3 H, ArOC$H_3$), 7.16-7.20 (m, 2 H, $H_{5,7}$), 7.35-7.39 (dd, 1 H, $H_3$, $J$ = 2.7, 9 Hz), 7.99-8.02 (d, 1 H, $H_8$, $J$ = 9 Hz), 8.63-8.65 (d, 1 H, $H_2$, $J$ = 4.2 Hz); GC/MS (relative abundance) 173.1 ($M^+$, 100.0), 158.0 (14.4), 130.1 (67.3), 103.1 (10.9), 77.0 (13.1).

**Synthesis of Alcohols 23b.** Distilled diisopropylamine (0.060 g, 0.06 mmol) was dissolved in THF (1 mL), cooled to -78 °C, and treated with *n*-BuLi (0.24 mL, 2.3 M in hexanes; 0.55 mmol). The reaction mixture was stirred at this temperature for 0.25 h and then warmed to 0 °C for 0.5 h. After the mixture was cooled to -78 °C, 6-methoxy-4-methylquinoline (0.082 g, 0.47 mmol) was added dropwise as a THF solution (1.5 mL). Once again the reaction mixture was warmed to 0 °C and stirred for 0.5 h. The resulting red solution of anion **22b** was cooled one last time to -78 °C and treated dropwise via syringe with a THF (2 mL) solution aldehyde **5b** (0.10 g, 0.41 mmol). The cold bath was replaced with a large, well-packed ice bath, and the reaction mixture was allowed to gradually warm to rt overnight. The mixture was quenched with $H_2O$ (2 mL) and concentrated in vacuo. The dark brown residue was suspended in $H_2O$ (15 mL) and extracted with EtOAc (2 × 30 mL). The organics were collected over $MgSO_4$, filtered, and concentrated in vacuo. Purification was achieved by eluting a 1-mm chromatotron plate with MeOH/$CH_2Cl_2$, 1:19 (0.099 g, 58.2%): $R_f$ = 0.42 (silica gel, MeOH/$CH_2Cl_2$, 1:9); IR ($cm^{-1}$, neat) 3100-3600, 1100, 1250; $^1H$ NMR (ppm) 3.41-3.53 (m, 2 H, NC$H_2$Ph), 3.95 (s, 3 H, ArOC$H_3$), 4.08-4.18 (m, 1 H, C*H*(OH)), 4.87-5.12 (m, 2 H, HC=C$H_2$), 6.16-6.30 (m, 1 H, *H*C=CH$_2$), 7.21-7.39 (m, 8 H, Ph and $H_{3,5,7}$ from quinoline ring), 7.98-8.00 (d, 1 H, $H_8$), 8.60-8.62 (two overlapping d, 1 H each, isomeric $H_2$); mass spectrum 416 ($M^+$), 401, 398, 398, 325, 307, 173, 91; exact mass ($EI^+$) calcd for $C_{27}H_{32}N_2O_2$ 416.2464, found 416.2461.

**Synthesis of Acetates 24b.** The purified alcohols (0.09 g, 0.22 mmol) were dissolved in THF (4.4 mL) and treated with triethylamine (0.033 g, 0.33 mmol), DMAP (catalytic amount), and acetic anhydride (0.048 g, 0.46 mmol). After the mixture was stirred at rt for 19.5 h, the solvent was removed in vacuo. The resulting residue was suspended in $H_2O$ (15 mL) and extracted with EtOAc (2 × 30 mL). The organics were combined over $MgSO_4$, filtered, and concentrated in vacuo to give crude **24b**, pure by TLC and NMR: $R_f$ = 0.22 (silica gel; EtOAC/Hex, 6:4); IR ($cm^{-1}$, neat) 1730, 1245; $^1H$ NMR (ppm) 2.04, 2.08 (s, 3 H, OCOC$H_3$), 4.02, 4.03 (s, 3 H, ArOC$H_3$), 4.26-4.46, 4.98-5.06 (m, 2 H, HC=C$H_2$), 5.29-5.36 (m, 1 H, C*H*(OAc)), 5.79-5.92, 6.03-6.16 (m, 1 H, *H*C=CH$_2$), 7.15-7.39 (m, 8 H), 7.57-7.63 (d, 1 H), 7.99-8.03 (d, 1 H), 8.66-8.68 (d, 1 H); mass spectrum 458 ($M^+$), 443 415, 399, 367, 91; exact mass ($EI^+$) calcd for $C_{29}H_{34}N_2O_3$ 458.2569, found 458.2568.

**Synthesis of Acetates 24a.** Reaction of distilled lepidine with aldehyde **5b** under similar conditions used to synthesize alcohols **23b** gave the corresponding des-6-methoxy alcohols. These alcohols (**23b**) were not purified, but rather acetylated, as in the synthesis of **24b**, directly to the corresponding des-6-methoxy acetates **24a** in 62.3% overall purified yield: $R_f$ = 0.03 (silica gel, EtOAc/Hex, 4:6; alcohols); $R_f$ = 0.18 (silica gel, EtOAc/Hex, 4:6; acetates); $^1H$ NMR (ppm, acetates) 1.93, 1.99 (s, 3 H, OCOC$H_3$), 3.03-3.19 (dd, 2 H, ArC$H_2$CH(OAc), $J$ = 7.2, 13.5 Hz), 3.35-3.49 (m, 2 H, NC$H_2$Ar), 4.47-4.65, 4.99-5.12 (m, 2 H, HC=C$H_2$), 5.29-5.36 (m, 1 H, C*H*(OAc), 5.90-6.22 (m, 1 H, *H*C=CH$_2$), 7.21-7.27 (m, 6 H, Ph, $H_3$), 7.58-7.63 (t, 1 H, $H_6$), 7.69-7.74 (t, 1 H, $H_7$), 8.11-8.23 (m, 2 H, $H_{5,8}$), 8.81-8.82 (d, 1 H, $H_2$).

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**Registry No.** (±)-**5a**, 134261-48-6; (±)-**5b**, 134261-60-2; **11**, 134261-49-7; **12**, 88946-48-9; **13a**, 134261-50-0; **13b**, 134261-59-9; **14**, 134261-51-1; **16**, 134261-52-2; (±)-**17**, 134261-53-3; (±)-**18**, 134261-54-4; (±)-**20**, 134261-55-5; (±)-**21**, 134261-56-6; (±)-**23a** (isomer 1), 134261-65-7; (±)-**23a** (isomer 2), 134261-66-8; (±)-**23b** (isomer 1), 134261-57-7; (±)-**23b** (isomer 2), 134261-61-3; (±)-**24a** (isomer 1), 134261-58-8; (±)-**24a** (isomer 2), 134261-64-6; (±)-**24b** (isomer 1), 134261-62-4; (±)-**24b** (isomer 2), 134261-63-5; $Ph_3P$=CHCOCH$_3$, 1439-36-7; $CH_3COCH=CH_2$, 78-94-4; 6-methoxy-4-methylquinoline, 41037-26-7; 4-methoxyaniline, 104-94-9; lepidine, 491-35-0.

**Supplementary Material Available:** NMR spectra of each compound that appears in the Experimental Section and X-ray crystallography data for *cis*-**18** (37 pages). Ordering information is given on any current masthead page.

# Electronic and Steric Effects in the Addition of Electrophilic 1,3-Dicarbonylalkyl Radicals to Styrenes

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The addition reactions of 1,3-dicarbonylalkyl radicals to ring-substituted styrenes have been kinetically investigated in MeOH and/or MeCN. It has been observed that the rate effect of ring substituents is nearly identical in the reactions of MeCOĊHCOMe (**1**), MeOCOĊHCOMe (**2**) and MeOCOĊHCOOMe (**4**), the $\rho$ value, in MeOH being -0.96, -1.01 and -1.06, respectively. Since the three radicals are relatively strong oxidants and have similar reduction potentials, an important contribution of the charge transfer structure RCOCHCOR$^-$ $CH_2CHAr^{\bullet+}$ to the addition transition state is suggested. It has also be found that in the reactions of **1** and **4** with $\alpha$-alkyl-substituted styrenes the rate of addition is strongly influenced by the nature of the alkyl group, decreasing in the order: Me > Et > $^i$Pr > $^t$Bu. The observed effects are much larger than those reported for the corresponding reactions of the nucleophilic cyclohexyl radical. It is suggested that the $\alpha$-alkyl substituents exert an effect of steric inhibition of resonance thereby ring delocalization of the charge and/or unpaired electron in the transition state is significantly reduced. Delocalization may be more important in the reactions of **1** and **4** than in those of the cyclohexyl radical since it is possible that the former utilizes a transition state occurring later along the reaction coordinate and/or characterized by a larger extent of charge transfer.

In the last two decades, the addition reactions of carbon-centered radicals to alkenes have been intensively investigated both from the theoretical and the practical point of view.[1-5] Most of the research has however been

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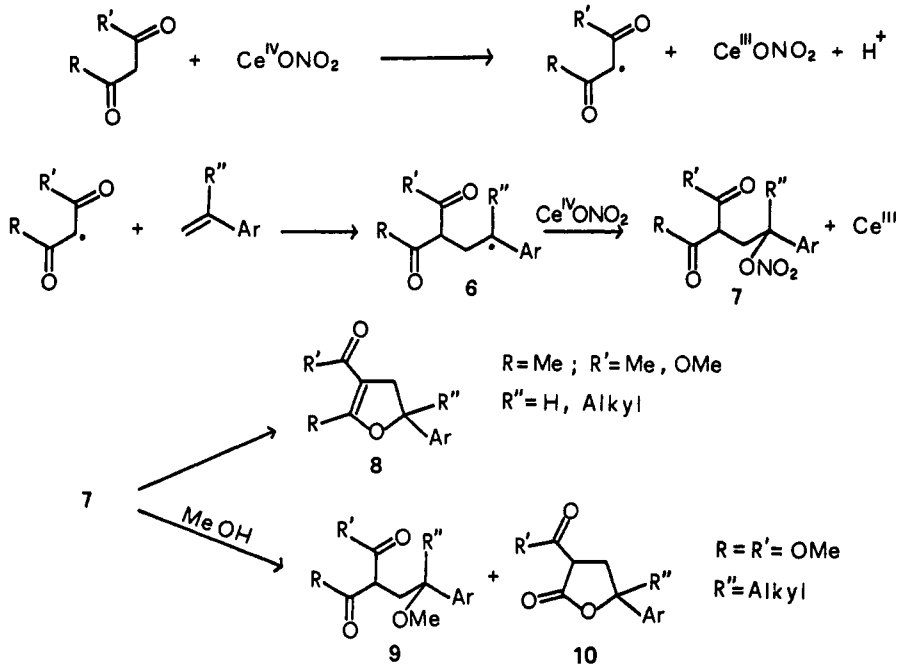
(1) Giese, B. In *Radicals in Organic Synthesis: Formation of Carbon-Carbon Bonds*; Pergamon Press: Oxford, 1986; and references cited therein. Hart, D. J. *Science* **1984**, *223*, 883.

0022-3263/91/1956-4772$02.50/0 

Scheme I




concentrated on the reactions of the nucleophilic alkyl radicals that are now known in satisfactory detail at least for what concerns the mechanistic aspects as well as the role of electronic and steric effects.[6,7]

Thus, at present it is generally agreed that substituents in the alkene influence the rate mostly by polar effects, whereas the stability of the formed intermediate radical seems to be less important. Steric effects can also play a significant role, but only when the substituent is at the position of the alkene attacked by the nucleophilic radical.

Substituents in the attacking radical can influence the reactivity by steric and polar effects. Very interestingly, electron-donating groups increase the nucleophilic character of the radical and make it more reactive as well as more selective.

The extension of the previous conclusions to the addition reactions of electrophilic carbon-centered radicals is not, however, straightforward. The SOMO orbital of the radical should now interact with the HOMO orbital of the alkene and not with the LUMO as it occurs in the reactions of nucleophilic radicals.[8] Moreover, electrophilic carbon-centered radicals are generally significantly more stable than alkyl radicals, and this might lead to a transition-state structure more shifted toward that of the products.

Thus, differences in the behaviors of nucleophilic and electrophilic radicals can certainly be envisaged, and in fact, it has recently been observed that these radicals behave differently in the regiochemistry of the ring-closure reactions of 5-hexenyl radicals.[9]

In spite of these points of interest, mechanistic studies concerning the addition reactions of electrophilic carbon-centered free radicals have so far received little attention, even though there are signs that the situation is changing,[10-15] probably on the wake of the relevant number of works that in the last few years have concerned the synthetic exploitation of the oxidative addition of carbonyl compounds to alkenes, a reaction involving the intermediacy of electrophilic radicals.[16]

In collaboration with Giese and Farshchi, we have recently carried out a kinetic study of the addition reactions of malonyl radicals to substituted styrenes. Malonyl radicals were generated both oxidatively, by reaction of cerium(IV) ammonium nitrate (CAN) with a dialkyl malonate, and reductively, by reaction of a dialkyl chloromalonate with tributyltin hydride. Interestingly, the reaction selectivity of the addition process turned out to be the same, under the two experimental conditions, thus suggesting that also in the CAN-promoted additions the generated malonyl radical is a free species not significantly complexed to the metal.

Having clarified this point, we have continued our study with the 2-fold aim of determining the influence of the structure of the radical on the reaction selectivity and of getting information on the sensitivity of the reaction to steric effects. Thus, in this paper we report on a kinetic investigation concerning the reactions of $\alpha,\alpha$-dicarbonylalkyl radicals MeCOĊHCOMe (1) and MeCOĊHCOOMe (2) with the ring Z-substituted styrenes 3a–3e (a, Z = H;

(2) Curran, D. P. *Synthesis* **1988**, 417, 489, and references cited therein. Beckwith, A. L. J. *Tetrahedron* **1981**, *37*, 3073.
(3) Giese, B. *Angew. Chem., Int. Ed. Engl.* **1989**, *28*, 969.
(4) Ramaiah, M. *Tetrahedron* **1987**, *43*, 3541 and references cited therein.
(5) (a) Shaik, S. S.; Canadell, E. *J. Am. Chem. Soc.* **1990**, *112*, 1446 and references cited therein. (b) Beckwith, A. L. J.; Schiesser, C. H. *Tetrahedron* **1985**, *41*, 3925.
(6) Giese, B. *Angew. Chem., Int. Ed. Engl.* **1983**, *22*, 753. Beranek, I.; Fischer, H. In *Free Radicals in Synthesis and Biology*; Minisci F., Ed.; NATO ASI Series: Kluwer Academic Publishers: Dordrecht, 1989; pp 303–316.
(7) Tedder, J. M. *Angew. Chem., Int. Ed. Engl.* **1982**, *21*, 401.
(8) However, it has been suggested that the SOMO–HOMO interaction is the dominant one also with nucleophilic radicals.[5a]
(9) Curran, P. D.; Chang, C.-T. *J. Org. Chem.* **1989**, *54*, 3140.
(10) Baciocchi, E.; Giese, B.; Farshchi, H.; Ruzziconi, R. *J. Org. Chem.* **1990**, *55*, 5688.
(11) Gleicher, G. J.; Mahiou, B.; Aretakis, A. J. *J. Org. Chem.* **1989**, *54*, 308.
(12) Giese, B.; He, J.; Mehl, W. *Chem. Ber.* **1988**, *121*, 2063.
(13) Snider, B. B.; Patricia, J. J.; Kates, S. A. *J. Org. Chem.* **1988**, *53*, 2137.
(14) Reference 12 and references cited therein.
(15) Fristad, W. E.; Peterson, J. R.; Ernst, A. B.; Urbi, G. B. *Tetrahedron* **1986**, *42*, 3429.
(16) (a) Dombroski, M. A.; Kates, S. A.; Snider, B. B. *J. Am. Chem. Soc.* **1990**, *112*, 2759. (b) Snider, B. B.; Buckman, B. O. *Tetrahedron* **1989**, *49*, 6969. (c) Curran, D. P.; Chen, M.-H.; Spletzer, E.; Seong, C. M.; Chang, C.-T. *J. Am. Chem. Soc.* **1989**, *111*, 8872. (d) Citterio, A.; Fancelli, D.; Finzi, C.; Pesce, L.; Santi, R. *J. Org. Chem.* **1989**, *54*, 2713. (e) Reference 13 and references cited therein. (f) Corey, E. J.; Ghosh, A. K. *Tetrahedron Lett.* **1987**, *28*, 175.

**Table I. Relative Reactivities in the CAN-Promoted Addition Reactions of 2,4-Pentanedione to Z-Substituted Styrenes at 20 °C**

| Z | $k_Z/k_H$[a] in MeCN | $k_Z/k_H$[a] in MeOH |
|---|---|---|
| p-$CH_3$ | 2.15 | 1.89 |
| | 2.20[b] | |
| | 1.91[c] | |
| H | 1.00 | 1.00 |
| p-Cl | 0.73 | 0.76 |
| m-Cl | 0.38 | 0.38 |
| m-$NO_2$ | 0.17 | 0.21 |

[a] Average of at least two determinations. Error 6%. [b] In the presence of $LiClO_4$ (0.12 M). [c] In the presence of $LiClO_4$ (0.59 M).

**b**, Z = p-Cl; **c**, Z = m-Cl; **d**, Z = p-Me; **e**, Z = m-$NO_2$) and of **1** and the malonyl radical **4** with the α-R-substituted styrenes **5a–5d** (**a**, R = Me; **b**, R = Et; **c**, R = $^i$Pr; **d**, R = $^t$Bu). The radicals **1**, **2**, and **4** have been generated by reaction of CAN with 2,4-pentanedione, methyl 3-oxobutanoate, and dimethyl malonate, respectively.

## Results and Discussion

The CAN-induced oxidative addition of carbonyl compounds to styrenes is illustrated in Scheme I. The key intermediate is the radical **6**, which undergoes an oxidative ligand transfer to give the alkyl nitrate **7**. From **7** the final products are obtained by intramolecular nucleophilic displacement of the nitrate group and/or solvolytic reactions.[10,17,18]

The reactions of 2,4-pentanedione and methyl 3-oxobutanoate (both in MeCN and MeOH) with the alkenes **3a–3e** and of 2,4-pentanedione with **5a–5d** always led to the formation of the dihydrofuran **8**, as expected on the basis of previous works concerning the oxidative addition of 1,3-diketones and β-keto esters to alkenes.[19–21] In all cases, the yields were very large: at least 80%, but generally much higher (see Experimental Section).

The CAN-promoted reactions of dimethyl malonate (**4**) take place with appreciable rate only in MeOH. With **5a–5d** the methoxy addition products **9** were obtained together with substantial amounts of the lactone **10**, the overall yield of the two products being ca. 90%. It is interesting to note that no formation of lactones was observed in the addition of malonyl radicals to the styrenes **3a–3e**.[10] Evidently, if an α-alkyl substituent is present on the styrene moiety, ring closure by the carbomethoxy group in the alkyl nitrate **7**, followed by expulsion of the methyl group, can significantly compete with solvent attack, which forms the methoxy adduct.

The relative rate constants of substituted styrenes with respect to styrene were determined by the competitive method. Two styrenes were reacted with 25–50% of the stoichiometric amounts of dicarbonyl compound and CAN and the moles of the two styrenes, before and after reaction, determined by GC. It has also been checked that changing the CAN concentration (up to a factor of 3) has no effect on the reactivity ratio values, which indicates that the trapping of the intermediate radical **6** by CAN is a fast process that makes the addition reaction irreversible.

For the reactions of 2,4-pentanedione, some competitive experiments were also carried out by using a large excess of the two styrenes and determining the relative amount of the two reaction products. An excellent agreement was observed with the results obtained with the previous method. All kinetic results are collected in Tables I–III.

**Table II. Relative Reactivities in the CAN-Promoted Addition Reactions of Methyl 3-Oxobutanoate to Z-Substituted Styrenes at 20 °C**

| Z | $k_Z/k_H$[a] in MeCN | $k_Z/k_H$[a] in MeOH |
|---|---|---|
| p-$CH_3$ | 1.89 | 1.65 |
| H | 1.00 | 1.00 |
| p-Cl | 0.69 | 0.69 |
| m-Cl | 0.38 | 0.38 |
| m-$NO_2$ | 0.19 | 0.16 |

[a] Average of at least two determinations. Error 5%.

**Table III. Relative Reactivities in the CAN-Promoted Addition Reactions of 2,4-Pentanedione and Dimethyl Malonate to α-R-Substituted Styrenes at 20 °C**

| α-R | $k_R/k_H$[a] 2,4-pentanedione MeCN | $k_R/k_H$[a] 2,4-pentanedione MeOH | $k_R/k_H$[a] dimethyl malonate MeOH |
|---|---|---|---|
| H | 0.50 | 0.51 | 0.52 |
| Me | 1.00 | 1.00 | 1.00 |
| Et | 0.58 | 0.70 | 0.65 |
| $^i$Pr | 0.13 | 0.12 | 0.27 |
| $^t$Bu | 0.0038[b] | 0.0034[b] | 0.013[b] |

[a] Average of at least two determinations. Error 5%. [b] Indirectly determined from the ratio $k_{iPr}/k_{tBu}$. Error 10%.

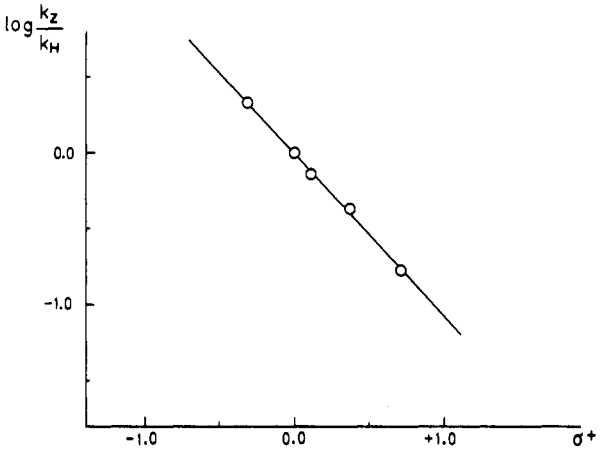



**Figure 1.** Hammett plot for the addition of **1** to ring-substituted styrenes in MeCN (ρ = −1.08; r = 0.998). Data from Table I.

**Electronic Effects.** The effect of the ring substituents on the rate of addition of the radicals **1** and **2** to styrenes is displayed in Table I and II, respectively. The reactions of the two radicals exhibit substituent effects that are very similar and also are almost independent of the solvent used (MeOH and MeCN). Nearly identical ρ values can therefore be calculated from the very good linear correlations between the logs of the relative reactivities and the $\sigma^+$ values of the ring substituents: −1.08 (MeCN) and −0.96 (MeOH) for **1**; −0.99 (MeCN) and −1.01 (MeOH) for **2**. The plot for the reaction of **1** in MeCN is reported in Figure 1.

If we now also consider that the reaction constant for the addition reactions of malonyl radical to ring-substituted styrenes is −1.06 in MeOH, we come to the obvious conclusion that the selectivity of the addition of α-oxoalkyl radicals to styrenes is not significantly influenced by the radical structure as well as by the nature of the solvent. The former conclusion is quite surprising since the stability of the radical is expected to decrease in a substantial way

(17) Baciocchi, E.; Ruzziconi, R. *Gazz. Chim. It.* **1986**, *116*, 671.
(18) The intermediacy of a carbocation cannot be excluded. This might be formed by oxidation of **6** by CAN and/or in the solvolysis of the alkyl nitrate.
(19) Baciocchi, E.; Ruzziconi, R. *J. Org. Chem.* **1986**, *51*, 1645.
(20) Heiba, E. I.; Dessau, R. M. *J. Org. Chem.* **1974**, *39*, 3457.
(21) Vinogradov, M. G.; Petrenko, O. N.; Verenchikov, S. P.; Nikishin, G. I. *Zh. Org. Khim.* **1980**, *16*, 714.

in the order 1 > 2 > 4,[22] and the same order should hold for the electrophilic character. Thus, by analogy with the properties of nucleophilic radicals, the prediction was that as we progressively replace the acetyl groups by the carbomethoxy groups the reaction selectivity of the radical should decrease, which is contrary to the observations.

It has, however, to be noted that radicals 1, 2, and 4 are relatively strong oxidants with very similar reduction potentials (between 0.73 and 0.75 V vs NHE in DMSO).[23] Thus, the insensitivity of the reaction selectivity to the radical stability might be explained on the basis of an important contribution of structures like 11, where substantial charge transfer from the alkene to the radical has taken place, to the transition state of the reaction.

$$[(RCO)_2CH]^-[CH_2CHC_6H_4Z]^{\bullet+}$$
11

In this situation, the selectivity of the addition process would mostly be influenced by the ability of the radical to accept a negative charge; an ability that, on the basis of the reduction potential values, appears to be very similar for the three radicals under study.

We have tried to test this hypothesis by determining the relative reactivity for the couple *p*-methylstyrene and styrene in the reaction with 1 in MeCN, in the presence of $LiClO_4$. We felt that an increase of the *p*-methylstyrene to styrene reactivity ratio might be observed under these conditions, since it has recently been reported that the oxidizing power of 1 in DMSO significantly increases in the presence of $LiClO_4$ (the reduction potential becomes 0.5 V more positive), probably owing to the ability of $Li^+$ to coordinate the anion. However, as shown in Table I, we found that the presence of $LiClO_4$ up to 0.6 M has practically no significant effect on the value of the *p*-methylstyrene to styrene reactivity ratio.

In spite of this negative result, we feel that the earlier suggestion still deserves further consideration since it cannot be excluded that the buildup of negative charge on the oxygen atoms in the transition state has not yet become big enough to produce a significant interaction with $Li^+$ ions. Moreover, in MeCN (the solvent for our reactions) $LiClO_4$ is certainly more strongly associated than in DMSO, and $Li^+$ may therefore be less available for coordination. Additional experimentation is necessary to clarify this interesting point.

As already mentioned, previous work has provided results indicating that, in the CAN-promoted additions of the malonyl radical, coordination of the radical with cerium ions is insignificant. It seems safe to extend this conclusion also to the reactions of 1 and 2 in view of the very similar behaviors of these radicals with respect to those of the malonyl radical.

**Steric Effects.** In Table III the relative reactivity data concerning the reactions of α-alkyl-substituted styrenes **5a–5d** with 1 and 4 are reported. It can be immediately seen that the rate of both reactions is significantly influenced by the nature of the α-alkyl group, the effects being slightly larger in the former. No significant solvent effect (MeOH vs MeCN) has been observed.

With respect to the unsubstituted styrene, the presence of an α-methyl group increases the reaction rate, as expected for an electrophilic process favored by electron-releasing groups. The effect is, however, relatively small (it is not much different from that of a ring *p*-methyl group), which suggests the presence of a significant rate-retarding steric effect. This is confirmed by the observation of a progressive decrease of the addition rate as we increase the steric requirements of the alkyl group, moving from methyl to ethyl, isopropyl, and *tert*-butyl.

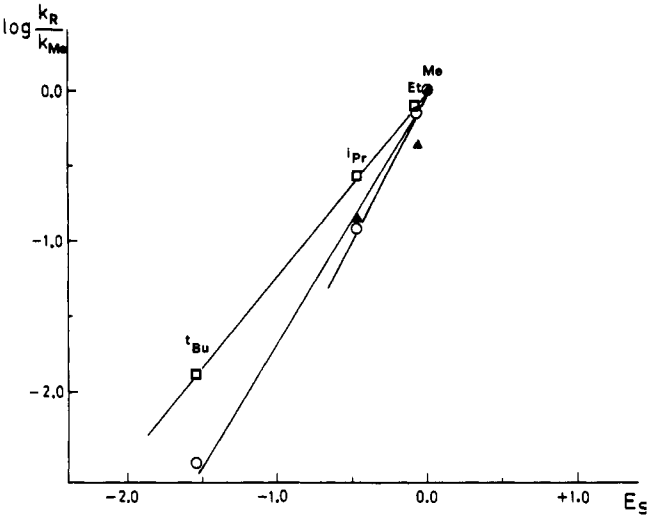



**Figure 2.** Plots of relative reactivity of alkyl-substituted styrenes against that $E_s$ values of the alkyl group: ○, reactions of 1; □, reactions of 4 (data from Table III); ▲, reactions of dicyanomethyl radical (data from ref 25).

Since we can reasonably assume a very similar electronic effect for the previous alkyl groups, the observed decrease in the relative reactivity values can quite confidently be attributed, at least for the most part, to the operation of steric effects. Accordingly, a plot of the logs of the relative reactivities against the steric substituent constants $E_s$[24] of the alkyl groups exhibits an excellent linearity for the two reactions (Figure 2) with a ρ value of 1.73 for the reaction of 1 and of 1.22 for the reaction of 4.

In Figure 2 some very recent data concerning the additions of dicyanomethyl radical to the same substrates are also plotted.[25] It is remarkable to note that this reaction exhibits a sensitivity to steric effects very similar to that shown by the reaction of 1, in spite of the fact that the steric demand of the latter radical is significantly larger than that of the former.[11] Another very intriguing observation is that the sensitivity to steric effects exhibited by the reactions of 1 and 4 as well as by that of the cyanomethyl radical with α-substituted styrenes is enormously higher than that found in the corresponding reactions of the cyclohexyl radical.[12] Thus, the α-methyl/α-*tert*-butyl ratio is ca. 300 in the reaction of 1 in MeOH and only 1.6 in the reaction of cyclohexyl radical!

The reasons of this dramatic difference are not clear, since we certainly cannot think of a very large difference in bulkiness of the cyclohexyl radical with respect to 1 and 4 and, moreover, we have already observed that the steric demand of the attacking radical does not play a significant role with regard to the effect of the α-alkyl substituents on the rate of addition to styrenes.

Since the steric requirements of the radical seem to be of secondary importance, a more significant role could be played by the character (electrophilic vs nucleophilic) of

(22) Birkhofer, H.; Hadrich, J.; Pakush, J.; Beckaus, H.-D.; Ruchardt, C.; Peters, K.; v. Schnering, H.-G. In *Free Radicals in Synthesis and Biology*; Minisci, F., Ed.; NATO ASI Series; Kluwer: Dordrecht, 1989; p 27.

(23) Bordwell, F. G.; Harrelson, J. A., Jr; Satish, A. V. *J. Org. Chem.* **1989**, *54*, 3101.

(24) Exner, O. In *Correlation Analysis of Chemical Data*; Plenum Press: New York, 1988; pp 152–157.

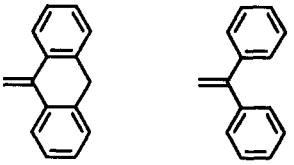
(25) Zipse, H.; He, J.; Giese, B.; Houk, K. N. Submitted for publication. The relative rates for the alkyl groups are Me:Et:$^i$Pr = 1:0.43:0.14. Private communication by Prof. Giese.

the radical. Accordingly, the available data seem to indicate that the sensitivity to the effects of α-substituents in the styrene moiety increases as we move from nucleophilic to electrophilic carbon-centered radicals. This is nicely confirmed by recent results concerning the cyanomethyl radical, a borderline radical between electrophilic and nucleophilic behaviors.[12] In the reaction of α-alkylstyrenes, this radical exhibits an α-methyl/α-*tert*-butyl reactivity ratio (ca. 14) that is intermediate between that found in the reaction of cyclohexyl radical and those found in the reactions of full-fledged electrophilic radicals like 1 and 4.

A tentative explanation might be that the transition state for the addition of carbonyl- and cyano-substituted alkyl radicals occurs later along the reaction coordinate than that for the addition of an alkyl radical, since the former are significantly more stable than the second. If this suggestion, which is in accord with ab initio calculations of Giese and associates,[26] is correct, the delocalization, in the transition state, of the developing charge and/or unpaired electron should play a much more important role in the reactions of electrophilic carbonyl- and cyano-substituted radicals than in those of nucleophilic alkyl radicals. As a matter of fact, in the case of the radicals 1 and 4 the importance of this delocalization is also suggested by the substantial effects of ring substituents on the addition rate.

Of course, such a delocalization requires that the phenyl ring keeps coplanar with the double bond. A consequence is that as the steric requirements of the α-alkyl group increase, the extent of charge delocalization in the ring can significantly be reduced since the phenyl group experiences increasing difficulty to align its π system with that of the double bond (steric inhibition of resonance).

This effect might be much less important in the addition reactions of nucleophilic alkyl radicals to styrenes because these reactions should utilize a very early transition state where, as already suggested, charge delocalization in the phenyl ring is of little importance. That this is the case, at least with the cyclohexyl radical, is clearly indicated by the observation of Giese and co-workers[12] that the addition of this radical to **12** is only 3.9 times faster than to **13** in spite of the fact that charge delocalization is much more efficient in the former alkene where the two aromatic rings are forced to be coplanar with the double bond by the bridging methylene group.



12 13

## Experimental Section

$^1$H NMR spectra were recorded at 80 MHz on a Bruker SY 80 and, when specified, at 200 MHz on a Bruker AC 200 spectrometer in $CDCl_3$ solution and in the presence of tetramethylsilane as an internal standard. IR spectra were registered on a Perkin-Elmer M 257 spectrophotometer. Mass spectra were recorded on a Hewlett-Packard 5890-5970 combined GC–MS at 70 eV. Elemental analyses were performed on a Carlo Erba M 1106 elemental analyzer. Melting points were determined with a Buchi M 510 instrument and were uncorrected. Gas chromatographic analyses were performed on a Hewlett-Packard 5880 A instrument (30 m, SP-B5, capillary column).

**Starting Materials.** Acetonitrile, methanol, 2,4-pentanedione, methyl 3-oxobutanoate, and dimethyl malonate, of the highest grade of purity (Aldrich), were used without further purification. Purified unsubstituted styrene and *p*-methyl-, *p*-chloro-, *m*-chloro-, and *m*-nitrostyrenes were available from a previous work.[10] α-Methylstyrene (Fluka) was fractionally distilled before use; 2-phenyl-1-butene, 3-methyl-2-phenyl-1-butene, and 3,3-dimethyl-2-phenyl-1-butene were prepared by the Wittig reaction from ethyl, isopropyl, and *tert*-butyl phenyl ketone,[27] respectively, and methyltriphenylphosphorane according to the following standard procedure: to a solution of diisopropylamine (7.7 g, 76 mmol) in 100 mL of anhydrous tetrahydrofuran cooled at −30 °C was added *n*-butyllithium (51 mL, 1.5 M in hexane, 76 mmol) dropwise under nitrogen. After 15 min, methyltriphenylphosphonium iodide (30.7 g, 76 mmol) was added under stirring. The cold bath was removed, and the mixture was allowed to react 2 h at room temperature. The ketone (76 mmol) was added dropwise, and the mixture was allowed to react for a period of time ranging from 1 to 10 h depending on the structure of the ketone. After filtration and solvent evaporation, light petroleum was added and most of the crystallized triphenylphosphine oxide was removed by filtration. Chromatography of the resulting solution on silica gel (light petroleum as the eluent) and successive distillation give α-alkyl-substituted styrene more than 99.9% pure by GLC analysis. **2-Phenyl-1-butene (5b)**: 68%; $bp_{15}$ 64–64.5 °C; $^1$H NMR δ 7.50–7.15 (m, 5 H), 5.28 (m, 1 H), 5.07 (m, 1 H), 2.52 (b q, *J* = 7.7 Hz, 2 H), 1.10 (t, *J* = 7.7 Hz, 3 H); MS *m/z* 132 ($M^+$, 67), 117 (100), 103 (9), 91 (33), 77 (16). **3-Methyl-2-phenyl-1-butene (5c)**: 71%; $bp_{17}$ 76–76.5 °C; $^1$H NMR δ 7.37–7.19 (m, 5 H), 5.13 (dd, *J* = 0.6 and 1.4 Hz, 1 H), 5.03 (t, *J* = 1.4 Hz, 1 H), 2.84 (b sept, *J* = 6.9 Hz, 1 H), 1.11 (d, *J* = 6.9, 6 H); MS *m/z* 146 ($M^+$, 37), 131 (100), 115 (13), 103 (30), 91 (42), 77 (26). **3,3-Dimethyl-2-phenyl-1-butene (5d)**: 51%; $bp_{17}$ 76–77 °C; $^1$H NMR δ 7.32–7.20 (m, 3 H), 7.17–7.10 (m, 2 H), 5.17 (d, *J* = 1.7 Hz, 1 H), 4.76 (d, *J* = 1.7 Hz, 1 H), 1.11 (s, 9 H); MS *m/z* 160 ($M^+$, 38), 145 (100), 104 (57), 91 (34), 77 (31), 57 (39).

**Structure Determination of the Reaction Products.** To a solution of CAN (5.0 g, 9.1 mmol) in 90 mL of solvent were added substituted styrene (20 mmol) and dicarbonyl compound (4.5 mmol) in 10 mL of the same solvent at 20 °C, and the mixture was allowed to react until CAN was completely reduced (5 min in the reaction with 2,4-pentanedione and methyl 3-oxobutanoate, 40 min in the reaction of dimethyl malonate, after iodometric titration). The mixture was poured into water (250 mL) and extracted with diethyl ether (3 × 100 mL); the collected extracts were washed with water (300 mL) and dried with sodium sulfate, and the solvent was evaporated under vacuum (15 mmHg). Chromatography of the residue on silica gel after elution with 8:2 petroleum ether–diethyl ether mixture allowed the isolation of the reaction products that were characterized as follows.

**Reaction with 2,4-Pentanedione. 3-Acetyl-2-methyl-5-phenyl-4,5-dihydrofuran [8 (R = R′ = Me, R″ = H, Ar = $C_6H_5$)]**: 91%; $^1$H NMR δ 7.35 (s, 5 H), 5.10 (four peaks, X portion of an ABX system, 1 H), 3.57–2.82 (eight quartets, *J* = 1.4 Hz, AB portion of an ABX system, 2 H), 2.31 (t, *J* = 1.4 Hz, 3 H), 2.21 (s, 3 H); IR (film) 3030–3000, 2920, 2860, 1671, 1620, 1605, 1495, 932, 760 $cm^{-1}$; MS *m/z* 202 ($M^+$, 40), 183 (13), 159 (10), 115 (26), 91 (10), 77 (11), 43 (100). Anal. Calcd for $C_{13}H_{14}O_2$: C, 77.20; H, 6.98. Found: C, 77.02; H, 7.04. **3-Acetyl-2-methyl-5-*p*-tolyl-4,5-dihydrofuran [8 (R = R′ = Me, R″ = H, Ar = *p*-$MeC_6H_4$)]**: 89%; $^1$H NMR δ 7.21 (s, 4 H), 5.57 (four peaks, X portion of an ABX system, 1 H), 3.53–2.80 (eight quartets, *J* = 1.4 Hz, AB portion of an ABX system, 2 H), 2.36 (s, 3 H), 2.30 (t, *J* = 1.4 Hz, 3 H), 2.20 (s, 3 H); IR (film) 3012, 2920–2860, 1670, 1596, 1515, 1225, 932, 817 $cm^{-1}$; MS *m/z* 216 ($M^+$, 22), 183 (9), 155 (7), 115 (9), 91 (8), 77 (5), 43 (100). Anal. Calcd for $C_{14}H_{16}O_2$: C, 77.75; H, 7.46. Found: C, 77.61; H, 7.39. **3-Acetyl-2-methyl-5-(4-chlorophenyl)-4,5-dihydrofuran [8 (R = R′ = Me, R″ = H, Ar = *p*-$ClC_6H_4$)]**: 90%; $^1$H NMR δ 7.43–7.18 (m, 4 H), 5.57 (four peaks, X portion of an ABX system, 1 H), 3.57–2.77 (eight quartets, *J* = 1.4 Hz, AB portion of an ABX system, 2 H), 2.31 (t, *J* = 1.4 Hz, 3 H), 2.22 (s, 3 H); IR (film) 3025, 3015, 2920, 2860, 1672, 1620, 1605, 1492, 1228, 932, 828, 89 $cm^{-1}$; MS *m/z* 236

(26) In ref 25, ab initio calculations have indicated a somewhat later transition state for the reaction of malonitrile radical with ethylene compared to that of addition of methyl radical.

(27) *tert*-Butyl phenyl ketone was obtained in 59% yield by reaction of lithium diphenylcuprate with pivaloyl chloride in THF at −50 °C.

($M^+$, 30), 217 (6), 175 (4), 115 (10), 77 (2), 43 (100). Anal. Calcd for $C_{13}H_{13}ClO_2$: C, 65.97; H, 5.53. Found: C, 66.25; H, 5.61. **3-Acetyl-2-methyl-5-(3-chlorophenyl)-4,5-dihydrofuran [8 (R = R′ = Me, R″ = H, Ar = *m*-ClC$_6$H$_4$)]**: 88%; $^1$H NMR $\delta$ 7.34–7.17 (m, 4 H), 5.57 (four peaks, X portion of an ABX system, 1 H), 3.58–2.77 (eight quartets, $J$ = 1.4 Hz, AB portion of an ABX system, 2 H), 2.33 (t, $J$ = 1.4 Hz, 3 H), 2.20 (s, 3 H); IR (film) 3060, 3000–2861, 1671, 1618, 1598, 1480, 1227, cm$^{-1}$; MS $m/z$ 236 ($M^+$, 11), 193 (3), 115 (9), 111 (5), 43 (100). Anal. Calcd for $C_{13}H_{13}ClO_2$: C, 65.97; H, 5.53. Found: C, 66.12; H, 5.71. **3-Acetyl-2-methyl-5-(*m*-nitrophenyl)-4,5-dihydrofuran [8 (R = R′ = Me, R″ = H, Ar = *m*-NO$_2$C$_6$H$_4$)]**: 85%; mp 58–59 °C; $^1$H NMR $\delta$ 8.2 (m, 2 H), 7.6 (m, 2 H), 5.82–5.59 (four peaks, X portion of an ABX system, 1 H), 3.67–2.81 (eight quartets, AB portion of an ABX system, 2 H), 2.36 (t, $J$ = 1.4 Hz, 3 H), 2.23 (s, 3 H); IR ($CS_2$) 3095–3005, 2950–2861, 1678, 1630, 1608, 1223, 1215, 992, 927, 735 cm$^{-1}$; MS $m/z$ 247 ($M^+$, 50), 230 (30), 200 (22), 115 (16), 77 (5), 43 (100). Anal. Calcd for $C_{13}H_{13}NO_4$: C, 63.15; H, 5.30; N, 5.66. Found: C, 62.98; H, 5.42; N, 5.74. **3-Acetyl-2,5-dimethyl-5-phenyl-4,5-dihydrofuran [8 (R = R′ = R″ = Me, Ar = C$_6$H$_5$)]**: 90%; $^1$H NMR $\delta$ 7.3 (m, 5 H), 3.15 (m, 2 H), 2.32 (t, $J$ = 1.4 Hz, 3 H), 2.17 (s, 3 H), 1.68 (s, 3 H); IR (film) 3060, 3030, 2975, 2930, 2865, 1672, 1625, 1595, 1495, 1245, 765, 700 cm$^{-1}$; MS $m/z$ 216 ($M^+$, 6), 173 (12), 131 (4), 115 (6), 91 (4), 77 (7), 43 (100). Anal. Calcd for $C_{14}H_{16}O_2$: C, 77.75; H, 7.46. Found: C, 77.98; H, 7.59. **3-Acetyl-5-ethyl-2-methyl-5-phenyl-4,5-dihydrofuran [8 (R = R′ = Me, R″ = Et, Ar = C$_6$H$_5$)]**; 90%; $^1$H NMR $\delta$ 7.40–7.24 (m, 5 H), 3.16 (m, 2 H), 2.33 (t, $J$ = 1.4 Hz, 3 H), 2.17 (s, 3 H), 2.03 (b q, $J$ = 7 Hz, 2 H), 0.83 (t, $J$ = 7 Hz, 3 H); IR (film) 3060, 3025, 2970–2880, 1673, 1625, 1600, 1494, 1243, 935, 761, 700 cm$^{-1}$; MS $m/z$ 230 ($M^+$, 12), 201 (23), 170 (18), 115 (11), 77 (10), 43 (100). Anal. Calcd for $C_{15}H_{18}O_2$: C, 78.23; H, 7.88. Found: C, 78.08; H, 7.67. **3-Acetyl-5-isopropyl-2-methyl-5-phenyl-4,5-dihydrofuran [8 (R = R′ = Me, R″ = $^i$Pr, Ar = C$_6$H$_5$)]**; 88%; $^1$H NMR $\delta$ 7.3 (m, 5 H), 3.41–2.99 (m, 2 H), 2.31 (t, $J$ = 1.4 Hz, 3 H), 2.18 (s, 3 H); 2.13 (sept, $J$ = 6.9 Hz, 1 H), 0.90 (d, $J$ = 6.9 Hz, 3 H), 0.80 (d, $J$ = 6.9 Hz, 3 H); IR (film) 3060, 3025, 2970–2800, 1673, 1625, 1607, 1492, 1245, 937, 756 cm$^{-1}$; MS $m/z$ 244 ($M^+$, 5), 201 (73), 159 (13), 105 (11), 77 (9), 43 (100). Anal. Calcd for $C_{16}H_{20}O_2$: C, 78.65; H, 8.25. Found: C, 78.81; H, 8.31. **3-Acetyl-5-*tert*-butyl-2-methyl-5-phenyl-4,5-dihydrofuran [8 (R = R′ = Me, R″ = $^t$Bu, Ar = C$_6$H$_5$)]**: 84%; $^1$H NMR $\delta$ 7.3 (m, 5 H), 3.54–3.03 (four quartets, $J$ = 1.4 Hz, AB system, 2 H), 2.29 (t, $J$ = 1.4 Hz, 3 H), 2.18 (s, 3 H), 0.93 (s, 9 H); IR ($CS_2$) 3090–3025, 2975–2875, 1677, 1629, 1608, 1252, 933, 704 cm$^{-1}$; MS $m/z$ 258 ($M^+$ 1), 201 (67), 159 (13), 115 (6), 105 (10), 77 (7), 43 (100). Anal. Calcd for $C_{17}H_{22}O_2$: C, 79.03; H, 8.58. Found: C, 78.90; H, 8.59.

**Reactions with Methyl 3-Oxobutanoate.** The crude reaction products of the addition of methyl 3-oxobutanoate to Z-substituted styrenes exhibit $^1$H NMR spectra that are very similar to those of the correponding products from 2,4-pentanedione, the only substantial difference lying in the position of the singlet at $\delta$ ~3.7 ($CH_3OCO$–) rather than $\delta$ ~2.2 ($CH_3CO$–) so that only the following representative products were isolated and characterized. **3-(Methoxycarbonyl)-2-methyl-5-phenyl-4,5-dihydrofuran [8 (R = Me, R′ = OMe, R″ = H, Ar = C$_6$H$_5$)]**: 90%; $^1$H NMR $\delta$ 7.33 (s, 5 H), 5.70–5.47 (four peaks, X portion of an ABX system, 1 H), 3.71 (s, 3 H), 3.51–2.75 (eight quartets, $J$ = 1.7 Hz, AB portion of an ABX system, 2 H), 2.28 (t, $J$ = 1.7 Hz, 3 H); IR (film) 3095–3005, 2950–2875, 1702, 1647, 1227. 1092, 990, 762, 700 cm$^{-1}$; MS $m/z$ 218 ($M^+$, 11), 186 (11), 171 (38), 144 (14), 115 (38), 77 (11), 43 (100). Anal. Calcd for $C_{13}H_{14}O_3$: C, 71.54; H, 6.46. Found: C, 71.68; H, 6.67. **3-(Methoxycarbonyl)-2-methyl-5-(*m*-nitrophenyl)-4,5-dihydrofuran [8 (R = Me, R′ = OMe, R″ = H, Ar = *m*-NO$_2$C$_6$H$_4$)]**: 81%; mp 87–88 °C; $^1$H NMR $\delta$ 8.2 (m, 2 H), 7.6 (m, 2 H), 5.69 (dd, $J$ = 10.8 and 8.2, 1 H), 3.72 (s, 3 H), 3.43 (ddq, $J$ = 14.4, 10.8 and 1.6 Hz, 1 H), 2.89 (ddq, $J$ = 14.4, 8.2 and 1.6 Hz, 1 H), 2.32 (t, $J$ = 1.6 Hz, 3 H); IR (film) 3095–3005, 2985–2863, 1710, 1700, 1653, 1348, 1220, 1089, 995, 761, 735 cm$^{-1}$; MS $m/z$ 263 ($M^+$, 17), 231 (18), 189 (8), 115 (27), 77 (6), 43 (100). Anal. Calcd for $C_{13}H_{13}NO_5$: C, 59.31; H, 4.98; N, 5.32. Found: C, 59.23; H, 5.07; N, 5.35.

**Reaction with Dimethyl Malonate.** Chromatography of the crude product on silica gel, after elution with 1:1 petroleum ether–diethyl ether mixture, allowed the isolation of the following products. **5c gave methyl 2-(methoxycarbonyl)-4-methoxy-5-methyl-4-phenylhexanoate [9 (R = R′ = OMe; R″ = $^i$Pr, Ar = C$_6$H$_5$)]** in 48% yield: $^1$H NMR $\delta$ 7.3 (m, 5 H), 3.74 (s, 3 H), 3.57 (s, 3 H), 3.49 (three peaks, X portion of an ABX system, 1 H), 3.18 (s, 3 H), 2.89–2.67 (seven peaks, AB portion of an ABX system, 2 H), 2.06 (septet, $J$ = 6.5 Hz, 1 H), 0.78 (d, $J$ = 6.5 Hz, 3 H), 0.71 (d, $J$ = 6.5 Hz, 3 H); IR (film) 3095–3010, 2960–2882, 1755, 1735, 1602, 1385, 1260, 1084, 765, 705 cm$^{-1}$; MS $m/z$ 265 ($M^+$ – $C_3H_7$, 64), 233 (5), 205 (44), 145 (100), 77 (27), 43 (36). Anal. Calcd for $C_{17}H_{24}O_5$: C, 66.21; H, 7.84. Found: C, 66.02; H, 7.87. Moreover, a viscous colorless oil was recovered whose $^1$H NMR, IR, and C, H analysis were consistent with a 2:1 mixture of diastereomeric **5-isopropyl-3-(methoxycarbonyl)-5-phenyl-γ-butyrolactones [10 (R′ = OMe, R″ = $^i$Pr, Ar = C$_6$H$_5$)]**: 42%; $^1$H NMR referred to the main isomer $\delta$ 7.36 (s, 5 H), 3.79 (s, 3 H), 3.3 (m, 1 H), 2.91 (tight m, 2 H), 2.19 (septet, $J$ = 6.5 Hz, 1 H), 0.93 (d, $J$ = 6.5 Hz, 6 H); referred to the minor isomer $\delta$ 7.32 (s, 5 H), 3.77 (s, 3 H), 3.73–3.63 (three peaks, 1 H), 2.8 (tight m, 2 H), 2.19 (septet, $J$ = 6.5 Hz, 1 H), 0.91 (d, $J$ = 6.5 Hz, 6 H); IR of the mixture (film) 3095–3005, 2970, 2880, 1782, 1740, 1685, 1450, 1200–1110, 705 cm$^{-1}$. Anal. Calcd for $C_{15}H_{18}O_4$: C, 68.68; H, 6.92. Found: C, 68.57; H, 7.05. After hydrolysis by reflux of the mixture with alcoholic potassium hydroxide for 1 h then acidification and decarboxylation at 160 °C, a single product was obtained after chromatography on silica gel (1:1 petroleum ether–diethyl ether as the eluent) to which the structure of **5-isopropyl-5-phenyl-γ-butyrolactone** (68%) was assigned on the basis of the following spectral and analytical characteristics: $^1$H NMR $\delta$ 7.34 (s, 5 H), 2.5 (tight m, 4 H), 2.17 (septet, $J$ = 6.5 Hz, 1 H), 0.92 (d, $J$ = 6.5 Hz, 3 H), 0.87 (d, $J$ = 6.5 Hz, 3 H); IR (film) 3095–3005, 2970–1880, 1775, 1400, 1237, 1201, 1018, 930, 705 cm$^{-1}$; MS $m/z$ 204 ($M^+$, 1), 161 (100), 133 (13), 105 (52), 91 (8), 77 (39), 43 (12). Anal. Calcd for $C_{13}H_{16}O_2$: C, 76.44; H, 7.89. Found: C, 76.22; H, 8.06. From **5d, methyl 2-(methoxycarbonyl)-5,5-dimethyl-4-methoxy-4-phenylhexanoate [9 (R = R′ = OMe, R″ = $^t$Bu, Ar = C$_6$H$_5$)]** was isolated in 30% yield: $^1$H NMR $\delta$ 7.27 (s, 5 H), 3.72 (s, 3 H), 3.65 (s, 3 H), 3.50 (t, $J$ = 4.6 Hz, 1 H), 3.22 (s, 3 H), 2.92 (dd, $J$ = 4.6 and 1.4 Hz, 2 H), 0.89 (s, 9 H); IR (film) 3095–3005, 2960–2880, 1753, 1735, 1630, 1285, 1155, 708 cm$^{-1}$; MS $m/z$ 307 ($M^+$ – Me, 1), 256 (71), 233 (6), 205 (45), 145 (100), 115 (16), 91 (15), 77 (23), 57 (20). Anal. Calcd for $C_{18}H_{26}O_5$: C, 67.06; H, 8.13. Found: C, 66.92; H, 8.17. Finally, a white solid was recovered to which the structure of **5-*tert*-butyl-3-(methoxycarbonyl)-5-phenyl-γ-butyrolactone [10 (R′ = OMe, R″ = $^t$Bu, Ar = C$_6$H$_5$)]** (57%) was assigned on the basis of the following characteristics: mp 117–118 °C; $^1$H NMR (200 MHz) $\delta$ 7.3 (broad s, 5 H), 3.79–3.65 (four peaks, X portion of an ABX system, 1 H), 3.48 (s, 3 H), 3.12–2.82 (seven peaks, AB portion of an ABX system, 2 H), 0.97 (s, 9 H); IR ($CS_2$) 3095–3010, 2980–2975, 1787, 1746, 1148, 982, 739, 703 cm$^{-1}$. Anal. Calcd for $C_{16}H_{20}O_4$: C, 69.54; H, 7.29. Found: C, 69.55; H, 7.36. **5a yielded methyl 2-(methoxycarbonyl)-4-methoxy-4-phenylpentanoate [9 (R = R′ = OMe, R″ = Me, Ar = C$_6$H$_5$)]**: 63%; $^1$H NMR (200 MHz) $\delta$ 7.3 (m, 5 H), 3.70 (s, 3 H), 3.59 (s, 3 H), 3.52–3.46 (three peaks, X portion of an ABX system, 1 H), 3.09 (s, 3 H), 2.54–2.33 (sym m, seven peaks, AB portion of an ABX system, 2 H), 1.55 (s, 3 H); IR (film) 3095–3015, 2980–2830, 1753, 1735, 1434, 1153, 1075, 770, 703 cm$^{-1}$; MS $m/z$ 265 ($M^+$ – Me, 1), 185 (7), 145 (7), 135 (100), 105 (8), 91 (6), 77 (12), 59 (13), 43 (40). Anal. Calcd for $C_{15}H_{20}O_5$: C, 64.27; H, 7.19. Found: C, 64.12; H, 7.25. Moreover, **3-(methoxycarbonyl)-5-methyl-5-phenyl-γ-butyrolactone [10 (R′ = OMe, R″ = Me, Ar = C$_6$H$_5$)]** (25%, ca. 1:1 mixture of diastereoisomers) was recovered: $^1$H NMR referred to one stereoisomer $\delta$ 7.37 (s, 5 H), 3.81 (s, 3 H), 3.67–3.40 (four peaks, 1 H), 2.88 (tight m, 2 H), 1.81 (s, 3 H); referred to the other stereoisomer $\delta$ 7.38 (s, 5 H), 3.98–3.60 (four peaks, 1 H), 3.71 (s, 3 H), 2.75 (sym m, 2 H), 1.72 (s, 3 H); IR of the mixture (film) 3095–3005, 2980–2850, 1780, 1735, 1602, 1447, 1135, 768, 702 cm$^{-1}$. Anal. Calcd for $C_{13}H_{14}O_4$: C, 66.66; H, 6.02. Found: C, 66.48; H, 6.15. **5b gave methyl 2-(methoxycarbonyl)-4-methoxy-4-phenylhexanoate [9 (R = R′ = OMe, R″ = Et, Ar = C$_6$H$_5$)]** in 31% yield: $^1$H NMR $\delta$ 7.3 (m, 5 H), 3.68 (s, 3 H), 3.48 (s, 3 H), 3.41–3.25 (three peaks, X portion of an ABX system, 1 H), 3.12 (s, 3 H), 2.84–2.23 (eight peaks, AB portion of an ABX system, 2 H), 2.14–1.53 (m, 2 H), 0.67 (t, $J$ = 7.2 Hz, 3 H); IR (film) 3095–3005, 2970–2875, 1752, 1737, 1602, 1433, 1152, 1071, 763,

702 cm$^{-1}$; MS $m/z$ 265 ($M^+ - C_2H_5$, 54), 205 (36), 149 (100), 145 (81), 115 (32), 91 (27), 77 (34), 59 (40). Anal. Calcd for $C_{16}H_{22}O_5$: C, 65.29; H, 7.53. Found: C, 65.03; H, 7.64. **5-Ethyl-3-(methoxycarbonyl)-5-phenyl-γ-butyrolactone [10 (R′ = OMe, R″ = Et, Ar = $C_6H_5$)]** was also recovered in 59% of yield (1.3:1 mixture of two diastereoisomers): $^1$H NMR (200 MHz) referred to the main stereoisomer δ 7.3 (tight m, 5 H), 3.78 (s, 3 H), 3.54-3.43 (four peaks, 1 H), 2.92-2.63 (m, 2 H), 2.08 (q, $J$ = 7.1 Hz, 2 H), 0.83 (t, $J$ = 7.1 Hz, 3 H); referred to the other stereoisomer δ 7.35 (tight m, 5 H), 3.67 (s, 3 H), 3.84-3.73 (four peaks, 1 H), 2.97-2.62 (m, 2 H), 1.98 (q, $J$ = 7.1 Hz, 2 H), 0.82 (t, $J$ = 7.1 Hz, 3 H); IR (film) 3095-3005, 2975-2850, 1780, 1740, 1602, 1450, 1195, 703 cm$^{-1}$. Anal. Calcd for $C_{14}H_{16}O_4$: C, 67.73; H, 6.49. Found: C, 67.97; H, 6.55.

**Kinetic Studies.** The relative rate constants of Z- and R-substituted styrenes with respect to styrene in the CAN-promoted oxidative addition of 2,4-pentanedione, methyl 3-oxobutanonate, and dimethyl malonate were determined by the competitive method. Kinetic data for the oxidative addition of dimethyl malonate to Z-substituted styrenes were available from a previous work.[10] To a solution of CAN (1-3 mmol) in 4 mL of solvent, a solution of dicarbonyl compound (ca. 0.5 mmol), substituted styrene (0.6-1.0 mmol), styrene (0.6-1.0 mmol), and $m$-chlorotoluene (ca. 0.75 mmol) as an internal standard in the same solvent (1.0 mL) was added at 20 °C. The mixture was allowed to react 2-5 min (reactions with 2,4-pentanedione and methyl 3-oxobutanoate) or 40 min (reactions with dimethyl malonate). The mixture was poured into water (50 mL) and extracted with hexane (3 × 25 mL). The collected organic phases were washed with water (75 mL), dried with anhydrous sodium sulfate, and analyzed by GLC after suitable dilution. The relative rate constants were determined by the equation $k_S/k_H = \log (S^\circ/S)/\log (H^\circ/H)$ where $S^\circ/S$ and $H^\circ/H$ are the molar ratios of substituted styrene and styrene, respectively, before and after the reaction. In all cases the amount of reacted styrenes corresponds (5%) to the amount of dicarbonyl compound consumed in the reaction. An identical procedure was followed for the reactions with dimethyl malonate where CAN was used in a 6:1 molar ratio with respect to the dicarbonyl compound, as well as for the reactions carried out in the presence of lithium perchlorate. In the reactions with 2,4-pentanedione, competitive experiments were also carried out using a large calculated excess of styrenes and the relative rates determined by the equation $k_S/k_H = (P_S/P_H)(H^\circ/S^\circ)$. Here, $P_S/P_H$ is the molar ratio of the reaction products formed from the competing styrenes and $H^\circ/S^\circ$ is the molar ratio between unsubstituted and substituted styrene before the reaction. In no cases the difference between the values determined by the two methods exceeded 3%.

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**Registry No. 5b**, 2039-93-2; **5c**, 17498-71-4; **5d**, 5676-29-9; **8** (R = R′ = Me, R″ = H, Ar = $C_6H_5$), 13463-61-1; **8** (R = R′ = Me, R″ = H, Ar = $p$-Me$C_6H_4$), 134391-03-0; **8** (R = R′ = Me, R″ = H, Ar = $p$-Cl$C_6H_4$), 134391-04-1; **8** (R = R′ = Me, R″ = H, Ar = $m$-Cl$C_6H_4$), 134391-05-2; **8** (R = R′ = Me, R″ = H, Ar = $m$-$NO_2C_6H_4$), 134391-06-3; **8** (R = R′ = R″ = Me, Ar = $C_6H_5$), 54023-32-4; **8** (R = R′ = Me, R″ = Et, Ar = $C_6H_5$), 134391-07-4; **8** (R = R′ = Me, R″ = i-Pr, Ar = $C_6H_5$), 134391-08-5; **8** (R = R′ = Me, R″ = t-Bu, Ar = $C_6H_5$), 134391-09-6; **8** (R = Me, R′ = OMe, R″ = H, Ar = $C_6H_5$), 134391-10-9; **8** (R = Me, R′ = OMe, R″ = H, Ar = $m$-$NO_2C_6H_4$), 134391-11-0; **9** (R = R′ = OMe, R″ = i-Pr, Ar = $C_6H_5$), 134391-12-1; **9** (R = R′ = OMe, R″ = t-Bu, Ar = $C_6H_5$), 134391-16-5; **9** (R = R′ = OMe, R″ = Me, Ar = $C_6H_5$), 134391-18-7; **9** (R = R′ = OMe, R″ = Et, Ar = $C_6H_5$), 134391-21-2; **10** (R′ = OMe, R″ = i-Pr, Ar = $C_6H_5$) (isomer 1), 134391-13-2; **10** (R′ = OMe, R″ = i-Pr, Ar = $C_6H_5$) (isomer 2), 134391-14-3; **10** (R′ = OMe, R″ = t-Bu, Ar = $C_6H_5$), 134391-17-6; **10** (R′ = OMe, R″ = Me, Ar = $C_6H_5$) (isomer 1), 134391-19-8; **10** (R′ = OMe, R″ = Me, Ar = $C_6H_5$) (isomer 2), 134391-20-1; **10** (R′ = OMe, R″ = Et, Ar = $C_6H_5$) (isomer 1), 134391-22-3; **10** (R′ = OMe, R″ = Et, Ar = $C_6H_5$) (isomer 2), 134391-23-4; CAN, 15078-94-1; α-methylstyrene, 98-83-9; ethyl phenyl ketone, 93-55-0; isopropyl phenyl ketone, 611-70-1; *tert*-butyl phenyl ketone, 938-16-9; methyltriphenylphosphonium iodide, 2065-66-9; lithium diphenylcuprate, 23402-69-9; pivaloyl chloride, 3282-30-2; 2,4-pentanedione, 123-54-6; $p$-methylstyrene, 622-97-9; styrene, 100-42-5; $p$-chlorostyrene, 1073-67-2; $m$-chlorostyrene, 2039-85-2; $m$-nitrostyrene, 586-39-0; methyl 3-oxobutanoate, 105-45-3; 5-isopropyl-5-phenyl-γ-butyrolactone, 134391-15-4.

# Stereochemical Control of Microbial Reduction. 17. A Method for Controlling the Enantioselectivity of Reductions with Bakers' Yeast

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The stereoselectivity of the bakers' yeast catalyzed reduction of β-keto esters to optically active β-hydroxy esters can be controlled by the introduction of a third reagent. To gain insight into the mechanism of this enzymatic reduction, β-hydroxy ester oxidoreductases were isolated from the cells of raw bakers' yeast. Four dominant competing enzymes were isolated, purified, and characterized. Among these, two reduce β-keto esters stereospecifically to the corresponding D-β-hydroxy esters. The other two afford the L-hydroxy esters. The rates of enzymatic reduction were determined in the presence and absence of the additives.

## Introduction

The development of methods for the synthesis of optically active compounds has become one of the most important goals in the fields of organic chemistry and biochemistry. In recent years, there have been dramatic developments in the asymmetric synthesis of organic compounds.[1] In particular, biological methods have been extensively developed within the last decade.[2]

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(1) Morrison, J. D., Ed. *Asymmetric Synthesis*; Academic Press: New York, 1985; Vols. 2-5.

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