Short Communication

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Reactivity and structure of derivatives of 2-hydroxy-1,4-naphthoquinone (lawsone)†

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The structures of two derivatives of 2-hydroxy-1,4-naphthoquinone (lawsone) are examined using the density functional theory (DFT) hybrid functional B3LYP. Using the optimized structure of lawsone acetate, the reactivity of acyl transfer is described. Also, the nucleophilicity of the conjugate base of lawsone is predicted using the conceptual descriptors related to softness within the DFT framework. Copyright © 2008 John Wiley & Sons, Ltd.

Keywords: naphthoquinone; lawsone; DFT; HSAB; active ester; enolate alkylation

INTRODUCTION

Naphthoquinone derivatives have been investigated for many years due to the plenitude of natural products containing this functional group and the importance of these compounds in biological and medicinal research.[1] From a chemical perspective, we are interested in the synthesis and activity of derivatives of naphthoquinones. The chemistry of these compounds is surprisingly complex;[2] we are investigating the use of the naphthoquinone group as a sensitive controller of selectivity. However, there is a paucity of recent studies that relate the structure of these compounds to their reactivity.[3]

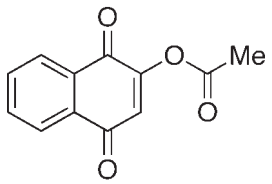
An important derivative of 1,4-naphthoquinone is 2-hydroxy-1,4-naphthoquinone or lawsone (compound **1** in Fig. 1). This compound is a natural product extracted from henna (*Lawsonia alba* or *Lawsonia inermis*).[4] The structure of lawsone has been analyzed by X-ray crystallography[5] and theoretical calculations.[6,7] All the data indicate that among the possible tautomeric forms, the structure with the 1,4-naphthoquinone group is the most stable by at least 10.3 kcal/mol (=43.0 kJ/mol) over the 1,2-naphthoquinone congener (the trione system is less stable but probably exists an equilibrium with the other tautomers in solution). This stability is due to the cancellation of the dipole moments of the carbonyl groups, combined with an intramolecular hydrogen bond, in the 1,4-isomer. This preference is confirmed in the IR spectrum (experimental data indicative of the intramolecular H-bond)[7] and in the UV spectrum that is influenced by the polarity and proticity of the solvents.[8,9]

We have developed new synthetic methods for the preparation of derivatives of lawsone and wished to further investigate the relation between our observations of the chemistry and spectroscopy of these compounds in the laboratory with the theoretical structure and properties calculated using modern computational chemistry programs. In this paper, we will show how the structure of naphthoquinones can be used to predict and explain the results of our experimental investigations about these compounds. We will be using the standard density functional theory (DFT) hybrid functional B3LYP[10–12] to calculate the minimized structure, the electronic properties, and the related descriptors according to the hard and soft acids and bases (HSAB) principle.

RESULTS AND DISCUSSION

2-Acetoxy-1,4-naphthoquinone (lawsone acetate)

We first investigated the acyl derivatives of lawsone, of which 2-acetoxy-1,4-naphthoquinone (lawsone acetate) is the most common member (compound **2**). The possibility of using acylnaphthoquinones as acyl transfer reagents (active esters) would be an interesting proposal.[13] Two questions are important to answer to have an efficient reagent: (1) Is the reagent reactive enough thermodynamically to transfer completely the acyl group to an external nucleophile? and (2) Is the reagent reactive enough kinetically to transfer the acyl group rapidly without engendering instability?



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The first question about the thermodynamic reactivity can be predicted using the p*K*a of the leaving group, in this case lawsone. The experimental value for the p*K*a of lawsone has been measured at 3.98,[14] which would indicate that the acetyl derivative **2** should be more reactive than acetic anhydride **3**. This

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† *Dedicated to Professor Julio Mata-Segreda on the occasion of his 60th birthday.*

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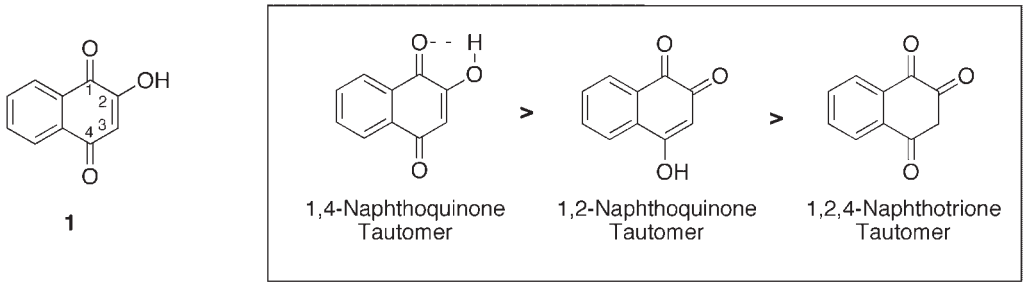


Figure 1. The structure and tautomeric forms of lawsone

reactivity is further illustrated if one considers this group as a vinylogous[15] anhydride (Fig. 2).

To predict the kinetic reactivity of these compounds, we studied the lowest energy conformation of **2** with the idea that from the structure and electronic properties we can intuit information about the reactivity. Also, the structural details should enable us to predict which derivatives are more stable or more reactive. We used the GAMESS[16] suite of programs to optimize the structure, which was checked by vibrational analysis (Hessian matrix), and MacMolPlt[17] to visualize the results of the calculations. The hybrid DFT B3LYP/6-31G* level of theory was used, which is an acceptable compromise between speed and accuracy for a molecule of this size.

Figures 3 and 4 are the results of this optimization. Most anhydrides (and esters) have a planar structure of the alkyl group relative to the carbonyl group.[18] However, freezing the dihedral angle of the acetate group to lie in the plane of the naphthoquinone ring does not reveal the global minimum (Fig. 3). When either of the planar structures is allowed to fully relax, the final minimum structure places the carbonyl group not quite perpendicular to the ring (the optimal dihedral angle between the acetate and the double bond is $\sim 118^{\circ}$).

As can be seen best in Fig. 4, the acetate group is not coplanar with the pi system of the ring. With this 'twisted system'[19] is predicted that, because of the lack or diminution of the orbital overlap between the oxygen and the pi system, the resonance stability usually seen in esters is absent. In general, this torsion should increase the electrophilicity of the carbonyl.

However, close inspection of the Space Filling model in Fig. 4 shows that there is another effect that should influence the reactivity of the acetate group. In this perspective, one sees that the carbonyl group at C1 in the naphthoquinone ring is blocking one face of the acetate. In a nucleophilic attack on the carbonyl along the Bürgi–Dunitz angle,[20] the kinetic reactivity is predicted to be halved since only one face is open to attack.

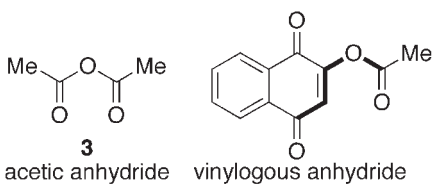


Figure 2. The comparison of an anhydride and lawsone acetate as a vinylogous anhydride

We describe this model as thermodynamically activated but kinetically deactivated.

This activity is seen experimentally. Lawsone acetate (**2**) can be recrystallized from ethanol without much decomposition, and is resistant to hydrolysis (our experimental data suggest it is more stable in water than *p*-nitrophenol acetate with a p*K*a of the leaving group of 7.1). These properties highlight the advantages of **2** as an acyl transfer reagent – it is a crystalline solid that can be stored and transferred without special conditions to exclude water. However, we have observed[21] that in the presence of catalytic amounts of Brønsted acids or (preferably) Lewis acids, the acetate group is transferred rapidly (Scheme 1).

To explain the catalysis by acids, we considered first which interactions occur between the substrate and the acid, and then what changes occur in the intermediates. The Highest Occupied Molecular Orbital (HOMO) at the optimized geometry was examined (Fig. 5) to provide a guide to the most basic site in the molecule. Although this is a Kohn–Sham orbital, the similarity to the familiar Hartree–Fock orbitals is well known.[22] The HOMO is clearly localized on the O4 carbonyl oxygen, which indicates that a soft–soft interaction with the acid would prefer this site. The Lowest Unoccupied Molecular Orbital (LUMO) (not shown) is delocalized throughout the quinone system, which may explain the reluctance of nucleophilic attack without catalysis.

The molecular electrostatic potential (MEP) is also shown (Fig. 6). Whereas there is no clear electron-poor site (dark blue), close inspection shows the O4 has the most basic site (red). The Lewis acid coordinates to the more basic carbonyl oxygen and activates the system.

Our hypothesis for the kinetic activation of lawsone acetate using acids is shown in Scheme 2. After coordination of the acid at the C4 carbonyl, the acetate carbonyl becomes more reactive toward nucleophilic attack. A possible explanation for this activation is shown by the resonance structure shown in Scheme 2 or by using the vinylogous principle in analogy to the activation of an anhydride carbonyl by the addition of a Lewis acid.

To provide more evidence for this activation, the structure of protonated lawsone acetate was calculated, again using B3LYP/6-31G*. The proton acts as the simplest Lewis acid for this model. A comparison of the Lowdin atomic charges measured at various carbons (Fig. 7) between the neutral and protonated species show a change in positive charge at the C4 carbonyl, the C2 carbon, and the acetate carbon. Attempted protonation at other sites (C1 carbonyl, acetate carbonyl) led to structures that were not minimum on the energy surface. These data confirm the prediction (Scheme 2) of the details of how lawsone acetate can

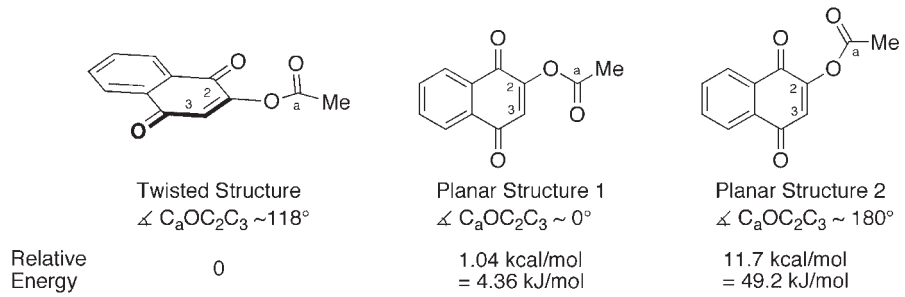


Figure 3. Comparison of planar and fully optimized structures

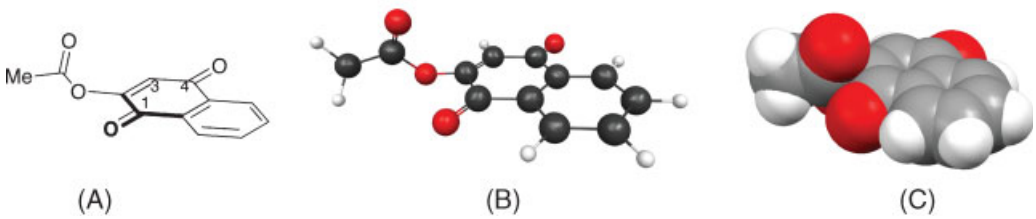
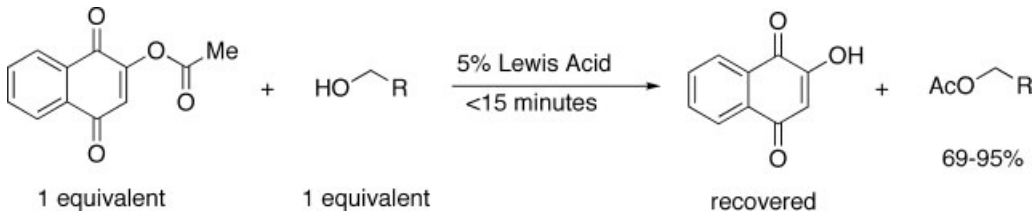


Figure 4. Optimized calculated geometry (B3LYP/6-31G*) for lawsone acetate (**2**). (A) Line drawing, (B) ball & stick, and (C) space filling



Scheme 1. Reactivity of lawsone acetate with alcohols

be utilized as an acyl transfer agent but show a limitation to the reagent since the catalyst activates different sites in the molecule.

Alkylation of lawsonate anion

Deprotonation of lawsone forms the lawsonate anion (**4**, Scheme 3), where the negative charge is delocalized among the O2 to O4 atoms. The lawsonate anion is a multident nucleophile and has caused problems in the regioselectivity of its alkylation.[23] It is possible to form various products (Scheme 4) in the presence of an alkylating agent. Furthermore, if the reaction proceeds under forcing conditions, the products of multiple alkylation are conceivable and are observed experimentally. We wished to determine the optimal conditions to control the regioselectivity of the reaction of the lawsonate anion with electrophiles.

It is well known that the regioselectivity of alkylation of simple enolates can be controlled using different experimental

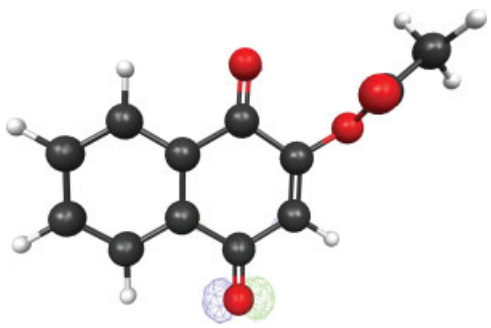


Figure 5. The HOMO of lawsone acetate calculated at the level B3LYP/6-31G*

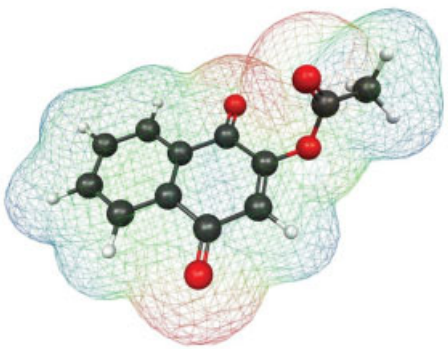


Figure 6. The molecular electrostatic potential mapped on the total electron density (0.002 e/Bohr^3)

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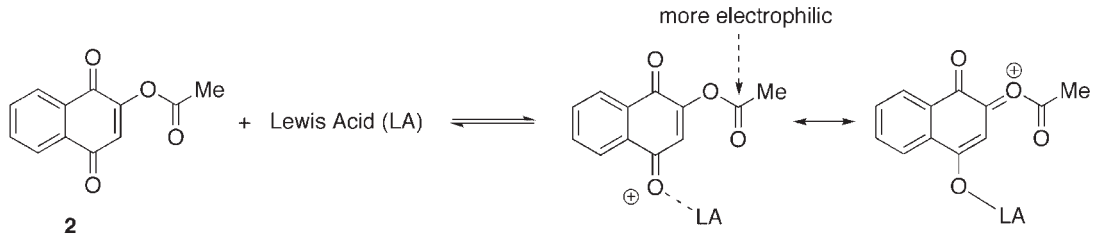

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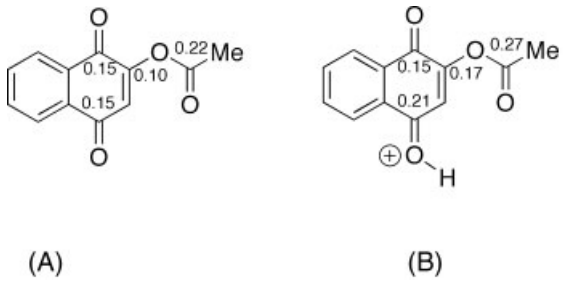
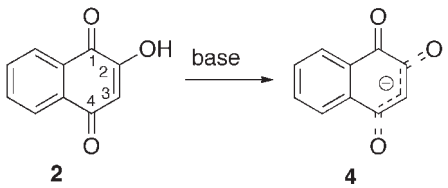
Scheme 2. Activation of lawsone acetate by Lewis acids



(A) (B)

Figure 7. Atomic charges at select atoms in the optimized structures. (A) Lawsone acetate with Lowdin charges and (B) Protonated lawsone acetate with Lowdin charges



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Scheme 3. Protonated and deprotonated forms of lawsone

conditions.[24,25] This selectivity has been explained using the HSAB principle,[26,27] and DFT calculations[28–31] on simple enolates support this explanation.

Within the conceptual DFT framework, it is possible to quantify these effects.[32,33] First, it is possible to define the chemical or global hardness (η) in terms of the ionization potential (IP) and electron affinity (EA), which can be approximated by the calculated energies of the different species as lawsonate gains or loses an electron (Eqn (1) and Fig. 8).[34] The optimized geometry of the anion is used in the calculations of the energies of all species (without taking into account the zero point energies).[34]

$$\eta = \mathrm{IP} - \mathrm{EA} \approx (E_{\mathrm{radical}} - E_{\mathrm{anion}}) - (E_{\mathrm{anion}} - E_{\mathrm{dianion}}) \quad (1)$$

More importantly for enolates, the global softness (S) can be defined as the reciprocal of the global hardness (Eqn (2)).[35] This value is related to the overall polarizability of the molecule.

$$S = \frac{1}{\eta} \quad (2)$$

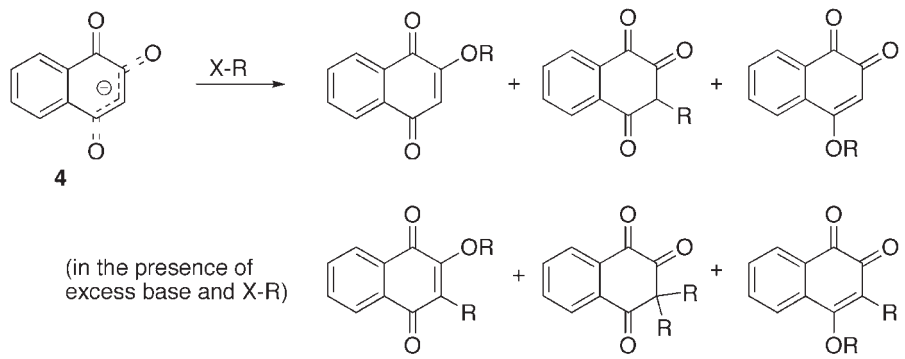
The nucleophilic condensed Fukui function[36] (f_k^-) for each nucleophilic atom k in the molecule can then be calculated using the atomic charges (q_k) in the enolate anion and the radical (Eqn (3)).

$$f_k^- = q_k(\mathrm{anion}) - q_k(\mathrm{radical}) \quad (3)$$

The local softness (s_k^-) for each nucleophilic atom k is then determined using Eqn (4). Both the local softness and the Fukui function indicate the relative reactivity among the different negatively charged atoms.

$$s_k^- = f_k^- S \quad (4)$$

Finally, Roy *et al.*[37,38] recommend using the index of relative nucleophilic softness at the atoms k to take into account electron



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Scheme 4. Possible products of alkylation of the lawsonate ion

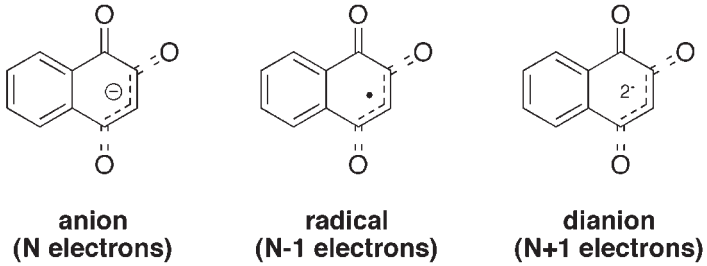


Figure 8. Species derived from lawsone used in the calculations

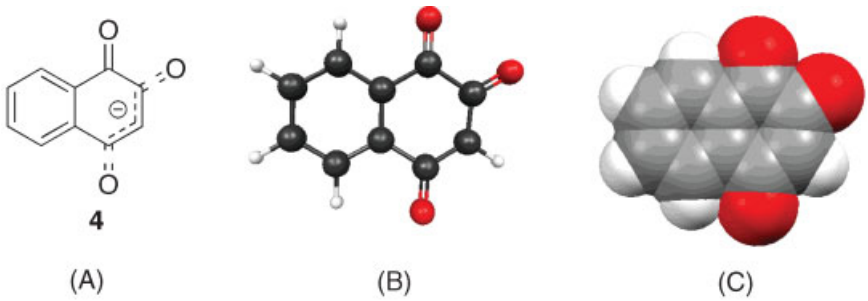


Figure 9. Optimized calculated geometry (B3LYP/6-31+G*) for lawsonate anion. (A) Line drawing, (B) ball & stick, and (C) space filling

correlation effects (Eqn 5).

$$\text{Relative softness} = \frac{s_k^-}{s_k^+} \qquad (5)$$
$$\text{where } s_k^+ = f_k^+ S = (q_k(\text{dianion}) - q_k(\text{anion}))S$$

It should be pointed out that the lawsonate anion is not the same as a simple enolate. To determine the nucleophilic power at the positions O2, C3, and O4, DFT hybrid calculations at the B3LYP/6-31+G* level in GAMESS were used to calculate the minimized structure of the anion (Fig. 9) as well as its atomic charges and energy. The inclusion of diffuse functions on the heavy atoms is important to take into account the delocalization of the negative charge. The Lowdin[39] population analysis was used to calculate the charges to avoid problems with negative Fukui functions.[40]

The optimized geometry of the anion is then used to calculate the single-point energies and charges of the radical and dianion. From these data, one can calculate the DFT local reactivity descriptors including the condensed Fukui function, local softness, and relative softness (Table 1).

The atomic charges (Table 1) show the expected behavior; the negative charge is populated on the more electronegative oxygen atoms at O2 and O4. At first glance, it would seem impossible to control the regioselectivity (the site selectivity among the nucleophilic atoms in the anion) with electrophiles. The difference among the nucleophilic sites is not impressive if one considers the Fukui function or local softness, which seem to show a strong competition between O2 and C3. The previous literature results seem to concur with this lack of selectivity.[23] The high value of the relative softness for the C3 was not

Table 1. Summary of DFT[a] local reactivity descriptors of the lawsonate anion (**3**)

Atom	Atomic charge[b]	Fukui function (f^-)	Local softness (s^-)[c]	Relative softness (s^-/s^+)
O2	−0.442	0.201	0.863	2.30
C3	−0.332	0.245	1.05	5.19
O4	−0.480	0.162	0.694	1.67

[a] Calculated using B3LYP/6-31+G* in GAMESS.
[b] Calculated using Lowdin population analysis.
[c] Determined from the global softness (S) = 4.286 h^{-1}.

Table 2. Summary of atomic charges[a] of the lawsonate anion (**3**) in different PCM solvents

Atom	Atomic charge gas phase	Atomic charge H_2O	Atomic charge EtOH	Atomic charge acetone	Atomic charge toluene
O2	−0.442	−0.528	−0.524	−0.520	−0.484
C3	−0.332	−0.334	−0.334	−0.334	−0.333
O4	−0.480	−0.517	−0.516	−0.516	−0.503

[a] Calculated using B3LYP/6-31+G* in GAMESS using Lowdin population analysis.

Table 3. Summary of Fukui function[a] of the lawsonate anion (**3**) in different PCM solvents

Atom	(f^-) Gas phase	(f^-) H_2O	(f^-) EtOH	(f^-) Acetone	(f^-) Toluene
O2	0.201	0.220	0.220	0.219	0.210
C3	0.245	0.274	0.272	0.272	0.260
O4	0.162	0.152	0.153	0.153	0.159

[a]Calculated using B3LYP/6-31+G* in GAMESS using Lowdin population analysis.

unexpected, and should be important for C-alkylation using soft electrophiles. However, alkylation on oxygen should be controlled by hard–hard interactions, and an electrophilic reagent with a positive charge should favor reaction at O2 or O4.

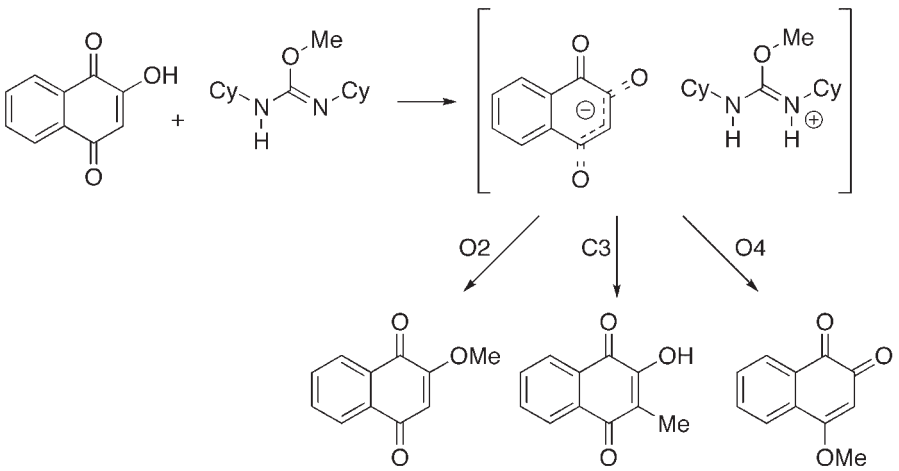
We also wished to determine if the solvent plays a role in the alkylation. Solvent effects were included using the Polarized Continuum Model (PCM)[41] as implemented in GAMESS. To compare solvation to the gas phase data, the lawsonate anion was optimized in four different solvents: water (dielectric permittivity (ε) = 78.39), ethanol (ε = 24.55), acetone (ε = 20.70), and toluene (ε = 2.379). Although there is not much change in the structural features in the different solvents, the DFT descriptors change dramatically. These results are shown in Tables 2 and 3.

The most noticeable change on solvation is the charge accumulation on O2, especially in polar/protic solvents (Table 2). In the gas phase, or a solvent of low polarity like toluene, the charge is unmistakably highest on O4. We cannot fully explain this displacement of electron density that polarizes the O2; more study is required to fully understand the effect. It is remarkable that the charge on C3 scarcely changes with solvation in polar/protic, polar/aprotic, or nonpolar/aprotic solvents.

There is a subtle influence on the Fukui function as a function of polarity (Table 3) – as the scale of polarity increases, O2 and C3 receive a higher value at the expense of O4. The higher value of the Fukui function at O2, combined with the high charge density, predicts that O2 will be the kinetic site of reaction under ionic conditions in polar/protic solvents.

Our experimental data (Scheme 5) are in general agreement with the calculated results. Lawsone and methyl dicyclohexylisourea instantly form the charged lawsonate and the isouronium ions on mixing, which further react to form the methylated products. The reaction was performed in different solvents and, after workup to remove the insoluble dicyclohexylurea, the product distribution was analyzed by ^{1}H NMR. The reaction was completely regioselective in the polar/protic solvents whereas in the nonpolar toluene a mixture of the regioisomers was produced (the product ratio in acetone could not be analyzed due to the formation of other products). It should also be noted that the reaction is considerably faster in water than the other solvents, although a considerable amount of lawsone was recuperated because of the hydrolysis of the intermediate.

It is interesting that each of the DFT descriptors mentioned in this paper have been directly used to explain or predict the regioselectivity in the case of simple enolates. Our experimental results and calculations on the lawsonate system show that the atomic charge and Fukui function can be used as a useful guide but there is not one descriptor that proved consistent with the data. We are continuing to investigate how to control selective reactions on this system with soft, neutral electrophiles,



H_2O	>95%	-	-
EtOH	>95%	-	-
Acetone	decomposition		
Toluene	59.6%	16.9%	23.5%

Scheme 5. Experimental results of the alkylation of Lawsone

which according to the index of relative nucleophilic softness should be greatly favored at the C3.

CONCLUSIONS

Examination of the minimized structure and of the electronic parameters of lawsone acetate can explain its reactivity (thermodynamics and kinetics) as an active ester. This reagent is thermodynamically activated but kinetically hindered. A mechanism is proposed for the accelerated acyl transfer in the presence of a catalyst.

In the alkylation of the lawsonate anion, DFT local descriptors provide more information about the reactivity. The enolate anion is a soft nucleophile with different sites of reactivity. The C3 has less negative charge but a much greater softness than the other atoms. The oxygen at the position 2 reacts selectively under ionic conditions in polar/protic solvents, which can be explained by a combination of atomic charge and the Fukui function under modeled solvation conditions. Our work shows a lack of DFT descriptors that can be used for reactions between more complex systems and hard electrophiles.

Acknowledgements

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