attempted a tautomeric analysis on the three *p*-substituted phenols. Heats of formation for the phenol and the corresponding cyclohexadienone tautomers were calculated. These results are presented in Table 3.

In all cases, as expected, the phenolic forms (**1a**, **b**, and **c**) are by far the most stable; electron-acceptor groups stabilise the phenolic form, whereas electron-donor groups destabilise it. In spite of the relative stabilisation produced in the cyclohexadienone ring by the methoxy group, the energy difference between (**5a**) and its phenolic form (**1a**) is still large (*ca.* 50 kJ mol^{-1}).

Table 3. Dipole moments (D), heats of formation (kJ mol^{-1}), and C–O bond lengths (Å) calculated by the MNDO method

Compound	Dipole moment	ΔH_f	$\Delta(\Delta H_f)$	d_{C-O}
(**1a**)	2.23	−253.93	50.12	1.3604
(**5a**)	3.21	−203.80		1.2274
(**1b**)	1.16	−110.25	62.55	1.3590
(**5b**)	2.98	−47.69		1.2278
(**1c**)	3.43	14.72	68.20	1.3554
(**5c**)	0.72	82.92		1.2266

In Table 3 the dipole moments of the pairs of tautomers are also shown. Although it is well known that the tautomeric equilibria are very sensitive to solvation (either specific solvation or effects caused by the dielectric constant of the solvent), the theoretical model used does not take account of solvent.

For a thorough understanding of the thermodynamics of the reaction, it was decided to study the enol intermediates (**3**) and final products (**4**) resulting from the cycloaddition processes. Preliminary results for phenol and ethylene [(**1b**) and (**2c**)] (for ease of calculation) were surprising (see Table 4). The overall reaction was extremely endothermic (by 80.75 kJ mol^{-1}). The calculations were repeated for *p*-methoxy and *p*-cyanophenols (**1a** and **c**); in both cases the overall reaction was found to be very endothermic (69.46 and 80.33 kJ mol^{-1}, respectively). However, when the calculations were carried out using maleic anhydride (**2f**) as dienophile, the overall reactions were slightly exothermic in all the cases [-22.59, -11.71, and -7.53 kJ mol^{-1} for (**1a**—**c**), respectively]. The reason for this is interesting: there is a significant gain in energy on saturation of the maleic anhydride carbon–carbon double bond. To give an indication of the amount of energy gained by this process, we calculated the values of ΔH_f for succinic anhydride and maleic anhydride. These were found to be -523.81 and -355.24 kJ mol^{-1}, respectively, and the energy gain on oxidation is *ca.* 170 kJ mol^{-1}. This value is to be compared with that found for cyclopentene–cyclopentane, $\Delta(\Delta H_f) = 111.28$ kJ mol^{-1}, or cyclohexene–cyclohexane, $\Delta(\Delta H_f) = 118.82$ kJ mol^{-1}.* There is an additional energy of *ca.* 50—60 kJ mol^{-1} on saturation of the carbon–carbon double bond of maleic anhydride that can only be attributed to a loss of strain in the five-membered ring. It is this remarkable effect that 'drives' the maleic anhydride–phenol reaction.

As a check that this is truly a steric effect and not an electronic one, calculations were carried out using the electron-poor ethene maleonitrile (**2d**). The overall reaction was found to be endothermic by *ca.* 22 kJ mol^{-1}.

Much of the experimental work described here was carried out using *N*-phenylmaleimide as the ethene. Unfortunately, budget and time constraints prevented an analysis with this particular alkene. However, to verify that the loss of strain is also important for maleimides, calculations were carried out on maleimide itself. The loss of strain in going from maleimide to unsubstituted succinimide was found to be similar to that gained in going from maleic anhydride to succinic anhydride, *i.e. ca.* 160 kJ mol^{-1} (calculated ΔH_f values for succinimide and maleimide are -367.43 and -205.81 kJ mol^{-1}, respectively).

The overall reaction with phenol and maleimide was found to be exothermic by 15.1 kJ mol^{-1}. As far as we can ascertain, this remarkable release of strain on saturation of the double bond in maleic anhydride and maleimides has not been reported previously. In the light of the evidence presented here it is not surprising that maleic anhydride and maleimides are such powerful dienophiles.

Table 4. Calculated energies (in kJ mol^{-1}) for the reactants and their cycloadducts (*endo*-isomers in enol and keto forms)

Reactants	ΔH_f (reactants)	ΔH_f (adduct) Enol	Keto	$\Delta(\Delta H_f)$ (reaction)
(**1a**), (**2c**)	-317.98	-212.96	-248.52	69.46
(**1b**), (**2c**)	-174.47	-56.06	-93.72	80.75
(**1c**), (**2c**)	-49.37	66.10	30.96	80.33
(**1a**), (**2f**)	-609.19	-596.22	-631.78	-22.59
(**1b**), (**2f**)	-465.68	-443.50	-477.39	-11.71
(**1c**), (**2f**)	-340.58	-312.54	-348.11	-7.53
(**1b**), (**2d**)	200.83	259.41	223.42	22.59
(**1b**), (**2e**)	-315.47	-292.88	-330.53	-15.06

As can be seen from Table 4, the energy gain on enolisation of the first-formed adduct *via* mechanism 1 is always around 35 kJ mol^{-1}. This is not surprising since enolisation is not expected to be greatly affected by the rest of the molecule. The energy jump from starting materials to the enolic cycloadducts for the addition of maleic anhydride to phenols is smallest for *p*-methoxyphenol and largest for *p*-cyanophenol. This is, of course, a reflection of the resonance energy loss on cycloaddition to the three phenols. The gain in energy due to release of strain in the maleic anhydride ring is the same in all three cases.

Thus, electron-donor groups in the phenol favour these cycloadditions *via* mechanisms 1 and 2, since electron-donor groups in the ring reduce the amount of energy lost on loss of aromaticity.

Conclusions

The remarkable stabilisation achieved on saturation of the five-membered ring of maleic anhydride or maleimide explains why the title reactions occur. As far as we can ascertain, this effect has not been previously reported. In the addition of a maleimide to a phenol, thermodynamic aspects of the calculations described in this paper point to mechanism 1 (direct addition to the phenol). Kinetic studies indicate that the reaction is largely governed by thermodynamics. The small difference in activation energy of the two competing cycloaddition pathways favours mechanism 1 for electron-poor alkenes. The thermodynamic aspects greatly favour mechanism 1; for example, in the addition of maleic anhydride to phenol, the first step *via* mechanism 2 is endothermic by 63 kJ mol^{-1}, whereas the first step *via* mechanism 1 is endothermic by only 21 kJ mol^{-1}, and all the other steps *via* both mechanisms are exothermic.

Although the results discussed here are not proof that mechanism 1 occurs, all the evidence appears to favour this direct addition to phenol.

The present results allow us to predict that thermal cycloadditions of alkenes to phenols will only occur when strained cyclic olefins are employed. Electron-rich cyclic olefins (for example dihydrofurans) might undergo thermal cycloaddition reactions with electron-poor phenols like *p*-cyanophenol. However, the greatest scope for further reactions is with maleic anhydride and maleimides, which should undergo these cycloaddition processes with all but the most electron-poor phenols.

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* Experimental values[10] of ΔH_f (kJ mol^{-1}) are: cyclopentane -76.98, cyclopentene 34.30, cyclohexane -123.42, and cyclohexene -4.60.

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