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Study of Very Reactive Tautomeric Phenol Dienones as Dienes in Diels−Alder Reactions

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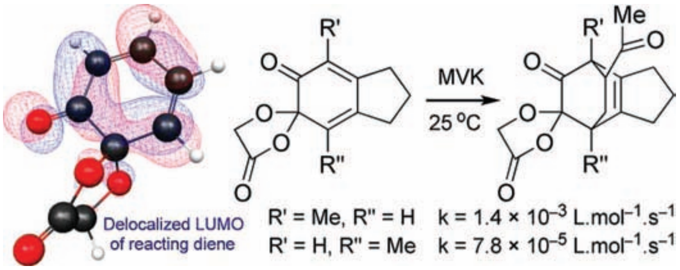
ABSTRACT



Masked *ortho*-benzoquinones are very reactive as diene partners in Diels−Alder reactions. Careful exploration of the orbital factors that govern their surprising behavior shows that their LUMO is almost as electron demanding as that of *o*-benzoquinone itself. Methyl substituents at either end of their diene system influence the activation energy through modification of the reaction pathway being more or less asynchronous.

The Diels−Alder (DA) reaction, although old, is still widely studied because of its broad use in organic synthesis and its interest in terms of fundamental understanding of its mechanism.[1] It is commonly accepted that the frontier molecular orbitals (FMO) theory helps in rationalizing the outcome of "normal" electron demand DA reactions (electron-rich diene/electron-poor dienophile). On the other hand, inverse electron demand cases are not as easily explained.[1c] In particular, their kinetics are not related to the FMO energy gap (diene LUMO/dienophile HOMO). In this letter, we disclose experimental and theoretical data concerning an electron-poor diene that reacts nearly as fast as electron-rich dienes. Masked *o*-benzoquinone (MOB), a tautomeric phenol, is formally a cisoid dienone.[2] Its reactivity can be modulated by substituent patterns in a controllable way. It is a highly valuable synthon for organic chemists.[3]

Both related isomeric dienones **1** and **2** (Scheme 1) were prepared from the same aldehyde synthon **7**. Aldehyde **7** was reduced to alcohol **8** that was immediately protected as its benzylidene ketal **9**.[4] Subsequent $\mathrm{S_N}2$ attack of the remaining phenolate onto methyl bromoacetate yielded ester **10** in 45% overall yield. Hydrogenation of **10** over palladium and under acidic conditions gave lactone **11** quantitatively. Diene **1** was finally obtained by sequential treatment of **11** with NaOH

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(1) (a) Takao, K.-I.; Munakata, R.; Tadano, K.-I. *Chem. Rev.* **2005**, *105*, 4779. (b) Dory, Y. L.; Hall, D.; Deslongchamps, P. *Tetrahedron* **1998**, *54*, 12279. (c) Spino, C.; Pesant, M.; Dory, Y. *Angew. Chem., Int. Ed.* **1998**, *37*, 3262. (d) Kong, S.; Evanseck, J. D. *J. Am. Chem. Soc.* **2000**, *122*, 10418. (e) Houk, K. N.; González, J.; Li, Y. *Acc. Chem. Res.* **1995**, *28*, 81.

(2) (a) Berney, D.; Deslongchamps, P. *Can. J. Chem.* **1969**, *47*, 515. (b) Bélanger, A.; Berney, D. J. F.; Borschberg, H.-J.; Brousseau, R.; Doutheau, A.; Durand, R.; Katayama, H.; Lapalme, R.; Leturc, D. M.; Liao, C.-C.; MacLachlan, F. N.; Maffrand, J.-P.; Marazza, F.; Martino, R.; Moreau, C.; Saint-Laurent, L.; Saintonge, R.; Soucy, P.; Ruest, L.; Deslongchamps, P. *Can. J. Chem.* **1979**, *57*, 3348. (c) Liao, C.-C.; Wei, C.-P. *Tetrahedron Lett.* **1989**, *30*, 2255. (d) Magziak, D.; Meek, S. J.; Pettus, T. R. R. *Chem. Rev.* **2004**, *104*, 1383. (e) Liao, C.-C. *Pure Appl. Chem.* **2005**, *77*, 1221.

(3) (a) Liao, C.-C.; Peddinti, R. K. *Acc. Chem. Res.* **2002**, *35*, 856. (b) Reeder, M. D.; Srikanth, G. S. C.; Jones, S. B.; Castle, S. L. *Org. Lett.* **2005**, *7*, 1089.

(4) Deslongchamps, P.; Bélanger, A.; Berney, D. J. F.; Borschberg, H.-J.; Brousseau, R.; Doutheau, A.; Durand, R.; Katayama, H.; Lapalme, R.; Leturc, D. M.; Liao, C.-C.; MacLachlan, F. N.; Maffrand, J.-P.; Marazza, F.; Martino, R.; Moreau, C.; Ruest, L.; Saint-Laurent, L.; Saintonge, R.; Soucy, P. *Can. J. Chem.* **1990**, *68*, 115.

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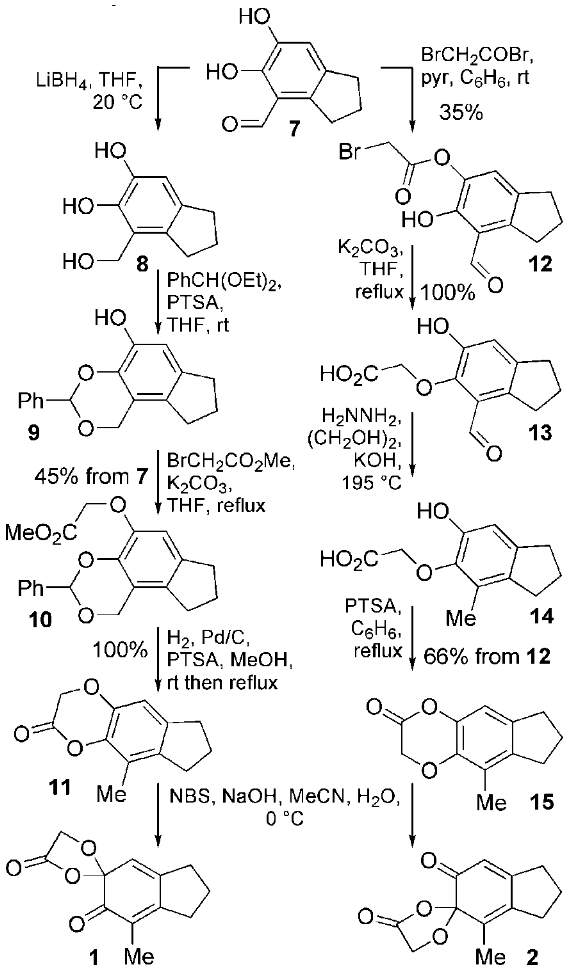
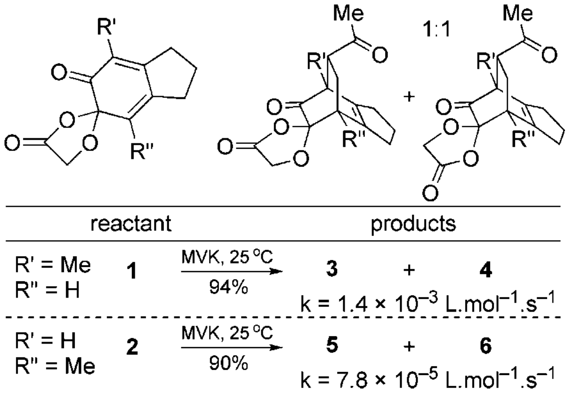
Scheme 1. Synthesis of Dienones **1** and **2**



Scheme 2. Comparative Kinetic Study of Dienones **1** and **2**



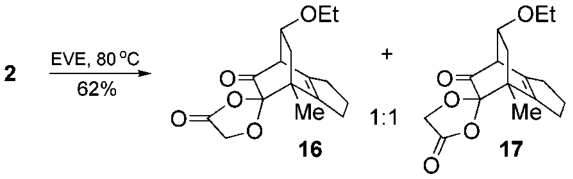
then NBS. Diene **1** is notably unstable and cannot be stored neat. It was kept in C_6D_6, the same solvent used in the next DA reaction. Although diene **2** is stable and can even be crystallized, it was also stored in C_6D_6 to ensure comparable kinetic data for the DA reaction.

The synthesis of **2** went as follows: **7** was acylated with bromoacetyl bromide to yield ester **12** (35%). Intramolecular phenolate alkylation then hydrolysis of the resulting lactone with K_2CO_3 produced **13** quantitatively. Aldehyde **13** was reduced to its corresponding methyl derivative by means of hydrazine. Hydroxy acid **14** lactonized to afford **15** (66% from **13**) ready for the preparation of dienone **2** in the same way that **1** had been obtained from isomeric lactone **11**.

We had already observed that **2** was an excellent diene.[2a,b] We noticed that its isomer **1** seemed even more potent as suggested by its instability. We then carried out a more precise comparative study of both dienes: In each case, a slight excess of methyl vinyl ketone (MVK, 275 μmol) was added to either **1** or **2** (250 μmol) in C_6D_6 (Scheme 2). The reaction was monitored by ^{1}H NMR spectroscopy by integration of the singlet signals corresponding to the methyl groups at the ring junctions in products **3**−**6**. Diene **1** was found to react 18 times faster than its regioisomer **2**, their second-order rate constants being 1.4×10^{-3} L•mol^{-1}•s^{-1} and 7.8×10^{-5} L•mol^{-1}•s^{-1}, respectively.

Although it was originally beyond the scope of our project,[2a,4] we wanted to assess the reactivity of MOB **2** with an electron-rich dienophile like ethyl vinyl ether EVE (Scheme 3).[5] Contrarily to MVK, a stoichiometric mixture of **2** and EVE did not react significantly at 25 °C.

Scheme 3. Reaction of Diene **2** with EVE



A large excess of EVE was added, and the reaction mixture was refluxed (80 °C) for 48 h. Even then, the reaction was not complete. A 1:1 mixture of adducts **16** and **17** was obtained with a total yield of 62% and with the same regioselectivity as that observed for adducts **5** and **6**.

We then carried out theoretical calculations to draw useful rules that can be applied to this kind of seemingly deactivated diene. Our primary calculations aimed to reveal what could be the reasons for the unexpectingly high reactivity of **1**−**2** as dienes. FMOs were examined by means of DFT calculations (B3LYP/6-31Gd)[6] for simple related systems (Figure 1). These systems were carefully selected to decompose all possible factors driving the reactivity of **1**−**2** as well as other similar dienones.

Calculations confirmed that cyclohexadiene **21**, corresponding to dienones **1**−**2**, is electron deficient. Its HOMO energy is very low at −7.18 eV and is unreactive, whereas its LUMO energy is very stable at −2.94 eV. To understand what factors might govern the high reactivity of such

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(5) Hou, H. F.; Peddinti, R. K.; Liao, C.-C. *Org. Lett.* **2002**, *4*, 2477.

(6) Pearson, E. L.; Kwan, L. C. H.; Turner, C. I.; Jones, G. A.; Willis, A. C.; Paddon-Row, M. N.; Sherburn, M. S. *J. Org. Chem.* **2006**, *71*, 6099.

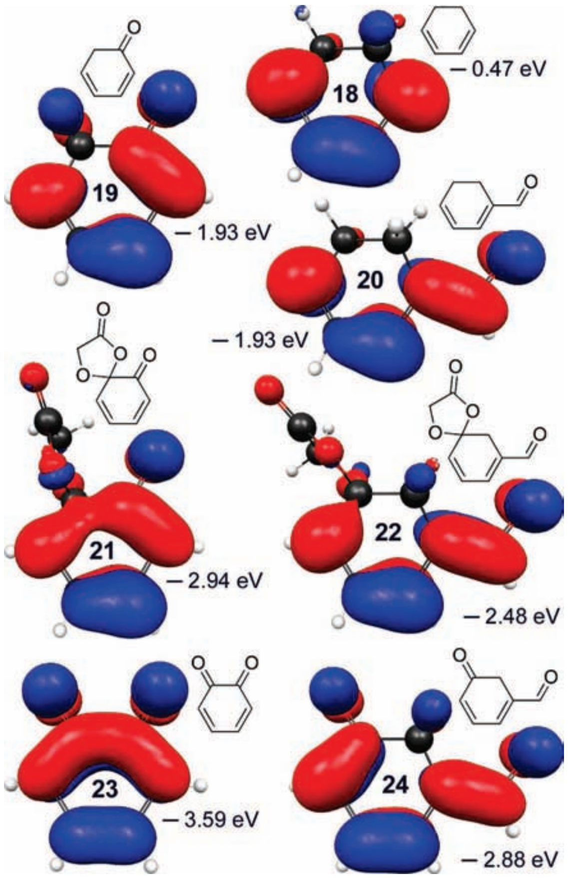

Figure 1. LUMO shapes and energies of various cyclohexadienes **18**−**24**.

systems, we underwent a careful LUMO shape−energy relationship study. The simplest cyclohexadiene **18** is electron rich, and its LUMO is unreactive (−0.47 eV). Addition of a conjugated carbonyl inside the cycle (**19**) or outside (**20**) produces exactly the same effect on the LUMO energy (−1.93 eV). When a gem dioxygen is introduced in **19** and **20** to give systems **21** and **22**, respectively, their associated LUMO energies become drastically different (−2.94 eV, −2.48 eV). Examination of their shapes shows that **21** LUMO is much better delocalized since it now involves participation of the "anomeric" carbon; such is not the case in **22**. This is reminiscent of *ortho*-quinone **23**, a very reactive electron-deficient diene (−3.59 eV) that benefits from the same delocalizing effect of the LUMO through both carbonyl carbons. This effect is also demonstrated in **24**, for which similar delocalization is not possible in its two carbonyls. Its LUMO energy is even higher (−2.88 eV) than that of **21**.

From these results, we suggest that **1**, **2**, **21**, and other MOBs are well described by the resonance forms depicted in Figure 2.

Having explained the reactivity issue of **1** and **2**, we then moved to rationalize the regioselectivity as well as the drastic difference of kinetic behavior of these two MOBs that differ only from each other by the position of one methyl group.

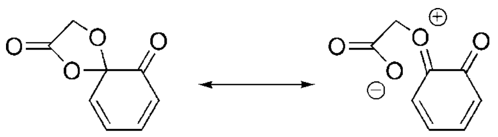

Figure 2. Canonical forms for **21** and other MOBs.

Since Diels−Alder reactions are kinetically driven, a straightforward means to understand the huge effect of one single methyl group would be to examine the transition states. We isolated all possible transition structures (TSs) at a reasonable level of theory (B3LYP/6-31Gd implemented in GAMESS).[7]

We found that out of eight possible TSs[8] from diene **1**, six could be discarded because they are too energetic (6.2−14.1 kcal/mol higher than the most stable TS **TS1a** (Figure 3)). the other feasible TS **TS1b** is slightly more energetic than **TS1a** by 0.02 kcal/mol. These figures correspond to a 51:49 population of adducts **3** and **4** as observed experimentally (Scheme 2). The whole picture is virtually the same from diene **2**: six TSs are higher in energy than **TS2a** (3.7−11.8 kcal/mol range), while the remaining TS **TS2b** relative energy is 0.32 kcal/mol. The 63:37 theoretical population of **5** and **6** is again in good aggreement with the

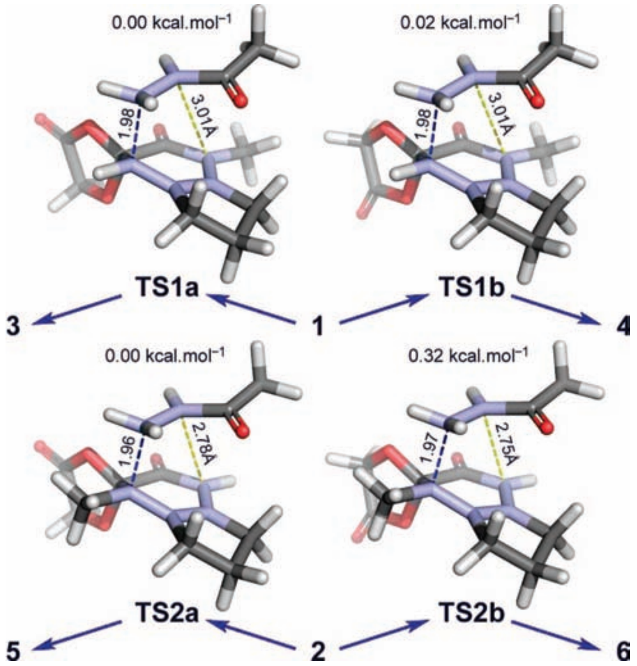

Figure 3. Relative energies and geometries of most favorable TSs, **TS1a**, **TS1b**, **TS2a**, and **TS2b**. Blue atoms are involved in the pericyclic reaction.

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(7) Schmidt, M. W.; Baldridge, K. K.; Boatz, J. A.; Elbert, S. T.; Gordon, M. S.; Jensen, J. J.; Koseki, S.; Matsunaga, N.; Nguyen, K. A.; Su, S.; Windus, T. L.; Dupuis, M.; Montgomery, J. A. *J. Comput. Chem.* **1993**, *14*, 1347.

50:50 experimental result. The lack of selectivity for the formation of adducts **3** and **4** and **5** and **6** is a consequence of a similar hindrance from the diene five-membered ring lactone to the approach of the dienophile, whatever its facial orientation (Figure 3).

All very asymmetrical TSs correspond to asynchronous processes.[1e] The location of the short bond (1.96−1.98 Å) indicates that the σ bond away from both diene and dienophile carbonyls is created first. Close examination of the TSs further reveals the true effect of the methyl substituent on the dienone. When this methyl group is away from the short forming bond as in **TS1a**,**b**, there is obviously no unfavorable steric interaction of any kind, and the long forming bond is indeed so long (3.01 Å) that it can be considered almost nonexistent yet. In **TS2a**,**b**, the methyl group is directly adjacent to the short forming bond, and it fights the approach of both Diels−Alder reaction partners through steric interactions across that short bond. The long forming bond becomes shorter in the process (2.75−2.78 Å), and **TS2a**,**b** are less asymmetrical than **TS1a**,**b**. Consequently, the Me group is responsible for the degree of asynchronicity in the transition state; it governs the kinetic behavior of **1** and **2** as dienes.

To gauge the asynchronicity of the reaction, IRC calculations were carried out from **TS1b** and **TS2b** (Figure 4).[9] They indicate that the fast reaction (from **TS1b**) is the more asynchronous process. In fact, this is likely the reason why the activation energies of both Diels−Alder reactions are different. In the fast process, both sigma bonds are formed sequentially, as shown by the two separated waves in the energy = f (reaction coordinate) curve. Consequently, delivery of energy to the system can be achieved in a progressive way, resulting in a low-energy barrier of 15.4 kcal/mol. On the contrary, both sigma bonds are formed in a more parallel mode during the slow reaction. It ensues that more energy is consumed when these bonds appear at the same time; this phenomenon shows up in the activation energy that is now substantially larger (18.4 kcal/mol). Although the 3 kcal/mol energy gap between **TS1** and **TS2** overestimates the observed difference in reaction rate of **1** and **2** with MVK, it is nevertheless in full qualitative agreement with the observed trend.

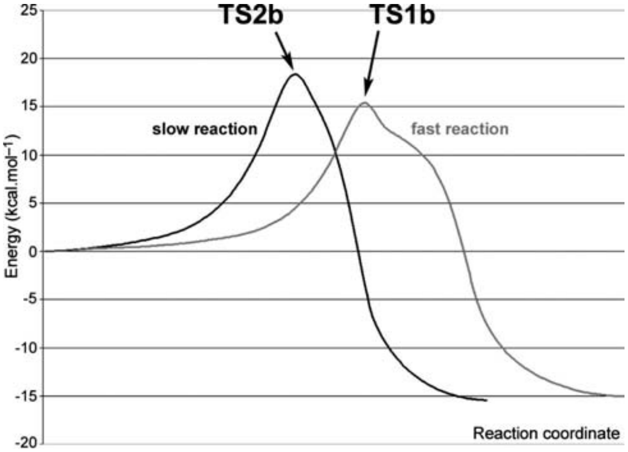

Figure 4. IRC profiles for **TS1b** and **TS2b**.

In conclusion, MOBs are very reactive electron-poor dienes related to *ortho*-benzoquinone since their LUMOs are stabilized in the same delocalizing way. Since the asynchronous approach of both reacting diene ends is partially responsible for the low activation energy, it can be modulated by the presence or absence of substituents near the σ bond that forms first. Owing to their high reactivity and selectivity, MOBs are very useful dienes for synthetic organic chemists.

Acknowledgment. We thank NSERC Canada for financial support.

Supporting Information Available: Experimental procedures, kinetic data, mdl mol files for all 16 transition structures (zip file), and IRC mpg files from **T2b** and **T2b**. This material is available free of charge via the Internet at http://pubs.acs.org.

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(8) (a) Wang, H.; Wang, Y.; Han, K.-L.; Peng, X.-J. *J. Org. Chem.* **2005**, *70*, 4910. (b) Arjona, O.; Medel, R.; Plumet, J.; Herrera, R.; Jiménez-Vázquez, H. A.; Tamariz, J. *J. Org. Chem.* **2004**, *69*, 2351. (c) Liao, C.-C.; Chu, C.-S.; Lee, T.-H.; Rao, P. D.; Song, L.-D.; Shiao, H.-C. *J. Org. Chem.* **1999**, *64*, 4102.

(9) (a) Gonzales, C.; Schlegel, H. B. *J. Chem. Phys.* **1989**, *90*, 2154. (b) Bernardi, F.; Olivucci, M.; Robb, M. A. *Acc. Chem. Res.* **1990**, *23*, 405.