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Sonochemical cycloadditions of *o*-quinones. The search for a cation radical pathway

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Abstract

Diels–Alder cycloadditions of an *o*-quinone monoketal with different furans, under argon, are considerably accelerated by ultrasonic irradiation. Moreover, these sonochemical reactions are regiospecific and proceed with a high diastereoselectivity. The results can be ascribed to the chemical role of ultrasounds which may favor a single electron transfer mechanism with respect to ionic or nonpolar pathways.

Keywords: cation radicals; Diels–Alder reactions; furans; *o*-quinones.

Activation of Diels–Alder reactions, especially by Lewis acids[1] or nonconventional irradiation techniques,[2] not only enhances the versatility of this powerful methodology, but also enables milder and more selective cycloadditions. Assuming that Diels–Alder reactions are sensitive to thermal and pressure effects, they would be susceptible to ultrasonic activation since the cavitational collapse is capable of creating extremely high local temperatures (~4500 K),[3] though accompanied by modest pressures (a few kbars), under almost adiabatic conditions (the duration of the hot spots is less than 100 nanoseconds with cooling rates $>10^{10}$ K/s).[3,4] The conditions provided by cavitation would be comparable to those of flash thermolysis. Unfortunately, little success has so far been encountered in ultrasound-assisted cycloadditions. This fact can be interpreted by the hypothesis of true sonochemistry,[5] pioneered by Luche, stating that chemical effects of ultrasounds will occur only if an elemental process is the sonication sensitive step, or when the high energy species released after the collapse participate as reaction intermediates. Accordingly, ultrasounds may favor a radical process by virtue of their ability in promoting single electron transfers. However, nonvolatile substrates have no probability to penetrate into the bubble to undergo these extreme conditions, although they may experience the shock waves in the bulk medium. On the other hand, the formation of cation or anion radicals does require appropriate

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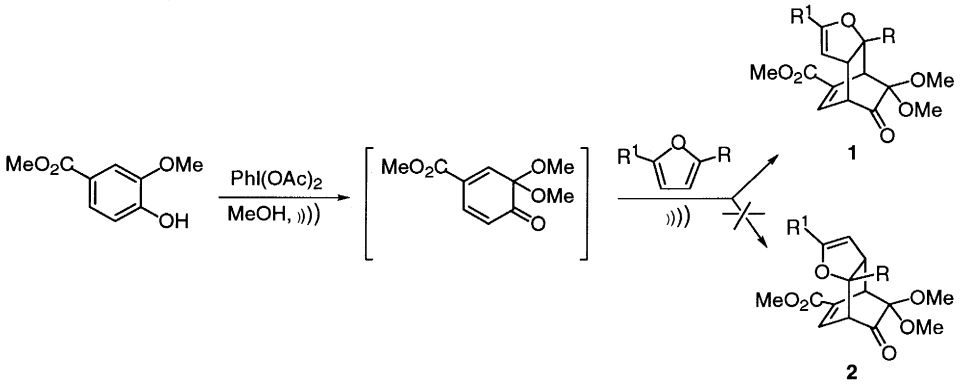
electrochemical potentials or the presence of radical holes, acting as intermediates, such as the aminium radicals exploited by Bauld et al.[6]

Suitable candidates for sonochemical cycloadditions are quinones,[2a] because these substances form redox pairs with potentials lower than those of most aromatic hydrocarbons,[7] and their cation radicals can easily be generated from catechols and catechol ethers.[8] In a series of recent papers, Liao et al. have reported that *o*-benzoquinones, generated by oxidation of catechols with a hypervalent iodine reagent (diacetoxyiodobenzene, DAIB), react with furans which act as dienophiles.[9] Such reactions require heating at 50°C or reflux for several hours. Arjona et al. have also described this cycloaddition with enol ethers.[10] Notably, these authors claim that the resulting cycloadducts have the regiochemistry opposite to those of furan-based cycloadditions on the basis of a small NOE effect (4%) between two distant protons. It should also be noted that Waldmann and his associates have reported a chemoenzymatic domino reaction of catechols with enol ethers to give similar adducts.[11] It appeared justified to explore this useful protocol under ultrasonic conditions and especially in order to elucidate the regiochemical pattern.

Reaction of methyl vanillate with DAIB in methanol under ultrasonic irradiation (bath, ~35 kHz), and under an argon atmosphere, gives rise to the corresponding *o*-quinone monoketal which is trapped by a series of furans (Scheme 1, Table 1). Remarkably, the process is largely accelerated: reactions can now be conducted at room temperature and are essentially complete within 15–50 min. Yields are moderate to good, since the rapid reaction also causes a partial decomposition of the starting catechol, presumably by oligomerization of phenol radicals. ^{1}H and ^{13}C NMR analyses of the crude samples evidenced the formation of a single stereomer, the same as the cycloadduct obtained under thermal conditions. This is particularly remarkable assuming that two regiochemistries are possible, each with *endo* or *exo* orientations. A careful inspection of NMR data clearly indicates that, in the case of 2-substituted furans, only the unsubstituted double bond reacts.



Scheme 1.

Liao et al. have attempted a theoretical analysis of the regioselectivity by computing the cycloadditions of quinones with methyl acrylate and methyl vinyl ketone both at PM3 and RHF/3-21G* levels;[9b] these authors note that in most cases the difference in the energy gaps for the two possible interactions are around 0.5 eV. We have similarly performed a semiempirical PM3 calculation of the experimental reaction involving oxidized methyl vanillate and furan itself. The energy gaps were $HOMO_{furan}-LUMO_{catechol}=0.29$ eV and $HOMO_{catechol}-LUMO_{furan}=0.40$ eV. While the former interaction accounts for an inverse electronic demand cycloaddition, the further calculation of the atomic coefficients suggests that the opposite regiochemistry (**2**), should be favored. Fortunately, crystals appropriate for X-ray diffraction analysis were obtained for the cycloadduct arising from reaction with

Table 1
Sonochemical cycloadditions of oxidized methyl vanillate with furans

Dienophile	R	R^1	Reaction time (min)	Adduct (% yield)[a]
Furan	H	H	20	**1a** (52)
2,5-Dimethylfuran	Me	Me	25	**1b** (55)
2-Furaldehyde	H	CHO	45	**1c** (57)
2-Acetylfuran	H	COMe	30	**1d** (53)
Ethyl 2-furoate	H	COOEt	15	**1e** (50)

[a]Only one diastereomer was detected by ^{1}H NMR analysis (400 MHz, $CDCl_3$)

furan, thereby confirming in an unequivocal fashion that the selective approach gives rise to the regiomer **1** (Fig. 1).[12]

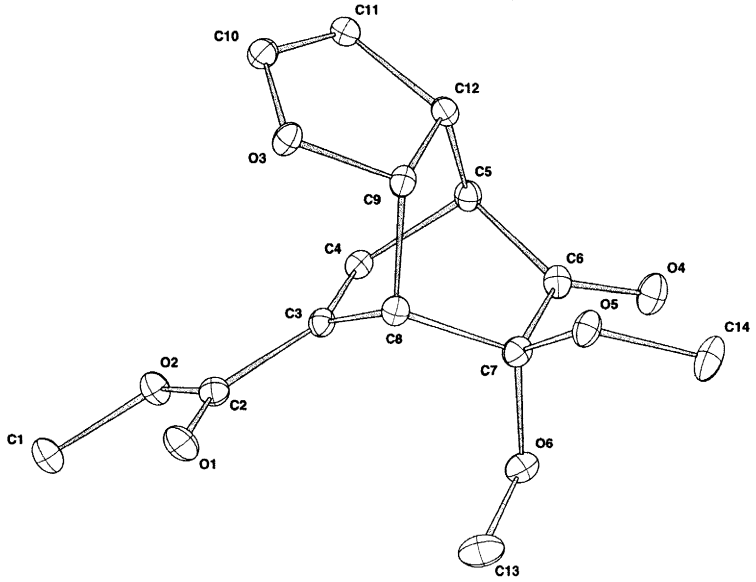
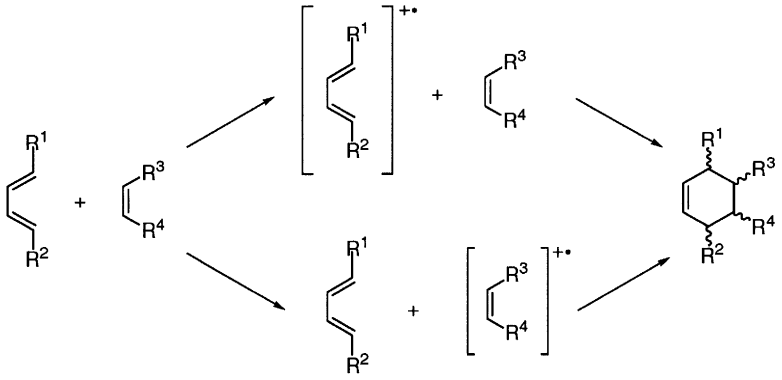


Fig. 1. X-Ray crystallographic view of cycloadduct **1a**

The acceleration of the reaction may be consistent with a radical pathway, cavitation providing energy for homolytic cleavage (Scheme 2). Thus, the possibility that the course of the cycloaddition had now switched from a concerted to one in which a SET process was now prevalent cannot be discarded. We have added methyl viologen to the reaction mixture since this redox indicator is a good electron acceptor[13] and the corresponding ion radical is bright red and can be detected by the naked eye. Addition of this substance under strictly oxygen-free conditions inhibits the formation of *o*-quinone. This might be ascribed to the competing formation of the radical cation from methyl viologen, but no discharge of the red color was observed. Previous formation of *o*-quinone by catechol oxidation, followed by addition of methyl viologen and furan, results in a complex reaction mixture and the formation of an orange color (the background quinone is yellow). It is known that the photolysis of alcohols with DAIB and iodine proceeds via a radical pathway.[14] Recently, sonolysis has emerged as an alternative to photolysis.[15] In our hands, the sonochemical cycloaddition of *o*-quinone with 2,5-dimethylfuran in the presence of DAIB/I_2 had a higher conversion rate (10 min versus 25 min). In principle, a cation radical Diels–Alder reaction should be nonstereospecific. However, Bauld and his coworkers have demonstrated

that these ion radical cycloadditions can be >98% stereospecific, which is consistent with a concerted, but highly non-synchronous mechanism.[16a] Nevertheless, this does not exclude the alternative two-step process involving distonic cation radical intermediates, because such radical cycloadditions are in fact telomerization reactions in which the dimerization process (which would otherwise produce the observed DA cycloadduct) has a much higher rate than the subsequent oligomerizations and, likewise, the second step may be faster than stereorandomizing bond rotations.[16b–d] There are CIDNP studies providing evidence for cation radical intermediates,[17] and Prokof'ev and his associates have also demonstrated the formation of radical pairs and electron transfers from hindered phenols in the presence of an ultrasonic field.[18]



Scheme 2. Alternative mechanisms for cation radical Diels–Alder reactions

In summary, we have shown that *o*-benzoquinones can be generated by ultrasonic irradiation and their [4+2]-cycloadditions with furans are accelerated with respect to thermal reactions. The redox umpolung provided by electron transfers may account for an alternative cation radical pathway, since as has been noted by Bauld, stereospecificity is not a rigorous proof of concertedness. The mild nature of the sonochemical reaction may well prove to be of interest from a synthetic viewpoint. We are currently evaluating the potential energy hypersurface by ab initio methods in order to locate the competing concerted and cation radical transition states, which will allow us to gain insights into these unusual pathways, thereby ascertaining the exact role of sonochemical activation. Such studies are currently under way in this laboratory.

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