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# Thermal and Sonochemical Studies on the Diels−Alder Cycloadditions of Masked *o*-Benzoquinones with Furans: New Insights into the Reaction Mechanism†

Martín Avalos,‡ Reyes Babiano,‡ Noemi Cabello,‡ Pedro Cintas,*,‡ Michael B. Hursthouse,§ José L. Jiménez,‡ Mark E. Light,§ and Juan C. Palacios‡

*Departamento de Química Orgánica, Facultad de Ciencias, University of Extremadura, E-06071 Badajoz, Spain, and Department of Chemistry, The University of Southampton, Highfield, Southampton SO17 1BJ, United Kingdom*

*pecintas@unex.es*

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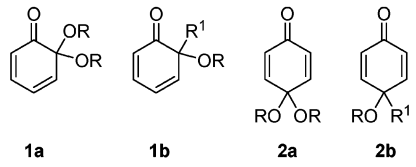
What does a Diels−Alder cycloaddition look like? This question is here addressed in the case of the increasingly significant cycloadditions of masked *o*-benzoquinones (MOBs), which serve as versatile dienes for the construction of complex and functionalized structures. So first, what the mechanism is not: It is not (by and large) a classical, concerted [4 + 2] cycloaddition. Experimental evidence is now supported by sonochemical studies, which were instrumental in elucidating the pathway. Reactions with furans are accelerated and improved under sonication, even when conducted at −10 °C. Variation of the acoustic energy, temperature, and solvent composition allows us to optimize the yields and provide insights into the mechanism. Ultrasound does not cause sonochemical switching, as an alternative radical pathway should be ruled out. Results are consistent with a polar mechanism as claimed recently in a theoretical study. Moreover, this also does justice to a series of seminal papers, largely ignored, that gave a clue to the crucial issue of furan regioselectivity based on a nucleophilic addition. Most effects caused by ultrasonic agitation are of mechanochemical nature and suggest the existence of a perfectly stirred reactor with enhanced mass transfer.

## Introduction and Background

Cyclohexa-2,4-dienones are highly reactive and unstable species that still remain underutilized in synthetic organic chemistry. Their protected derivatives 6,6-dioxacyclohexa-2,4-dienones **1a** (*o*-quinone monoketals) as well as 6-carbo-6-oxacyclohexa-2,4-dienones **1b** (*o*-quinols) can easily be generated by chemical or electrochemical oxidation of phenols and alkyl aryl ethers.[1,2] The enhanced reactivity of *o*-quinone monoketals can at first glance be attributed to their linearly conjugated dienone system, whereas *p*-quinone counterparts (**2a** and **2b**) possess cross-conjugated, yet relatively stable, double bonds (Chart 1).

**CHART 1**




R = alkyl, aryl, acyl
$R^1$= alkoxy, aryloxy, acyloxy, alkyl, aryl

*o*-Quinone monoketals, often referred to as masked *o*-benzoquinones (MOBs), are both electrophilic substrates and reactive dienes exhibiting electronically different double bonds. Notably, the chemical reactivity of these cyclohexa-2,4-dienones can further be fine-tuned by an appropriate choice of substituents at the ketal 6-position and the six-membered ring, which also contribute to prevent their main side reaction, i.e., the rapid dimerization of the conjugated $\pi$-system. In this regard, the ketal group largely stabilizes the masked *o*-quinone and behaves as a regio- and stereodirecting group in both C−C and C-heteroatom bond-forming reactions.[2]

Diels−Alder reactions of *o*-quinone monoketals and *o*-quinols date back from the late 1950s,[3] although considerable attention to this domain has been paid during the past decade.[4] There is a salient dichotomy of the cyclohexa-2,4-dienone moiety, which challenges the mechanistic interpretation of Diels−Alder cycloadditions,

* Corresponding author. Tel: +34-924-289380; Fax: +34-924-271149.

† This work is dedicated to Prof. Jean-Louis Luche, on his retirement, for his pioneering work in sonochemistry, maturing and innovating this discipline, but mostly for his generosity and long-standing friendship.

‡ Departamento de Química Orgánica.

§ Department of Chemistry

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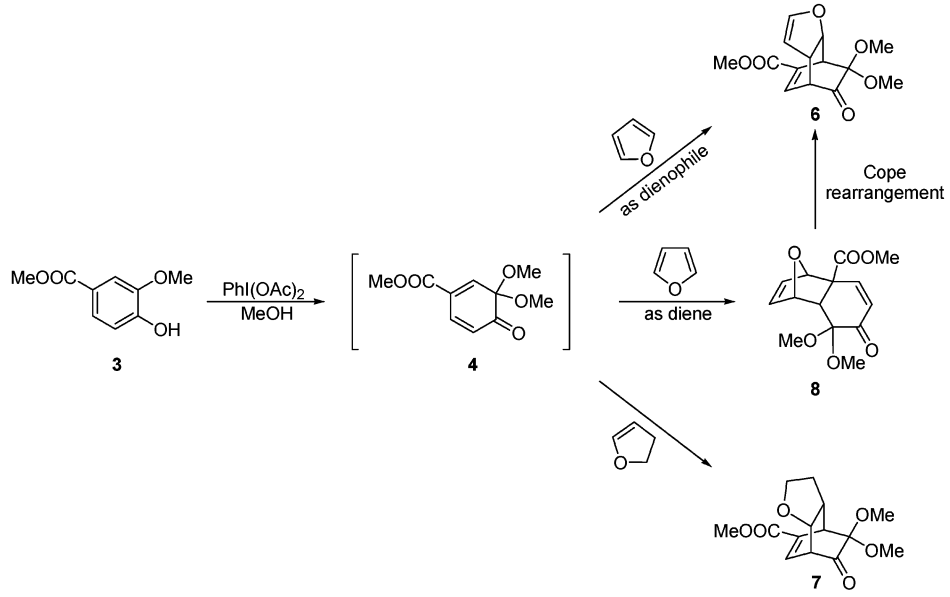
**SCHEME 1**




to react either as diene or dienophile, although the former role is usually prevalent. Dienophilic reactivity has been described toward electron-rich dienes.[5] It is worth mentioning the diene reactivity of MOBs against furans, the latter substances playing their unusual role of 2$\pi$ components. These reactions have been extensively studied by Liao and co-workers, who have demonstrated the great potential of this methodology in the synthesis of highly functionalized bicyclo[2.2.2]octenones.[6] Remarkably, 2,3-dihydrofuran and 3,4-dihydro-2*H*-pyran react in the above-mentioned cycloadditions with opposite regioselectivity (Scheme 1), a fact pointed out by Arjona et al. based on NOE experiments[7] and subsequently confirmed by Liao and his associates with other vinyl ethers and thioethers.[8]

In this context and in an apparently unconnected research, Tamaru and co-workers also found a regiodivergent behavior between furan and 2,3-dihydrofuran in their reactions with some allenesulfonamides, and such results were rationalized by assuming the intermediacy of zwitterionic species rather than via hetero-Diels−Alder reactions.[9]

As correctly pointed out by Liao et al. in their pioneering work,[6a] the formation of bicyclo[2.2.2]octenones could take place via a [4 + 2] cycloaddition, in which furan (**5**) is shifted to its unusual role of dienophile, or through a [2 + 4] cycloaddition, in which furan serves as the 4$\pi$ component to give **8** followed by a Cope rearrangement (Scheme 1). The impossibility of detecting cycloadducts of type **8** ruled out the latter pathway. When these cycloadditions were attempted with pyrrole and thiophene derivatives, in addition to the expected cycloadducts, C-alkylated products resulting from the attack of these heterocycles to the phenolic unit could also be isolated.[10] The latter structures cannot satisfactorily be rationalized by a concerted pathway but rather by a putative nucleophilic addition, because it is well-known that both pyrrole and *N*-alkylpyrroles react with electrophiles to yield the corresponding α-substituted products.[11] Despite these anomalies, it was suggested that Diels−Alder cycloadditions of MOBs should proceed via a concerted asynchronous pathway based on the extremely high endo stereoselection, which was also supported by the identification of transition structures at a modest ab initio level of theory.[8b,10] In a subsequent study at a higher B3LYP/6-31G* level, Domingo and Aurell found that the cycloaddition between 2-methylfuran and a masked *o*-quinone should be occurring by a stepwise mechanism involving

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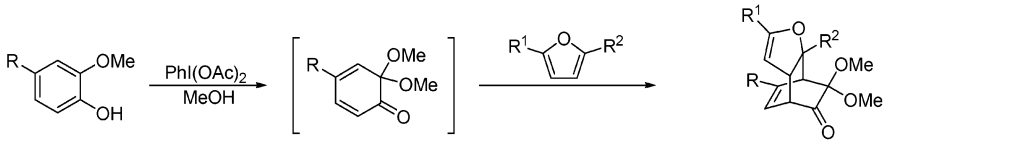
**SCHEME 2**




**3** R = COOMe
**9** R = Me
**10** R = H

**4** R = COOMe
**15** R = Me
**16** R = H

**5** $R^1 = R^2 = H$
**11** $R^1$ = CHO, $R^2 = H$
**12** $R^1$ = COOEt, $R^2 = H$
**13** $R^1$ = COMe, $R^2 = H$
**14** $R^1 = R^2$ = Me

**6** R = COOMe, $R^1 = R^2 = H$
**17** R = COOMe, $R^1$ = CHO, $R^2 = H$
**18** R = COOMe, $R^1$ = COOEt, $R^2 = H$
**19** R = COOMe, $R^1$ = COMe, $R^2 = H$
**20** R = COOMe, $R^1 = R^2$ = Me
**21** R = Me, $R^1 = R^2 = H$
**22** R = $R^1 = R^2 = H$

the nucleophilic attack of the furan ring to the 2,4-dienone system. Inclusion of solvent effects also indicated that methanol appears to stabilize the polar transition state.[12] Still, a theoretical analysis alone does not imply that this reaction follows a stepwise mechanism. Moreover, the marked levels of regio- and stereoselectivities observed for these MOBs are not shared by related systems. Thus, in a chemoenzymatic approach in which *o*-quinones are generated by tyrosinase-mediated oxidation of 2-hydroxy-4-substituted phenols and then reacted with enol ethers, mixtures of bicyclo[2.2.2]octenones with varied selectivity are obtained.[13]

To shed light into this complex scenario, we reasoned that these transformations, and particularly the thermal activation required for completion, could be investigated under milder and controlled conditions in an attempt to detect and isolate, if any, the possible reaction intermediates. Our attention was turned to sonochemical activation, because it is well established that ultrasonic agitation, by virtue of the thermal and pressure effects resulting from cavitation, may ameliorate the results obtained under classical activation.[14] Furthermore, although ultrasonically driven cycloadditions have so far encountered a limited success, the existence of a sonochemical effect has been observed when quinones are used or an oxidizer is present, thereby suggesting the sonochemical formation of some oxidized intermediate from the diene.[15] In our preliminary screening, we did observe that the masked *o*-quinone **4**, generated from methyl 4-hydroxy-3-methoxybenzoate (methyl vanillate, **3**), reacted with several furans under sonication, in an ultrasonic bath, to yield the corresponding cycloadducts in moderate to good yields in shorter reaction times and under milder conditions than under conventional heating.[16] Sonication, however, modifies neither the regioselectivity nor endo stereoselection attained under thermal conditions.[17] The present work complements such previous results exploring in detail the role of sonochemical parameters and solvent effects. Thus, the first aim is to give a series of experimental evidence that consistently support a stepwise nucleophilic mechanism instead of concerted or radical pathways. The second purpose is to show that such results constitute a particular example of the electrophilic reactivity of *o*-quinones that, although might have been anticipated from previous literature, has largely been ignored in this context. Throughout this paper the importance of stepwise cycloadditions, perhaps more frequent than once thought, will be stressed so they can adequately be integrated into synthetic repertories of conjugated dienes.

## Results and Discussion

**Sonochemical versus Thermal Effects.** A direct comparison between thermal and sonochemical reactions requires the existence of similar experimental conditions, especially solvent and temperature control. With this aim, both types of reactions were conducted at room temperature in anhydrous methanol under argon and using a slight excess (1.5 equiv) of the oxidizing agent (diacetoxyiodo)benzene ($PhI(OAc)_2$, DAIB)[18] and a large excess of the furan derivative (10 equiv). Sonochemical reactions were initially performed in a conventional cleaning bath operating at ca. 35 kHz. Transformations were monitored by $^1H$ NMR ($CDCl_3$, 400 MHz) and thin-layer chromatography until complete disappearance of the starting MOB. Experimental results (Scheme 2, Table 1) reveal that sonication consistently provides ameliorated yields in shorter reaction times. Reactions of methyl vanillate (**3**) with furans **5**, **11**, **12**, and **13** yield only the corresponding endo cycloadducts **6**, **17**, **18**, and **19**, respectively, with configuration 1*RS*,2*RS*,6*RS*,7*SR*.[19]

The reaction of **3** with 2,5-dimethylfuran would also afford the endo cycloadduct **20**. However, this substance could not be isolated under thermal conditions, but compound **23** in 36% yield resulting from the addition of

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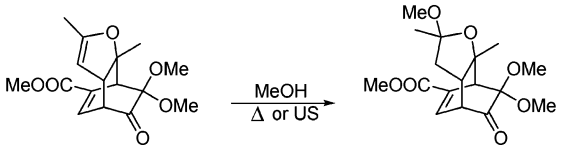
(17) In some cases, sonication may modify the levels of regio- and stereoselection of organic reactions: Luche, J.-L.; Cintas, P. In *Advances in Sonochemistry*; Mason, T. J., Ed.; JAI Press: Greenwich, CT, 1999; Vol. 5, pp 147–174.
(18) For recent reviews on polyvalent iodine compounds, see: (a) Zhdankin, V.; Stang, P. J. *Chem. Rev.* **2002**, *102*, 2523. (b) Varvoglis, A. *Hypervalent Iodine in Organic Synthesis*; Academic Press: San Diego, 1997.
(19) Since these cycloadducts are obtained as racemic mixtures, we have adopted the terminology proposed by Eliel and Wilen for the nomenclature of racemates: Eliel, E. L.; Wilen, S. H. *Stereochemistry of Organic Compounds*; Wiley: New York, 1994; p 119. Sometimes the starred symbols *R**, *S** have also been used for the notation of racemates. This practice may certainly be misleading. For the appropriate use of the starred nomenclature, see the latter reference, pp 119–120 and references therein.

**TABLE 1. Thermal and Sonochemical Reacctions of Compound 3 with Furans at Room Temperature[a]**

| | ultrasonic irradiation[b] | | mechanical agitation | |
|---|---|---|---|---|
| cycloadduct | *T* (min) | yield (%)[c] | *T* (min) | yield (%)[c] |
| 6 | 20 | 52 | 40 | 38 |
| 17 | 45 | 57 | 60 | 40 |
| 18 | 15 | 50 | 70 | 46 |
| 19 | 30 | 53 | 90 | 40 |
| 20 | 25 | 10 | 60 | |
| 23 | 25 | 55 | 60 | 36 |

[a] At 25 ± 5 °C using 1.5 equiv of $PhI(OAc)_2$ and 10 equiv of furan derivative per equiv of phenol. [b] In an ultrasonic bath at 25 ± 5 °C. [c] Yields refer to isolated and chromatograhically homogeneous substances.

**SCHEME 3**




**20** **23**

methanol to the enolic double bond (Scheme 3). Under sonication, by virtue of its accelerating effect, we were able to isolate **20** prior to addition of methanol, in 10% yield, together with **23** in an improved 55% yield. Unlike methyl vanillate, creosol (**9**) and guaiacol (**10**) did not react with furan at room temperature. Harsh conditions (refluxing methanol for several hours) were required to obtain poor yields of the corresponding cycloadducts **21** (8%) and **22** (12%). Unfortunately, no sonochemical improvement could be attained with an ultrasonic bath. In all cases, NMR inspection of the crude mixtures evidenced the formation of a single cycloadduct. As expected, spectroscopic data of the structures isolated under conventional conditions were identical to those of sonicated samples. In a series of cases (cycloadducts **6**,[16] **17**, **22**, and **23**), we were also fortunate to obtain suitable crystals for their unequivocal characterization by X-ray diffraction analyses.[20] Such a structural analysis reveals that an electron-withdrawing substituent at the furan ring (e.g. **17**) does not modify the regiochemical outcome.

The present results suggest that these cycloadditions were extremely sensitive to steric hindrance and only the unsubstituted double bond of the furan ring reacted. It is worth mentioning that an aldehydo group remained unaffected under these oxidizing conditions as compound **17** could easily be isolated without detecting further oxidation of the furan ring. Likewise, cycloadduct **23** had been previously detected,[6a] although its unequivocal stereochemistry could not be assigned. No suitable crystals for X-ray diffractometry could be obtained for **21**, arising from the reaction of creosol with furan. Nevertheless, its spectroscopic data were similar to those of the rest of the cycloadducts, thus suggesting that both the regiochemical and stereochemical patterns were equally preserved.

The diene character of these MOBs has further been tested in the reactions of methyl vanillate (**3**) with vinyl systems,[4a] under both conventional and sonochemical conditions. Scheme 4 and Table 2 summarize the results with vinyl acetate and vinyl benzoate. These processes occurred at room temperature and were regiospecific, although endo/exo mixtures were now obtained. The stereochemistry of cycloadducts **26**, **28**, and **29** could also be determined by single-crystal X-ray diffraction analyses of such substances.[20]

**Sonochemical Reactions: Optimization of External Parameters.** As mentioned before, our preliminary studies using a cleaning bath showed that the sonochemical reactions proceeded faster (by a factor of 2−3) with higher yields (by about 20%) than the corresponding silent reactions.[16] Although such results were fairly reproducible, the use of ultrasonic baths to carry out sonochemical studies is often discouraged, because it is well-known that neither the ultrasonic frequency at which the bath operates nor temperature control can be determined with accuracy. Furthermore, the amount of power dissipated into the reaction from the bath is relatively small, generally less than 5 W/cm$^2$.[21] Our attention was then turned to an ultrasonic probe as the best method of introducing high-power ultrasound into a chemical reaction. In fact, the ultrasonic power delivered by the horn is directly related to the magnitude of vibration of the tip, and this can be controlled by the power input to the transducer. Importantly, input powers larger than 100 W/cm$^2$ are usually obtained.[22] Accordingly, a further reassessment has been achieved on the model cycloaddition of methyl vanillate (**3**) with furan using an ultrasonic probe. This has allowed us to optimize a series of external parameters that largely influence the sonochemical reaction. To obtain a plausible rationale of the sonochemical activation, the following points have been evaluated: (a) the influence of both the temperature and viscosity of the medium on the reaction outcome; (b) the step, if any, sensitive to sonication, i.e., the oxidation of the phenol or the subsequent cycloaddition; and (c) the nature of the sonochemical effect; i.e., is there any activation related to mechanochemistry, or is there any chemical role of sonic waves due to a nonclassical mechanism involving radical species?[23]

**Influence of the Sonochemical Conditions.** The apparatus used for sonication is shown in Figure 1 (see Experimental Section for details), incorporating a unit operating at a frequency of 30 kHz. Reactions have been performed at different temperatures using three energy levels: one just above the cavitational threshold (3.6 W/cm$^2$), a second one at an intermediate value (10.8 W/cm$^2$), and finally at the highest level (17.4 W/cm$^2$) available from the equipment.

Table 3 summarizes the results obtained. The accelerating effect is clearly visible as nonirradiated reactions required prolonged reaction times to get comparable yields. For the highest energy level, the yields are the

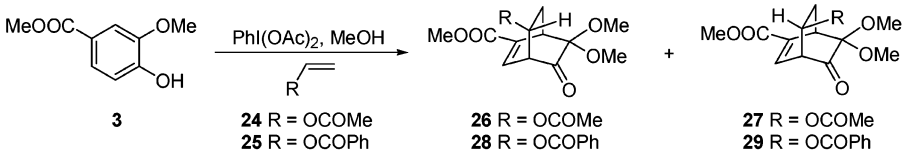
(20) Crystallographic data described in this work have been deposited with the Cambridge Crystallographic Data Centre, for which the following CCDC registry numbers have been assigned: CCDC-140977 (**6**), CCDC-142058 (**17**), CCDC-188164 (**22**), CCDC-146526 (**23**), CCDC-146527 (**26**), CCDC-146525 (**28**), CCDC-146524 (**29**). Such data are available, on request, from the Director, Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK (e-mail: deposit@ccdc.cam.ac.uk).

(21) ref 14d, Chapter 2, pp 65−66.

(22) ref 14d, Chapter 3, pp 90−91.

(23) A part of this study has been presented at an international conference: (a) Cabello, N.; Cintas, P.; Luche, J.-L. *Abstracts of Papers*, 8th Meeting of the European Society of Sonochemistry, Villasimius, Italy, September 2002, pp 85−86. (b) Cabello, N.; Cintas, P.; Luche, J.-L. *Ultrasonics Sonochem*. **2003**, *10*, 25.

**SCHEME 4**




**3** **24** R = OCOMe, **25** R = OCOPh; **26** R = OCOMe, **28** R = OCOPh; **27** R = OCOMe, **29** R = OCOPh

**TABLE 2. Thermal and Sonochemical Reactions of Methyl Vanillate (3) with Vinyl Esters at Room Temperature[a]**

| | ultrasonic irradiation[b] | | | mechanical agitation | | |
|---|---|---|---|---|---|---|
| cycloadduct | *T* (min) | yield (%)[c] | endo/exo[d] | *T* (min) | yield (%)[c] | endo/exo[d] |
| 26 | 50 | 48 | 3/1 | 90 | 42 | 3/1 |
| 27 | | 15 | | | 14 | |
| 28 | 90 | 43 | 3.5/1 | 120 | 33 | 3.5/1 |
| 29 | | 13 | | | 10 | |

[a] At 25 ± 5 °C using 1.5 equiv of $PhI(OAc)_2$ and 10 equiv of vinyl ester. [b] In an ultrasonic bath at 25 ± 5 °C. [c] Isolated yields. [d] Determined by $^1H$ NMR at 400 MHz.

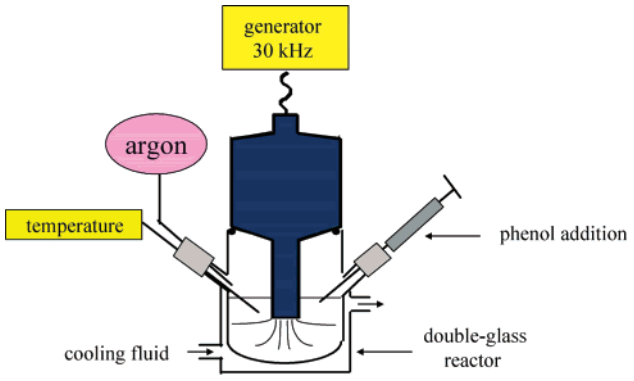



**FIGURE 1.** Temperature-controlled probe reactor for sonochemical reactions.

lowest and remain practically constant as temperature varies. At 10.8 W/cm$^2$ the yields increase slightly, although a modest 50% is the average value. Higher yields are obtained at the lowest irradiation level (3.6 W/cm$^2$), with an important variation as function of temperature, reaching 70% yield at −10 °C.

The existence of a maximum when the temperature decreases reflects the paradoxical effect of this parameter in sonochemical reactions. It is well-established that *a sonochemical reaction can indeed be accelerated by lowering the temperature* because cavitation increases under these conditions. However, this cannot be indefinitely continued as solvent viscosity limits the cavitation of the fluid as well as the propagation of sonic waves.[14b–d]

Solvent effects were then examined, although taking into account that in all cases methanol was necessary to generate the ketal group. Solvent mixtures also exhibit different polarity, which leads to consider the latter parameter. Since the dielectric constant ($\epsilon$) may not reflect solvent polarity with accuracy, we sought a correlation between chemical reactivity and the solvent polarity parameter, $E_T$, based on the transition energy for the longest wavelength solvatochromic absorption band of a betaine dye. Thus, the $E_T$ value for a solvent is simply defined as the transition energy of the dissolved dye measured in kcal/mol. The normalized $E_T$ values have also been recommended using tetramethylsilane ($E_T$ = 0.000) and water ($E_T$ = 1.000) as extreme reference solvents.[24] Accordingly, Table 4 collects both reaction times and yields of cycloadduct **6** as function of some solvent polarity parameters. Irradiations were conducted at 10.8 W/cm$^2$ in a 1:1 (v/v) methanol–cosolvent mixture at −10 °C, a temperature at which solvent viscosity can play an important role during sonochemical activation. The viscosities of the mixtures were calculated graphically and the polarities are referred to the pure cosolvent.

Such results evidence two different behaviors of the reaction media: pure methanol and its mixtures with $CH_3CN$ or $CH_2Cl_2$, on one hand, and mixtures of methanol and ethereal solvents, on the other hand. The best yields are obtained with solvent mixtures of the first class, having the higher polarities and viscosities, while the less polar and viscous ones give rise to poor yields. Two salient conclusions emerge from these experimental data: (a) at the optimal temperature, the rate limitation by diffusion appears to be overcome by cavitational effects, and (b) polarity appears to be a more important parameter than viscosity. The latter effect is appealing as Diels–Alder cycloadditions are seldom sensitive to solvent polarity. One could then envisage a polar mechanism consistent with such observations.

**What is the Sonication-Sensitive Step?** The present cycloadditions of MOBs are sequential reactions involving two well-differentiated stages, i.e., formation of the *o*-quinone fragment from a phenolic precursor and the subsequent trapping by a reactive dienophile. One should first determine if cavitation is actually playing any role on the first, second, or both steps. Therefore, oxidation experiments have been carried out in the absence of furan. A methanolic solution of methyl vanillate was reacted with DAIB at 5 °C. The unreactive oxidizer was then quenched with $NaBH_4$, 1 and 5 min after the end of the addition, and the remaining phenol was isolated. It should be mentioned that reduction of quinones by $NaBH_4$ does not regenerate the phenol but provides boron-containing derivatives.[25] After 1-min reaction, the starting vanillate was recovered in 20% yield from the sonicated experiment and in 35% under magnetic stirring. After 5 min, however, both the sonicated and nonsonicated reactions gave similar results (ca. 5–8% recovery). Thus, it appears that sonication has little or no effect on the first step, which is much faster than the cycloaddition with furan, the step actually sensitive to cavitational effects.

**Mechanistic Pathway.** As noted earlier, most sonochemical cycloadditions have encountered a limited success, and even under such circumstances, the role exerted

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**TABLE 3. Cycloadditions of Methyl Vanillate (3) and Furan (5) as Function of Temperature and Acoustic Energy**

| | 0 W/cm$^2$ | | 3.6 W/cm$^2$ | | 10.8 W/cm$^2$ | | 17.4 W/cm$^2$ | |
|---|---|---|---|---|---|---|---|---|
| temp (°C) | *T* (min) | yield (%) | *T* (min) | yield (%) | *T* (min) | yield (%) | *T* (min) | yield (%) |
| 20 | 40 | 38 | 20 | 44 | 15 | 50 | 15 | 49 |
| 10 | | *a* | | *a* | 50 | 53 | 35 | 51 |
| 0 | 90 | 42 | 35 | 46 | 60 | 46 | 45 | 48 |
| −10 | 120 | 48 | 50 | 70 | 35 | 57 | 25 | 48 |
| −20 | 330 | 56 | 150 | 60 | | *b* | | *b* |

[a] No experiment conducted at this temperature. [b] At high-energy values, thermal control at −20 °C could not be obtained.

**TABLE 4. Sonochemical Reactions of 3 and 5 in Different Methanol−Cosolvent Mixtures[a]**

| property | $CH_3CN$ | $CH_3OH$[b] | $CH_2Cl_2$ | $Et_2O$ | $(MeO)_2CH_2$ |
|---|---|---|---|---|---|
| dipole moment (20 °C, D) | 3.44 | 2.87 | 1.60 | 1.15 | 0.74 |
| dielectric constant (25 °C) | 35.94 | 32.66 | 8.93 | 4.20 | |
| $E_T$ (kcal/mol) | 45.6 | 55.4 | 40.7 | 34.5 | 35.8 |
| $E_T$ (normalized) | 0.46 | 0.76 | 0.31 | 0.12 | 0.16 |
| viscosity (-10 °C, cp) | 0.80 | 1.00 | 0.85 | 0.65 | 0.76 |
| yield of 6 (%) | 53 | 46 | 40 | 11 | 12 |
| time (min) | 100 | 70 | 120 | 180 | 240 |

[a] Reactions were irradiated with an ultrasonic probe (10.8 W/cm$^2$) at −10 °C. [b] Pure methanol.

by cavitation cannot yet be precisely defined. According to the widely accepted hot spot theory, the cavitational collapse causes solvent pyrolysis as well as ionization and/or homolytic cleavage of the reaction partners,[26] thereby releasing enough kinetic energy that drives the chemical reaction. This high-energy microenvironment also leads to jet formation and strong shock waves, which propagate into the liquid surrounding the bubble.[27]

If there were activation of a concerted cycloaddition by cavitation, both reagents would be present inside the hot spot. In practice, however, their vaporization will occur differently, as dienes and dienophiles often possess different vapor pressures and solubility. Still, a sonochemical effect may actually be occurring without involving the simultaneous vaporization of both substrates. Thus, activation of only one of the reagents as a radical or radical cation would give rise to a SET mechanism taking place in the bulk solution. The use of radical holes as pioneered by Bauld and his associates has clearly evidenced the existence of such radical cycloadditions.[28−30] The original radical cations can enter uncontrollable polymerization reactions next to the desired cycloaddition, a feature limiting the preparative scope of radical-type cycloadditions. Luckily, oligomerization and polymerization reactions have usually lower rates than the dimerization step, which is reminiscent of a Diels−Alder reaction. The acceleration under ultrasound might then be consistent with a fast chain reaction, cavitation providing energy for homolytic cleavage.

A crucial question, however, to be answered is which component of the solution is actually undergoing electron transfer. Keeping in mind the differences between electrochemistry and sonochemistry, the former gives a few clues, nevertheless. Radical nuclear substitutions of aromatic hydrocarbons indicate that these substances are more easily oxidized than acetate ion. From voltammetric data, it is now generally accepted that most oxidations of aromatic hydrocarbons involve removal of one electron from the hydrocarbon to afford a radical cation. The reactions following generation of the radical cation can sometimes be complex. Phenol radical cations, however, readily undergo proton loss (in fact, they are strong acids with p*K* values of ca. −5).[31] Moreover, radical oxidations induced photochemically suggest the formation of alkoxy radicals when DAIB and alcohols are photolyzed.[32] Further studies claim that sonolysis of such substrates also lead to alkoxy radicals.[33] Japanese authors have, however, highlighted the important differences between sonolysis and photolysis. Under ultrasound, the various reaction paths available to radical cations tend to favor the coupling and dimerization.[34] In addition, radical pathways involving solvent fragmentation under sonication have recently been presented.[35] With these premises, the possibility of alternative radical ion mechanisms as depicted in Scheme 5 has been suggested without conclusive evidences.[16,36]

In this regard, sonochemical cycloadditions with quinones seem to be noticeable, as they could evidence the existence of nonconcerted mechanisms. It has been demonstrated that a radical pathway is not involved when anthracene and maleic anhydride are sonicated. When *p*-benzoquinone is used as dienophile, ultrasonic irradiation improves the yield, yet modest, at room temperature, compared with the same process in hot toluene. Addition of tris(4-bromophenyl)aminium hexachloroantimoniate (TBPA) largely enhances the yield, even

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(29) Whereas radical cation chain cycloadditions are well-documented, radical anion chain cycloadditions have been reported only in a few recent reports. See, for instance: Roh, Y.; Jang, H.-Y.; Lynch, V.; Bauld, N. L.; Krische, M. J. *Org. Lett*. **2002**, *4*, 611.
(30) For theoretical studies, see: (a) Bauld, N. L. *J. Am. Chem. Soc.* **1992**, *114*, 5800. (b) Haberl, U.; Wiest, O.; Steckhan, E. *J. Am. Chem. Soc.* **1999**, *121*, 6730.
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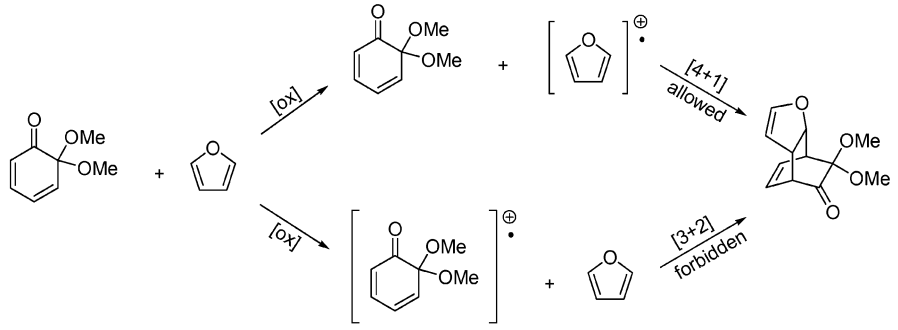
(33) Costa, S. C. P.; Miranda Moreno, M. J. S.; Sá e Melo, M. L.; Campos Neves, A. S. *Tetrahedron Lett*. **1999**, *40*, 8711.
(34) (a) Kimura, T.; Fujita, M.; Sohmiya, H.; Ando, T. *J. Org. Chem*. **1998**, *63*, 6719. (b) Kimura, T.; Fujita, M.; Ando, T. *Ultrasonics Sonochem*. **1999**, *6*, 93.
(35) (a) Ando, T.; Kimura, T.; Fujita, M.; Levêque, J.-M.; Luche, J.-L. *Tetrahedron Lett*. **2001**, *42*, 6865. (b) Kimura, T.; Harada, H.; Ando, T.; Fujita, M.; Levêque, J.-M.; Luche, J.-L. *Chem. Commun*. **2002**, 1174.
(36) Low, C. M. R. In *Current Trends in Sonochemistry*; Price, G. J., Ed.; Royal Society of Chemistry: Cambridge, 1992; pp 59−86.

**SCHEME 5**




at −50 °C, a fact that could point to the formation of the anthracene radical cation.[37]

However, when sonication of **3** and furan (at 10.8 W/cm$^2$ and −10 °C) is conducted in methanol under an oxygen atmosphere, the cycloadduct **6** was obtained in 43% yield, whereas this process under argon gave rise to a similar 46% yield. In a mixture of methanol−diethyl ether, using commercially available, undistilled ether (containing peroxides or radical inhibitors), no adduct was observed. The use of purified ether as cosolvent increased the yield up to 10% only. Therefore, the observation of such weak effects would hardly support an unambiguous radical pathway.

In the present model, the generation of a radical cation derived from the masked *o*-quinone appears to be improbable, due to the oxidizing properties of quinones and their lower vapor pressures. Furan could easily be vaporized, owing to its greater volatility (bp 32 °C), capable of penetrating into the microbubbles. In fact, radical cations derived from furan and other five-membered heterocycles have been obtained by pulsed electron ionization and their dimerization reactions studied. Such reactions, involving either the cation or radical cation from furan, with a furan neutral molecule were interpreted as Diels−Alder-type condensation reactions.[38] If the furan radical cation were indeed formed, it could be released into the bulk solution and further react with the *o*-quinone by the allowed [4 + 1] mechanism.[39] Nevertheless, pyrolysis can also favor ring cleavage,[40] thereby leading to sterile results.

A radical mechanism would then be sensitive to electron acceptors and trapping agents. Introduction of TBPA has become widely used as a method of initiation of radical cation reactions (Chart 2).[28] TBPA, however, restricts its effectiveness as an initiator to substrates that have oxidation potentials in the range 1.3−1.7 V (versus SCE).[41,42] Attempts to induce radical-cation-initiated cycloadditions failed, as no appreciable effect on the yield could be observed. Trapping experiments with the solid free radical 2,2-diphenyl-1-picrylhydrazyl (DPPH)[43] furnished cycloadduct **6** in 28% yield, although a complete inhibition could not be observed either. To avoid misinterpretations due to competing oxidations, control experiments evidenced that oxidations of methyl vanillate, furan, and methanol by DPPH were almost negligible under the reaction conditions. Finally, addition of 1,3-dinitrobenzene (MDNB) was also tested. Sonication of methyl vanillate and furan, at 10.8 W/cm$^2$ and −7 °C, in the presence of such an electron acceptor, gave a significantly reduced chemical yield (13% versus 45% in the absence of MDNB, Table 5). However, MDNB would disfavor the [4 + 1] pathway.[28a]

Still, the latter results do not suggest definitive conclusions, since the oxidizer, used in excess in the preparation of the masked quinone, could interfere in the cycloaddition step. Next, experiments were then conducted with the masked *o*-quinone derived from creosol (**15**), because it is stable enough to be isolated. Unfortunately, compound **15** reacted sluggishly with furan at reflux to give a modest 8% yield of the corresponding cycloadduct. The same result was obtained in the presence of MDNB (20

**CHART 2**

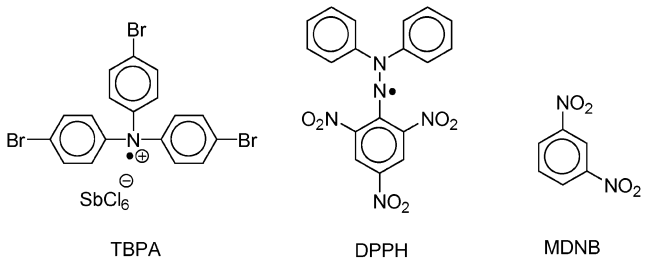



**TABLE 5. Cycloadditions of 3 and 5 in the Presence of Radical Initiators or Inhibitors**[a]

| additive[b] | temp (°C) | yield (6, %)[c] | *T* (min) |
|---|---|---|---|
| Ar | −10 ± 1 | 46 | 70 |
| $O_2$ | −8 ± 1 | 43 | 70 |
| DPPH(5%) | −7 ± 1 | 28 (45) | 60 |
| MDNB (20%) | −7 ± 1 | 13 (45) | 60 |
| TBPA (15%) | −7 ± 1 | 55 (46) | 60 |

[a] Conducted with an ultrasonic probe (10.8 W/cm$^2$). [b] Equivalents with respect to methyl vanillate. [c] Isolated yields, although the reaction with DPPH was messy and could not be completely purified. Yields in parentheses denote absence of the inhibitor or initiator.

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(42) Yueh, W.; Bauld, N. L. *J. Chem. Soc., Perkin Trans. 2* **1995**, 871.

(43) Mizukoshi, Y.; Nakamura, H.; Bandow, H.; Maeda, Y.; Nagata, Y. *Ultrasonics Sonochem.* **1999**, *6*, 203.

**TABLE 6. Thermal and Sonochemical Cycloadditions of Furan and 2,5-Dimethylfuran with Methyl Vanillate**

| | nonirradiated | | |
|---|---|---|---|
| dienophile | thermal[a] | rt[b] | sonochemically |
| furan ($E_0 = 1.7$ V) | 50 °C, 40 min (80%) | rt, 40 min (40%) | rt, 20 min (52%) |
| 2,5-diMeFuran ($E_0 = 1.2$ V)[c] | 50 °C, 50 min, reflux, 5 h (81%) | rt, 60 min (40%) | rt, 25 min (55%) |

[a] Reference 6a. [b] This work and ref 16. [c] Product isolated resulted from the addition of methanol to the enol ether moiety.

mol %) under the same reaction conditions. No improvement was observed with $(NH_4)_2Ce(NO_3)_6$ (CAN, 20 mol %) or $FeCl_3$ (5 mol %), with or without sonication. It is reported that Ce(IV) salts oxidize 2,3-dihydrofuran to its radical cation.[44]

In a further experiment, the cycloaddition of **15** with furan was conducted in methanol in the presence of TBPA (15 mol %). Under such conditions, however, the rapid dimerization of the masked *o*-quinone was observed, even at room temperature. After 30 min, the resulting dimer was exclusively detected by NMR monitoring without a trace of the starting *o*-quinone monoketal. Although TBPA can be used in the presence of alcohols,[28a] methanol could be detrimental, as nucleophiles also react with radical cations.[45] Nevertheless, a parallel reaction run in $CH_2Cl_2$ (TBPA: 15 mol %, rt, 30 min), also led to dimerization and no cycloadduct was detected either.

Assuming that furan is the only oxidizable component (and otherwise capable of penetrating into the microbubble) and the fact that [4 + 1] cycloadditions are fast processes, even at very low temperatures,[28] the cycloaddition should be independent of the MOB involved. This is not actually observed, which renders the [4 + 1] pathway improbable. In fact, 2,5-dimethylfuran would react more easily than furan, due to a lower oxidation potential.[46] The opposite is observed, although steric hindrance with respect to unsubstituted furan should also be important. The sonochemical process still offers a good advantage (Table 6).

With the above premises, a radical or radical-cation mechanism seems unlikely, even though previous results involving quinones suggest a relationship between the participation of radical ions and the sonochemical effect observed.[15,37] Alternative hypotheses have also suggested the existence of Diels−Alder cycloadditions involving charge-transfer complexes, but a complete electron transfer has been questioned.[47]

But a classical concerted mechanism also casts doubt, especially regarding the regioselectivity observed and the dienophilic role of furans. Sonochemical studies also reveal solvent effects, and the simultaneous vaporization of both substrates inside the microbubbles is unlikely. Computational studies give different conclusions depending on the theory chosen, and only a relatively high DFT level now suggests the possibility of zwitterionic intermediates, ruling out the Cope rearrangement as an alternative pathway.[12]

A crucial problem in this puzzle is that some seminal papers evidencing this "anomalous" behavior of furan derivatives have long been ignored, demonstrating again that "the original literature is never obsolete".[48] Thus, in the early 1960s, Eugster and Bosshard were probably the first in proposing a zwitterionic intermediate for the addition of furan to 2-acetyl-1,4-benzoquinone.[49] Gorgues et al. further studied the reactivity of α-alkynyl aldehydes toward furan, 2-methylfuran, and cyclopentadiene. With furan, under neutral conditions, the Diels−Alder cycloadduct was obtained, while acidic conditions afforded a Michael-type adduct.[50] Remarkably, these authors did not suggest two alternative mechanisms but a unique polar intermediate evolving into different products depending on the reaction conditions.

Keeping in mind the scheme of Eugster and Bosshard, it could reasonably be adapted to MOB cycloadditions. Thus, two sequential Michael-type additions, in which furan serves as nucleophile rather than dienophile, would give rise to what can be seen as a Diels−Alder cycloadduct (Scheme 6).

Such a scheme offers a series of interesting pluses: (a) it fully accounts for the observed regioselectivity, (b) the sequential mechanism is consistent with solvent effects as evidenced by our sonochemical findings, and (c) the yield depletion observed with certain electron acceptors (e.g. MDNB) can be explained, as these substances will be able to oxidize the polar intermediate. It is interesting to note that some side, once thought anomalous, products were formed in the cycloadditions with nitrogen and sulfur-containing five-membered heterocycles.[10] Solvent polarity seems to play a definitive role in stabilizing the zwitterionic intermediate, although from the viewpoint of the cavitational collapse, other solvent parameters should also be evaluated. In a study of the [$(2\sigma + 2\pi) + 2\pi$] cycloaddition between homofuran and tetracyanoethylene, Herges and Ugi found that in a low-polarity solvent, the Diels−Alder cycloadduct was the exclusive product. On increasing the medium polarity, the cycloadduct yield decreased at the expenses of an addition product formed through a polar intermediate.[51]

A further insight into the Michael-type pathway comes from Lewis acid catalysis. Thus, Cu(II) triflate often accelerates the Michael reactions of ketones with furan, but it has little or no effect on Diels−Alder cycloadditions.[52] In our hands, the reaction of methyl vanillate and furan in the presence of DAIB and Cu(II) triflate (5 mol %) took place at room temperature to afford the corresponding cycloadduct (**6**) in 55% yield within 40 min. Only a 38% yield was obtained without triflate within the same period. Ultrasonic irradiation (10.8 W/cm$^2$) also improved the yield with Cu(II) triflate, even at −10 °C: 70% in 50 min versus 45% in 70 min without this

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(48) The late Jerry March is to be congratulated on this wise aphorism. See: March, J. *Advanced Organic Chemistry*, 4th ed.; Wiley: New York, 1992; p 1240.
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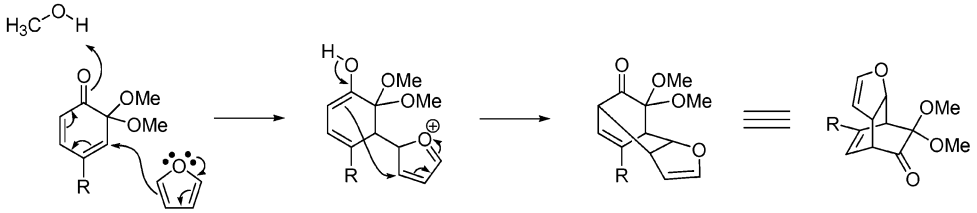
**SCHEME 6**



additive. Notably, addition of a well-established Diels–Alder reaction catalyst, lithium perchlorate,[53] gave rise to a significant decomposition, and no cycloadduct could be isolated under such conditions.

**Is There Any Sonochemical Effect?** Sonochemists have learned that sonication may indeed accelerate and/or favor SET processes, under both homogeneous and heterogeneous conditions, whereas no chemical effect should be observed on polar mechanisms (false sonochemistry).[54] However, heterogeneous ionic reactions benefit from the mechanical effects of sound waves such as emulsion, erosion, and shock waves at or near the surface. In any event, a mixing effect has often been neglected for homogeneous sonochemical reactions. Alternative interpretations to justify accelerations and other effects have claimed the existence of supercritical conditions generated after bubble collapse, but this possibility appears to be improbable based on recent experiments.[55]

The mechanical effect should be invoked here in connection with the in situ generation of the masked *o*-quinone. At each point of impact of the oxidizer added, the *o*-quinone concentration is higher than in the bulk solution and dimerization rapidly occurs, which is otherwise responsible of the moderate yields usually attained in MOB cycloadditions. The competing dimerization can easily be monitored by UV/vis spectroscopy due to a characteristic peak at ~230 nm observed in methanol solution. In a separate experiment using a 5 times more concentrated solution of methyl vanillate in the absence of furan, dimerization took place in about 10 min (with respect to 50 min in dilute solution). Accordingly, sonication facilitates the almost immediate dispersion of the MOB. At least for discrete volumes, a high-frequency sonochemical reactor behaves like an ideal flow system that induces a perfect mixing in the whole volume and no mechanical stirring has to be added. This behavior can be associated with the existence of ultrasonically induced phenomena such as an acoustic fountain and convective currents occurring within the reactor.[56] Thus, acoustic agitation avoids local supersaturation of reagents, even though in some cases viscosity can counterbalance the effective propagation of ultrasound. Yields and rates are enhanced by sonication because dimerization is disfavored and the probability of interaction between the *o*-quinone and furan increases. The micromixing effect in homogeneous reactions has equally been invoked to rationalize the sonophotopinacolization of benzophenone[57] or the greatly diminished Würtz homocoupling in sonochemical Barbier reactions.[58]

To sum up, our experimental results show that the mechanism of the cycloadditions of MOBs with furans and other heterocycles is presumably a stepwise double Michael reaction. In addition, a radical pathway is apparently not involved. Sonochemical activation opens a new avenue of investigation regarding the mechanistic pathway by virtue of the physical phenomena associated with cavitation and the influence exerted by the latter on solvent properties and vaporization of substrates inside the bubble. Therefore, the present results seem to point in the direction of a revision of classical concerted cycloadditions involving reaction partners with different redox potentials and volatilities, as they could be sensitive to the chemical and/or mechanical effects provided by ultrasound.

## Experimental Section

**General Methods.** Solvents were dried and distilled prior to use following standard procedures. Furan, 2-furaldehyde, 2-acetylfuran, and 2,5-dimethylfuran were stored under argon. Other reagents were obtained from commercial suppliers and used without further purification. All the reactions were conducted under an argon atmosphere unless otherwise specified. Reactions were monitored by thin-layer chromatography on silica gel plates ($GF_{254}$) using UV light at 254 and 360 nm, iodine vapors, and a 10% ethanolic solution of phosphomolybdic acid as developing agents. Flash chromatography[59] was performed using 230–400 mesh silica gel. Melting points were measured on a capillary apparatus and are uncorrected. IR spectra were recorded as films on NaCl plates or as KBr pellets. $^1$H and $^{13}$C NMR spectra were recorded at 400 and 100 MHz, respectively, in $CDCl_3$ and using TMS ($\delta = 0.00$ ppm) as the internal reference. Ultrasound-induced reactions have been performed at ESIGEC, Université de Savoie, Le Bourget du Lac, France. Mass spectra were performed at the Servicio de Espectrometría de Masas of the University of Córdoba, Spain. Elemental analyses were measured at the Departamento de Química Orgánica of the University of Extremadura, Spain. X-ray diffraction analyses have been obtained at the Department of Chemistry, University of Southampton, UK.

**Sonochemical Reactions.** Sonications were carried out at a constant frequency of 30 kHz with a horn of end diameter 9

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mm. The reaction vessel is a three-necked, round-bottomed, jacketed reactor. Sampling of the reaction mixture is accomplished through a rubber septum with a syringe. The reaction temperature is controlled by circulation of water or ethylene glycol through an external thermostated jacket, and the temperature is measured by a thermocouple dipped in the reaction itself. All sonications were conducted under argon, except when an atmosphere of oxygen was deliberatively employed, using anhydrous solvents. Reactions have been performed at different temperatures using three energy levels: 3.6, 10.8, and 17.4 W/cm$^2$.

**Thermal Reactions. General Procedure.** To a solution of DAIB (0.3 g, 0.9 mmol) in anhydrous methanol at room temperature under argon was dropwise added the furan derivative (6.0 mmol). To this mixture, a solution of methyl vanillate (0.11 g, 0.6 mmol) in anhydrous methanol (5 mL) was slowly added over 10 min with stirring. The transformation was monitored by thin-layer chromatography until the complete disappearance of the *o*-quinone monoketal. Then, the reaction mixture was evaporated and the residue was purified by flash chromatography (the corresponding eluent is specified in each case). The following compounds not reported earlier have been obtained according to the above thermal and sonochemical protocols.

**Methyl (1*RS*,2*RS*,6*RS*,7*SR*)-4-Formyl-10,10-dimethoxy-3-oxa-11-oxotricyclo[5.2.2.0$^{2,6}$]undec-4,8-dien-9-carboxylate (17)** was purified by flash chromatography using a gradient of ethyl acetate−petroleum ether (1:2) and finally ethyl acetate−petroleum ether (1:1): mp 153−155 °C (from diethyl ether); IR (KBr) 3111, 2953, 2857,1748, 1711, 1700, 1624, 1437, 1239, 1045 cm$^{-1}$; $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 9.33 (s, 1H), 7.12 (dd, $J$ = 2.0, 6.7 Hz, 1H), 5.80 (d, $J$ = 2.8 Hz, 1H), 5.41 (dd, $J$ = 3.9, 9.5 Hz, 1H), 4.41 (dd, $J$ = 2.0, 3.9 Hz, 1H), 3.79 (s, 3H) 3.73 (dt, $J$ = 2.8, 9.5 Hz, 1H), 3.50 (dt, $J$ = 2.8, 6.7 Hz, 1H), 3.39 (s, 3H), 3.35 (s, 3H); $^{13}$C NMR (100 MHz, $CDCl_3$) 198.1, 181.0, 163.6, 157.8, 135.9, 134.4, 117.9, 92.9, 80.9, 52.2, 51.8, 50.5, 50.1, 45.7, 43.2. Anal. Calcd for $C_{15}H_{16}O_7$: C, 58.44; H, 5.23. Found: C, 58.19, H: 5.18.

**Methyl (1*RS*,2*RS*,6*RS*,7*SR*)-10,10-dimethoxy-3-oxa-11-oxotricyclo[5.2.2.0$^{2,6}$]undec-4,8-diene-4-ethoxycarbonyl-9-carboxylate (18):** mp 106−108 °C (from diethyl ether−petroleum ether); IR (KBr) 2972, 2845,1720, 1710, 1643, 1439, 1377, 1250, 1050 cm$^{-1}$; $^1$H NMR ($CDCl_3$, 400 MHz) $\delta$ 7.14 (dd, $J$ = 1.6, 6.6 Hz, 1H), 5.70 (d, $J$ = 2.5 Hz, 1H), 5.36 (dd, $J$ = 4.0, 9.6 Hz, 1H), 4.40 (dd, $J$ = 1.6, 4.0 Hz, 1H), 4.22 (q, $J$ = 7.0 Hz, 2H), 3.80 (s, 3H), 3.64 (dt, $J$ = 2.5, 9.6 Hz, 1H), 3.44 (dd, $J$ = 2.5, 6.6 Hz, 1H), 3.38 (s, 3H), 3.34 (s, 3H), 1.30 (t, $J$ = 7.0 Hz, 3H); $^{13}$C NMR ($CDCl_3$, 100 MHz) 198.6, 163.9, 159.3, 150.5, 136.4, 134.2, 109.9, 93.0, 80.7, 61.4, 52.3, 52.2, 50.5, 50.2, 45.9, 43.3, 14.0. Anal. Calcd for $C_{17}H_{20}O_8$; C, 57.95; H, 5.72. Found: C, 57.49; H, 5.78.

**Methyl (1*RS*,2*RS*,6*RS*,7*SR*)-4-acetyl-10,10-dimethoxy-3-oxa-11-oxotricyclo[5.2.2.0$^{2,6}$] undec-4,8-diene-9-carboxylate (19)** was purified by flash chromatography using diethyl ether−petroleum ether (1:1) as eluent: IR (film) 2930, 2355, 1737, 1441, 1254, 1051; $^1$H NMR ($CDCl_3$, 400 MHz) $\delta$ 7.11 (dd, $J$ = 2.0, 6.8 Hz, 1H), 5.66 (d, $J$ = 2.9 Hz, 1H), 5.36 (dd, $J$ = 3.9, 9.6 Hz, 1H), 4.40 (dd, $J$ = 2.0, 3.9 Hz, 1H), 3.80 (s, 3H), 3.68 (dt, $J$ = 2.6, 9.6 Hz, 1H), 3.45 (dd, $J$ = 2.6, 6.8 Hz, 1H), 3.39 (s, 3H), 3.35 (s, 3H), 2.21 (s, 3H). $^{13}$C NMR ($CDCl_3$, 100 MHz) 198.6, 190.2, 163.9, 156.8, 136.3, 134.2, 109.4, 93.0, 80.4, 52.2, 50.5, 50.2, 46.1, 43.4, 26.7; HRMS (EI) *m*/*z* (relative intensity, %) 294 ($M^+$ − CO, 32); calcd for $C_{15}H_{18}O_6$ ($M^+$ − CO) 294.1103, found 294.1107.

**Methyl (1*RS*,2*RS*,6*RS*,7*SR*)-10,10-dimethoxy-2,4-dimethyl-3-oxa-11-oxotricyclo[5.2.2.0$^{2,6}$]undec-4,8-diene-9-carboxylate (20)** could only be obtained under ultrasonic irradiation and was isolated as an unstable colorless oil after chromatographic purification using ethyl acetate−petroleum ether (1:2): $^1$H NMR ($CDCl_3$, 400 MHz) $\delta$ 7.04, (dd, $J$ = 1.3, 6.4 Hz, 1H), 4.43 (d, $J$ = 2,0 Hz, 1H), 4.03 (d, $J$ = 1.3 Hz, 1H), 3.81 (s, 3H), 3.40 (s, 3H), 3.24 (s, 3H), 3.23 (m, 1H), 2.92 (d, $J$ = 2.0 Hz, 1H), 1.62 (s, 3H), 1.61 (s, 3H); $^{13}$C NMR ($CDCl_3$, 100 MHz) 201.1, 164.5, 156.2, 136.1, 134.7, 95.6, 94.4, 87.5, 53.6, 53.3, 52.0, 50.3, 49.5, 48.1, 24.3, 13.3.

**(1*RS*,2*RS*,6*RS*,7*SR*)-10,10-Dimethoxy-9-methyl-3-oxatricyclo[5.2.2.0$^{2,6}$]undec-4,8-dien-11-one (21)** was purified by flash chromatography using diethyl ether−petroleum ether (1:2) as eluent: IR (film) 2963, 2839,1735, 1616, 1443, 1231, 1136, 1067 cm$^{-1}$; $^1$H NMR ($CDCl_3$, 400 MHz) $\delta$ 6.23 (t, $J$ = 2.4 Hz, 1H), 5.70 (dd, $J$ = 2.1, 6.6 Hz, 1H), 5.07 (dd, $J$ = 3.9, 9.5 Hz, 1H), 4.69 (t, $J$ = 2.4 Hz, 1H), 3.45 (dd, $J$ = 2.1, 3.9 Hz, 1H), 3.39−3.37 (m, 1H), 3.37 (s 3H), 3.35 (s, 3H), 3.03 (dd, $J$ = 2.4, 6.6 Hz, 1H), 1.91 (d, 3H, $J$ = 1.5 Hz); $^{13}$C NMR ($CDCl_3$, 100 MHz) 201.3, 147.8, 140.6, 118.6, 100.3 (C-5), 94.0 (C-10), 79.8 (C-2), 51.6 (C-7), 50.3 ($CH_3O$), 50.2 ($CH_3O$), 48.3, 44.3, 22.7; HRMS (EI) *m*/*z* (relative intensity) 236 ($M^+$,4), 208 ($M^+$ − CO, 100); calcd for $C_{13}H_{16}O_4$ ($M^+$) 236.1049, found 236.1032.

**(1*RS*,2*RS*,6*RS*,7*SR*)-10,10-Dimethoxy-3-oxatricyclo-[5.2.2.0$^{2,6}$]undec-4,8-dien-11-one (22)** was purified by flash chromatography using ethyl acetate−petroleum ether (1:4) as eluent: mp 77−78 °C; IR (film) 2965, 2835, 1738, 1616, 1462, 1230, 1138, 1065; $^1$H NMR ($CDCl_3$, 400 MHz) $\delta$ 6.27−6.23 (m, 2H), 6.15 (t, $J$ = 6.6 Hz, 1H), 5.10 (dd, $J$ = 3.8, 9.6 Hz, 1H), 4.73 (t, $J$ = 2.3 Hz, 1H), 3.67 (t, $J$ = 4.5 Hz, 1H), 3.45 (dd, $J$ = 2.0, 9.6 Hz, 1H), 3.37 (s, 3H), 3.34 (s, 3H), 3.17 (dt, $J$ = 2.0, 6.6 Hz, 1H); $^{13}$C NMR ($CDCl_3$, 100 MHz) 201.1, 147.8, 130.3, 127.7, 100.3, 93.8, 79.7, 52.0, 50.2, 50.0, 45.0, 43.4. HRMS (EI) *m*/*z* (relative intensity) 194 ($M^+$ − CO, 100); calcd for $C_{11}H_{14}O_3$ ($M^+$ − CO) 194.0943, found 194.0939.

**Methyl (1*RS*,4*RS*,7*RS*)-7-O-benzoyl-3,3-dimethoxy-2-oxobicyclo[2.2.2]oct-5-ene-5-carboxylate (28):** mp 103−104 °C (from petroleum ether); IR (KBr) 3060, 2925, 2830, 1740, 1710, 1700, 1615, 1440, 1260, 1050 cm$^{-1}$; $^1$H NMR ($CDCl_3$, 400 MHz) $\delta$ 7.95 (d, $J$ = 7.7 Hz, 2H), 7.57 (t, $J$ = 7.4 Hz, 1H), 7.43 (t, $J$ = 7.7 Hz, 2H), 7.14 (dd, $J$ = 1.2, 6.4 Hz, 1H), 5.56 (dt, $J$ = 3.2, 8.4 Hz, 1H), 3.85 (s, 3H), 3.83−3.81 (m, 2H), 3.37 (s, 3H), 3.33 (s, 3H), 2.81 (ddd, $J$ = 2.7, 8.4, 14.2 Hz, 1H), 1.55 (dt, $J$ = 3.2, 14.2 Hz, 1H); $^{13}$C NMR ($CDCl_3$, 100 MHz) 198.1, 165.5, 164.1, 138.4, 134.3, 133.3, 129.6, 129.6, 129.5, 128.4, 92.8, 69.3, 54.7, 52.2, 50.3, 50.1, 37.7, 30.2. Anal. Calcd for $C_{19}H_{20}O_7$: C, 63.33; H, 5.59. Found: C, 62.90; H, 5.59.

**Methyl (1*RS*,4*RS*,7*SR*)-7-O-benzoyl-3,3-dimethoxy-2-oxobicyclo[2.2.2]oct-5-ene-5-carboxylate (29):** mp 147−148 °C (from petroleum ether); IR (KBr) 3060, 3040, 2925, 2820, 1720, 1710, 1620, 1430, 1250, 1050 cm$^{-1}$; $^1$H NMR ($CDCl_3$, 400 MHz) $\delta$ 7.98 (d, $J$ = 7.7 Hz, 2H), 7.57 (t, $J$ = 7.3 Hz, 1H), 7.43 (t, $J$ = 7.7 Hz, 2H), 7.08 (dd, $J$ = 1.8, 6.7 Hz, 1H), 5.31 (dt, $J$ = 4.8, 6.7 Hz, 1H), 3.83 (m, 1H), 3.83 (s, 3H), 3.71 (dd, $J$ = 3.5, 6.7 Hz, 1H), 3.42 (s, 3H), 3.34 (s, 3H), 2.17−2.15 (m, 2H); $^{13}$C NMR ($CDCl_3$, 100 MHz) 199.0, 165.5, 164.0, 139.9, 133.8, 133.3, 129.6, 129.5, 128.4, 93.5, 70.9, 53.9, 52.2, 50.2, 50.1, 38.3, 28.5. Anal. Calcd for $C_{19}H_{20}O_7$; C, 63.33; H, 5.59. Found: C, 63.43; H, 5.45.

**Crystallographic Data for Compound 17.**[20] Crystal size 0.35 × 0.20 × 0.10 mm$^3$, $C_{15}H_{16}O_7$, $M_r$ = 308.28, monoclinic, $P2_1/n$, $a$ = 11.4222(3) Å, $b$ = 7.6762(2) Å, $c$ = 16.9394(5) Å, $\beta$ = 103.1774(16)°, $V$ = 1446.12(7) Å$^3$, $Z$ = 4, $D$(calcd) = 1.416 g cm$^{-3}$, $\lambda$(Mo K$\alpha$) = 0.71073 Å, $\mu$ = 0.113 mm$^{-1}$, $F$(000) = 648, $T$ = 150(2) K, GooF$^2$ = 1.033, index ranges = $-13 \le h \le 13$, $-7 \le k \le 9$, $-20 \le l \le 20$, independent reflections = 2553 [$R_{int}$ = 0.0392] of a total of 9755 collected reflections, $R(F)$ obeying $F^2 > 2\sigma(F^2)$ = 0.0358, $wR(F^2)$ = 0.0877, $R$(all data) = 0.0456, $wR(F^2)$ = 0.0929.

**Crystallographic Data for Compound 22.**[20] Crystal size 0.40 × 0.30 × 0.15 mm$^3$, $C_{12}H_{14}O_4$, $M_r$ = 222.23, triclinic, $P$-1, $a$ = 8.602(5) Å, $b$ = 11.967(5) Å, $c$ = 12.306(5) Å, $\alpha$ = 65.889-(5)°, $\beta$ = 72.343(5)°, $\gamma$ = 71.447(5)°, $V$ = 1074.0 Å$^3$, $Z$ = 4, $D$(calcd) = 1.374 g cm$^{-3}$, $\lambda$(Mo K$\alpha$) = 0.71069 Å, $\mu$ = 0.103 mm$^{-1}$, $F$(000) = 472, $T$ = 120(2) K, GooF$^2$ = 1.113, index ranges = $-10 \le h \le 10$, $-13 \le k \le 14$, $-14 \le l \le 14$, independent reflections = 7771 [$R_{int}$ = 0.0000] of a total of 7771

collected reflections, $R(F)$ obeying $F^2 > 2\sigma(F^2) = 0.0619$, $wR(F^2) = 0.1228$, $R$(all data) = 0.1274, $wR(F^2) = 0.1440$.

**Crystallographic Data for Compound 23.**[20] Crystal size 0.30 × 0.17 × 0.10 mm$^3$, $C_{17}H_{24}O_7$, $M_r = 340.36$, orthorombic, $P2_12_12_1$, $a = 7.0027(2)$ Å, $b = 10.4275(4)$ Å, $c = 24.4633(13)$ Å, $V = 1786.33(13)$ Å$^3$, $Z = 4$, $D$(calcd) = 1.266 g cm$^{-3}$, $\lambda$(Mo Kα) = 0.71073 Å, $\mu = 0.098$ mm$^{-1}$, $F(000) = 728$, $T = 296(2)$ K, GooF$^2$ = 0.973, index ranges $= -6 \le h \le 8$, $-10 \le k \le 12$, $-29 \le l \le 29$, independent reflections = 3070 [$R_{int} = 0.0473$] of a total of 8726 collected reflections, $R(F)$ obeying $F^2 > 2\sigma(F^2) = 0.0485$, $wR(F^2) = 0.1101$, $R$(all data) = 0.0868, $wR(F^2) = 0.1248$.

**Crystallographic Data for Compound 26.**[20] Crystal size 0.20 × 0.10 × 0.10 mm$^3$, $C_{14}H_{18}O_7$, $M_r = 298.28$, monoclinic, $P2_1/c$, $a = 14.9070(14)$ Å, $b = 8.7441(10)$ Å, $c = 11.339(2)$ Å, $\beta = 96.590(5)°$, $V = 1468.3(3)$ Å$^3$, $Z = 4$, $D$(calcd) = 1.349 g cm$^{-3}$, $\lambda$(Mo Kα) = 0.71073 Å, $\mu = 0.109$ mm$^{-1}$, $F(000) = 632$, $T = 296(2)$ K, GooF$^2$ = 0.846, index ranges $= -17 \le h \le 17$, $-10 \le k \le 10$, $-13 \le l \le 13$, independent reflections = 2557 [$R_{int} = 0.0936$] of a total of 7298 collected reflections, $R(F)$ obeying $F^2 > 2\sigma(F^2) = 0.0659$, $wR(F^2) = 0.1659$, $R$(all data) = 0.1620, $wR(F^2) = 0.2227$.

**Crystallographic Data for Compound 28.**[20] Crystal size 0.30 × 0.20 × 0.15 mm$^3$, $C_{19}H_{20}O_7$, $M_r = 360.35$, triclinic, $P1$, $a = 7.1473(3)$ Å, $b = 8.9633(3)$ Å, $c = 14.8920(7)$ Å, $\alpha = 107.3569(16)°$, $\beta = 93.0568(15)°$, $\gamma = 101.3560(16)°$, $V = 886.34(6)$ Å$^3$, $Z = 2$, $D$(calcd) = 1.350 g cm$^{-3}$, $\lambda$(Mo Kα) = 0.71073 Å, $\mu = 0.103$ mm$^{-1}$, $F(000) = 380$, $T = 296(2)$ K, GooF$^2$ = 0.981, Index ranges $= -8 \le h \le 8$, $-10 \le k \le 10$, $-17 \le l \le 17$, independent reflections = 3112 [$R_{int} = 0.0380$] of a total of 6575 collected reflections, $R(F)$ obeying $F^2 > 2\sigma(F^2) = 0.0453$, $wR(F^2) = 0.1139$, $R$(all data) = 0.0810, $wR(F^2) = 0.1338$.

**Crystallographic Data for Compound 29.**[20] Crystal size 0.20 × 0.20 × 0.10 mm$^3$, $C_{19}H_{20}O_7$, $M_r = 360.35$, triclinic, $P$-1, $a = 8.2118(2)$ Å, $b = 8.3456(2)$ Å, $c = 13.6733(4)$ Å, $\alpha = 100.3304(9)°$, $\beta = 93.8833(10)°$, $\gamma = 108.8783(14)°$, $V = 864.29(4)$ Å$^3$, $Z = 2$, $D$(calcd) = 1.385 g cm$^{-3}$, $\lambda$(Mo Kα) = 0.71073 Å, $\mu = 0.106$ mm$^{-1}$, $F(000) = 380$, $T = 150(2)$ K, GooF$^2$ = 1.031, index ranges $= -9 \le h \le 9$, $-9 \le k \le 9$, $-13 \le l \le 16$, independent reflections = 3015 [$R_{int} = 0.0260$] of a total of 6157 collected reflections, $R(F)$ obeying $F^2 > 2\sigma(F^2) = 0.0379$, $wR(F^2) = 0.0931$, $R$(all data) = 0.0447, $wR(F^2) = 0.0981$.

**Evaluation of MOB Dimerization by UV/Vis Spectroscopy.** To a solution of DAIB (0.3 g, 0.9 mmol) in anhydrous methanol (20 mL, spectrophotometric grade solvent) at room temperature was added dropwise, over 10 min and under magnetic stirring, a solution of methyl vanillate (0.11 g, 0.6 mmol) in anhydrous methanol (5 mL). From this mixture, a 15-mL sample was taken and diluted with methanol to a final volume of 200 mL. UV spectra were recorded using q cuvettes with a 10-mm light path. The same procedure was applied to more concentrated solutions prepared from DAIB (0.75 g, 2.3 mmol) in anhydrous methanol (10 mL), to which a solution of methyl vanillate (0.275 g, 1.5 mmol) in anhydrous methanol (2.5 mL) was added.

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**Supporting Information Available:** $^1$H and $^{13}$C NMR spectra for compounds **17**−**22**, **28**, and **29**. This material is available free of charge via the Internet at http://pubs.acs.org.

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