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On the mechanism of the addition of organolithium reagents to cinnamic acids

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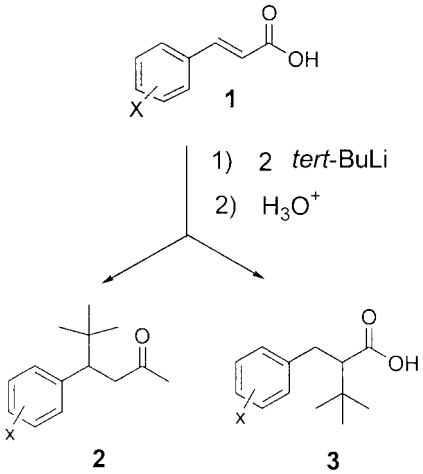
Abstract—The regioselectivity of the addition of *tert*-butyllithium to cinnamic acid is subject to reaction conditions and to substituent electronic effects. Significant effects are observed in the presence of several additives including a radical trap such as α-methylstyrene. Competition experiments by addition of the organolithium reagent to mixtures of substituted cinnamic acids show that the relative rates of both conversion of the starting acids and formation of the 1,3-adducts are subject to electronic effects, whereas rates for 1,4-addition are independent of the substituents. These features are in agreement with a polar addition mechanism, but a fast SET equilibrium followed by slow radical combination would be possible as well. © 2001 Elsevier Science Ltd. All rights reserved.

1. Introduction

Reports on the synthetic applications of addition of organolithium reagents to activated double bonds of acrylic acids,[1–5] styrene,[6] cinnamyl alcohols, ethers, amines and dioxolanes,[7] or cinnamic aldehydes,[8] esters,[9] or amides,[10,11] have been recently published. Many of these additions afford single regioisomers, but cinnamic acid **1a**, its esters or primary or secondary amides afford mixtures of 3- and 2-alkyl-substituted phenylpropanoic acids **2a** and **3a** (Scheme 1), or their corresponding derivatives, on reaction with alkyllithium or magnesium reagents. This behaviour was first observed by Crossland on reaction of *tert*-butylmagnesium chloride with ethyl cinnamoate and later by Klumpp for *tert*-butyllithium and cinnamic acid **1a**.[12–15] Mixtures of Michael and *contra*-Michael adducts were also reported independently by Mortier and by ourselves on reaction of cinnamic acid with other alkyllithium reagents.[4,5,16] However, the mechanism of these additions has not yet been clarified. According to Crossland and Klumpp, a single electron transfer (SET) would first afford the *tert*-butyl radical and a cinnamic radical lithium enolate **A**, as shown in Scheme 2 for cinnamic acid **1a** (Scheme 2, path a). Diffusionless radical combination would give the 1,4-adduct as an enolate (path b), whereas diffusion of the *tert*-butyl radical would lead to the 1,3-addition of the radical to a second molecule of cinnamic acid lithium salt (path c) giving the benzylic radical **B** and this would undergo a second SET (path d) with the radical enolate **A**, with formation of the benzylic anion form of the 1,3-adduct and recovery of one molecule of cinnamic acid lithium salt. This stepwise radical mechanism was supported by lower amounts of the 1,3-adduct reported by Crossland when the reaction was carried out in the presence of α-methylstyrene, as a radical trap.



1a; X = H
1b; X = *p*-MeO
1c; X = *p*-Me
1d; X = *m*-MeO
1e; X = *p*-Cl
1f; X = *m*-Cl

Scheme 1.

Keywords: lithium; organolithium Michael reaction; carboxylic acids; linear free-energy relations.

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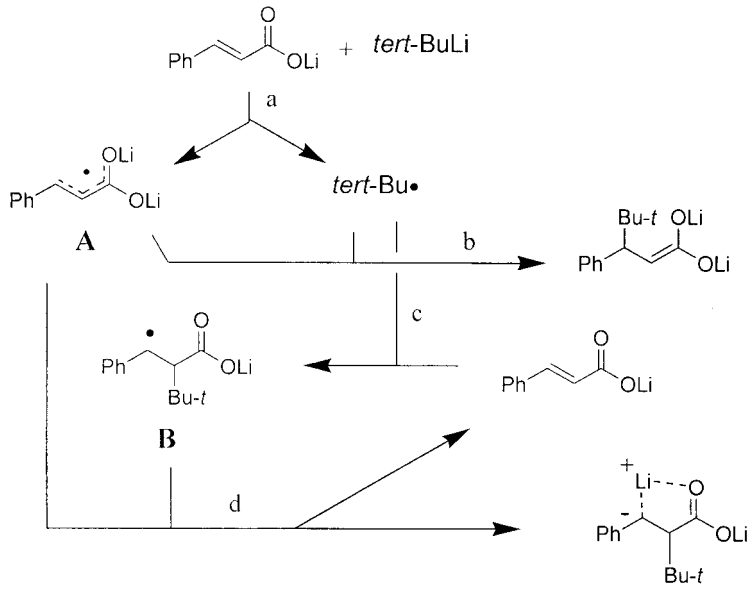
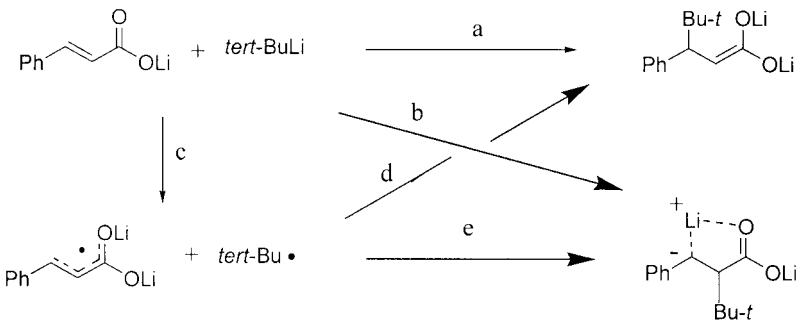


Scheme 2.

In previous work, attention was paid to the scope of this unusual addition and to the experimental conditions which modified the regioselectivity. Several organolithium reagents were then allowed to react with cinnamic acid, whereas *tert*-butyllithium was added to a variety of β-aryl-acrylic acids.[16] Klumpp had found that addition of *n*-butyllithum to cinnamic acid led to the 1,4-adduct along with a small amount (6%) of the 1,3-adduct.[15] With the same acid as acceptor we confirmed the latter result and found that *sec*-butyllithium afforded a 60:40 ratio for Michael and *contra*-Michael adducts and that phenyllithium gave exclusively the Michael adduct.[4,5,16] Some of the regioselectivity trends then observed for alkyllithium reagents on addition to cinnamic acid and to other β-aryl-acrylic acids could be simply explained through steric hindrance, but significant electronic effects were found when additions of *tert*-butyllithium to *para*- and *meta*-substituted cinnamic acids were carried out. Inverted regioselectivity trends for 1,4/1,3 ratios were obtained for *p*-dimethylamino- and *m*-chloro-cinnamic acids (84:16 to 21:79, respectively) and linear correlations were obtained for the logarithms of the 1,4/1,3 regioselectivity ratios versus the substituent σ constants($\rho = -1.02$). We felt thus that a simple polar addition mechanism (Scheme 3, paths a, b) could give account of the observed regioselectivity. However, the evidence for the polar nature of the addition then became blurred by the fact that a linear correlation was obtained as well for a radical $\sigma^{\cdot}$ constant[17] and, more importantly, because the decrease of 1,3-addition product in the presence of α-methylstyrene reported by Crossland was confirmed. *p*-Dinitrobenzene was assayed as well as a radical trap, but the reaction became very complex and conclusions could not be drawn.

In the present study we want to provide new experimental support for the polar mechanism of the addition of *tert*-butyllithium to cinnamic acids **1**. A wider variety of the reaction conditions for cinnamic acid **1a** has shown now that significant effects on the regioselectivity of the addition may be caused by a variety of additives other than α-methylstyrene. On the other hand, competition experiments by addition of limited amounts of the organolithium reagent to mixtures of substituted cinnamic acids **1b** to **1f** and cinnamic acid **1a** have shown that the relative rates of conversion of the starting acids and formation of the 1,3-adducts are both subject to electronic effects, whereas 1,4-addition is independent of the substituents. The study of the acidic reaction mixtures by GLC-MS has not afforded any clear evidence for side-products expected from radical intermediates.



Scheme 3.

Table 1. Addition of *tert*-butyllithium to cinnamic acid **1a**. Influence of reaction conditions on regioselectivity

Entry	Method[a]	Starting **1a**		*tert*-BuLi		Additive		Crude yield (%)	Recovered **1a** (%)	Regioselectivity ratios **2a/3a**
		mmol	mL	mmol	mL		mmol			
1	A[b]	2.25	20	4.5	10	—		82	—	37:63
2	A[b]	2.25	5	4.5	8	—		70	—	49:51
3	A[b]	2.25	20	4.5	100	—		70	20	39:61
4	B[b]	2.25	10	4.5	2.8	—		96	—	47:53
5	A	0.5	20	1.2	10	—		—	—	53:47
6	B	0.5	30	1.2	0.8	—		64	6	38:62
7	B	2.25	30	5.0	2.9	—		80	3.5	45:55
8	B[c]	2.25	30	5.0	2.9	—		62	trace	62:38
9	B	2.25	30	5.0	2.9	LiBr	5	81	trace	58:42
10	B	2.25	30	5.0	2.9	Benzene	30	88	trace	68:32
11	A[b]	2.25	20	4.5	10	MS[d]	5	84	13	50:50
12	B	2.25	30	5.0	5	MS	2.2	82	trace	48:52
13	B	2.25	30	4.3	2.9	MS	37.7	78	trace	48:52
14	B	1.0	15	5.0	2.5	Hexane	15	95	trace	50:50

[a] Method A: Slow addition of acid **1a** in THF to the stirred organolithium reagent at −70°C in pentane/THF; Method B: Slow addition of the organolithium reagent in pentane to the stirred acid **1a** in THF at −70°C
[b] Regioselectivity ratios established by ^{1}H NMR.[16]
[c] Addition carried out at 0°C.
[d] MS stands for α-methylstyrene.

2. Results

Regioselectivity ratios had formerly been obtained through ^{1}H NMR spectra of crude reaction acid fractions. Relative amounts of all components of these mixtures have been established now by GLC after esterification with diazomethane. Chromatographic peaks for the adducts have been unambiguously identified thanks to the exclusive esterification of the 1,4-adducts by the Fischer method, and the esterification of both regioisomers with diazomethane, as previously done for the study of composition of mixtures through ^{1}H NMR spectra.[16] Ethyl 3-phenylpropanoate has been used as reference and calibration curves have been established against this reference for the methyl esters of all the starting acids and their adducts.

Modification of the regioselectivity of the addition of *tert*-butyllithium to cinnamic acid **1a** as a function of reaction conditions is shown in Table 1. Inversion in the order of addition of the reagents, their relative amounts (entries 1 to 7) and changes of concentrations are accompanied by modification of the 1,4/1,3 ratios, although the regioselectivity trend is either preserved or only slightly inverted (entry 5). More significant changes, with clear inversion of regiochemical trend, are observed when the reaction is carried out at 0°C (entry 8), or in the presence of lithium bromide, or benzene (entries 9 and 10). What is more important, the effect of α-methylstyrene (MS) as additive (entries 11–13) is completely comparable to that caused by hexane (entry 14). The effect of diverse ligands on the addition of *n*-butyllithium to secondary cinnamamides reported by Normant are in keeping with the present observations.[10,11]

In connection with the above results, some experiments of addition of limited amounts of the organolithium reagent to cinnamic acid **1a** and to *p*-chlorocinnamic acid **1e** have shown that regioselectivity ratios depend to a small extent, but reproducibly, on the relative amounts of starting acid and organolithium reagent. Thus for 0.5 mmol of cinnamic acid 1,4/1,3 ratios 32/68, 47/53 and 36/64 have been obtained for addition of 0.3, 0.75 and 0.9 mmol of *tert*-butyllithium. Similarly, for the same amount of *p*-chlorocinnamic acid **1e** additions of 0.45, 0.81 and 1.17 mmol led to 25/75, 40/60 and 45/55 1,4/1,3 ratios, respectively.

The fact that regioselectivity could be a function of reaction conditions was cause for concern. Indeed, in the competition experiments the mixture of cinnamic acids is subjected to limited amounts of reagent (see below) and this limitation may differ from one competing acceptor to another on account of their relative reactivity; the competition results could then be unreliable. In order to find the extent of the error owing to this origin, regioselectivities have been established for additions of slight excess of *tert*-butyllithium to cinnamic acids under the same conditions as for the competition experiments and compared to the regioselectivities obtained in these experiments. 1,4/1,3 Ratios (**2**:**3**) for cinnamic acid **1a** and substituted cinnamic acids

Table 2. Addition of *tert*-butyllithium to cinnamic acids[a]

Starting acid **1**	Crude yield (%)	Recovered acid **1** (%)	**2** (%)	**3** (%)	Regioselectivity ratios **2**:**3**
1a	75	9	34.5	56.4	38:62
1b	74	10	73.0	16.6	81:19
1c	85	7	62.0	30.5	67:33
1d	90	7	30.2	62.4	33:67
1e	82	trace	48.0	52.0	48:52
1f	89	trace	26.2	73.7	26:74

[a] *tert*-Butyllithium (1.2 mmol) in pentane (0.8 mL) added to cinnamic acid **1x** (0.5 mmol) in THF (30 mL) at −70°C.

Table 3. Competition experiments[a]

Starting acids	Crude yields (%)[b]	Recovered starting acids (%)[c]		Obtained 1,4-adducts (%)[c]		Obtained 1,3-adducts (%)[c]		Competition ratios (CR)[d,e]			Regioselectivity ratios	
		1a	**1x**	**2a**	**2x**	**3a**	**3x**	**1x/1a**	**2x/2a**	**3x/3a**	**2a/3a**	**2x/3x**
1b/1a	69	7	24	19.1	19.4	19.0	4.8	0.69	1.01	0.25	50:50	80:20
1c/1a[f]								0.67	0.98	0.64		
1d/1a	71	17	18	14.1	14.0	16.9	25.0	0.98	0.99	1.48	45:55	36:64
1e/1a	75	60	57	8.3	8.1	11.0	18.8	1.09	0.98	1.71	43:57	31:69
1f/1a	70	29	8	11.8	11.2	14.8	38.0	1.45	0.95	2.57	44:56	22:78
		1b	**1c**	**2b**	**2c**	**3b**	**3c**	**1c/1b**	**2c/2b**	**3c/3b**	**2b/3b**	**2c/3c**
1c/1b	73	40	41	14.7	14.3	3.9	10.1	0.97	0.97	2.59	79:21	58:42

[a] *tert*-Butyllithium (1.2 mmol) in pentane (0.8 mL) added to a mixture of cinnamic acid **1a** (0.5 mmol) and a substituted cinnamic acid **1x** (0.5 mmol) in THF (30 mL) at −70°C.
[b] Crude yields are estimated for a complete conversion of starting acids to adducts.
[c] Amounts estimated from integration GLC peaks, calibration curves with ethyl 3-phenylpropanoate as reference and measured amounts of aliquots.
[d] Given for conversion of starting acids **1** and formation of adducts **2** and **3**.
[e] For estimation of conversion yields of starting acids, the yields for recovered acids **1** are corrected by a recovery coefficient, obtained from the crude yields of the mixture and summation of the estimated yields of all components in the mixture.
[f] Ratios estimated by combining results of competition reactions **1b/1a** and **1c/1b**.

1b–**1f** both as single acceptor and under competition conditions are shown in Tables 2 and 3, respectively. Regioselectivity ratios for *p*- and *m*-methoxy- and for *m*-chlorocinnamic acids **1b**, **1d**, and **1f**, vary very little, but more important changes are observed for cinnamic and *p*-chlorocinnamic acids **1a** and **1e**. An equivalent comparison for *p*-methylcinnamic acid could not be done. These changes are indicative of the limitation of the present method. However, and most significant, the regioselectivity ratios **2a/3a** for cinnamic acid in the competition experiments do not vary to any great extent; the values of the competition ratios now obtained are thus reliable within experimental error, although significant value should not be granted to small differences.

Competition experiments have been carried out by addition of 1.2 mmol of *tert*-butyllithium in pentane (1.5 M) to 0.5 mmol each of both cinnamic acids in 30 mL of THF at −70°C. These standard conditions justify the assumption that, within experimental error, the amounts of reactive or product compounds now obtained keep a proportion with their respective relative rates of conversion or formation. Reactivity, solubility, or isolation difficulties associated with the nature of some substituents, as well as overlap of some of the GLC peaks, have severely constrained the number of substituted cinnamic acids now employed, especially when compared to our previous work.[16] For *p*-methylcinnamic acid **1c**, overlapping difficulties were overcome by combining results of the competition reactions of this acid with *p*-methoxycinnamic acid **1b** and of the latter with cinnamic acid **1a**.

Crude yields, estimated yields of conversion of the starting acids and yields of adducts obtained in the competition experiments, along with competition ratios are given in Table 3. Observation of competition ratios (CR) reveal that conversion of the starting acids is speeded up by electron-withdrawing groups and slowed down by electron-donating substituents. The same trend is observed for 1,3-addition, with a competition ratio ranging from 2.57 for *m*-chlorocinnamic acid **1f** to 0.25 for *p*-methoxycinnamic acid **1b**. However and most significantly, no electronic effects are observed for 1,4-addition, all ratios ranging between 0.95 and 1.01. When the logarithms of the competition ratios (CR) are plotted against the Hammett susbtituent σ constants, good linear correlations are obtained (Fig. 1), with positive reaction constants for the converted starting acids (ρ=0.52, R^2=0.932) and for formation of 1,3-adducts (ρ=1.44, R^2=0.880), and a practically zero reaction constant (ρ=−0.035, R^2=0.728) for 1,4-addition. It was most interesting to observe now that correlations against radical $\sigma^{\cdot}$ constants for the rather limited number of *para*-substituted cinnamic acids now available deviate strongly from linearity.

Significant information for clarification of reaction mechanisms may be obtained from observation of side-products. In the former study we stated that the organolithium additions gave no other acidic compounds other than the 1,3- and 1,4-adducts, as this could be concluded from observation of the NMR spectra of crude mixtures. We were interested now to find whether side-products could be found by the more sensitive chromatographic technique. Again the aforementioned adducts were the sole significant products when the esterified crude reaction mixtures were studied by GLC. Peaks for the esters of recovered cinnamic acids and 1,4- and 1,3-adducts accounted for over 98% of the integration. Small GLC peaks at higher retention times were occasionally observed and GLC-MS analysis showed molecular peaks M^+ corresponding to pyrazolines **4** and pyrazoles **5** derived from 1,3-dipolar cycloaddition of excess diazomethane to unreacted cinnamic acids. Spectra of other chromatographic peaks were in agreement with compounds containing a *tert*-butyl group and two cinnamic acid structural unities, such as, for instance **6** or **7**, which could result from a Michael addition of the carbanionic form of the 1,3-adduct of cinnamic acid. Another group of small

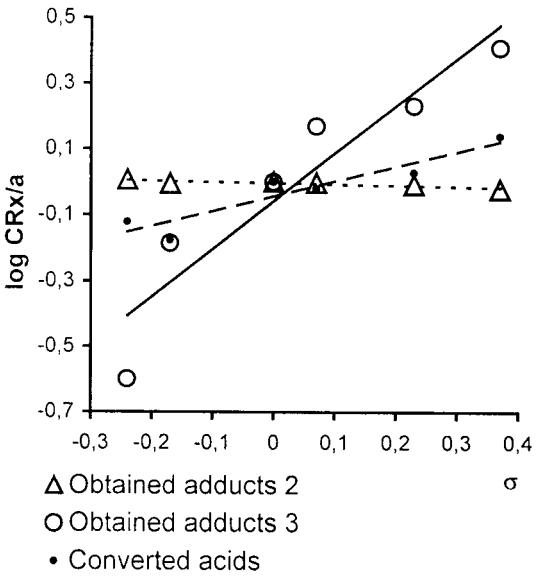
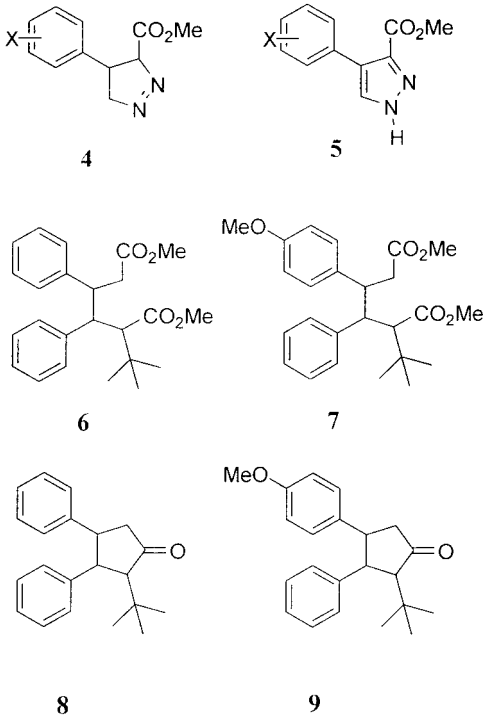


Figure 1.



peaks might derive from the former ones, as their MS spectra were in agreement with the cyclopentanones **8** or **9**, which could result from a *domino*-1,3 addition–Michael addition–Dieckmann cyclization, with decarboxylation of the resulting keto acid after isolation of the acidic fraction of the reaction mixture.[18]

3. Discussion

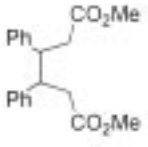
The regioselectivities obtained under diverse reaction conditions show that the decrease of 1,3-addition observed by Crossland and by ourselves on addition of α-methylstyrene does not prove the intermediacy of a radical species. These effects may rather be explained by the diverse solvated ion pair aggregation forms in which carboxylic acids, their lithium salts and lithium enolates may be present in solution. It is well established that the equilibria between aggregates may be modified by changes in solvent polarity or by lithium halides or other additives present in the solution. This may be the case for the actual acceptors in the reacting mixture, which are constituted initially by the free acid and afterwards by mixtures of their lithium salts and of the final carbanionic adducts. [Luche has shown that for organolithium reagents, addition to carboxylic acids and deprotonation may be competitive processes. The same might apply for additions to unsaturated carboxylic acids.[19]] The above additives may thus contribute to modify the relative accessibility of the C-2 and C-3 carbon atoms of the acceptor to the attacking organolithium or radical species. Regioselectivity changes found on addition of limited amounts of reagents most probably reflect the mobility of the ion pair aggregation equilibria during the progress of the reaction.

Once it was found that the experimental data that supported the stepwise radical mechanism (Scheme 2) advanced by Crossland and Holm[14] could be understood through aggregation effects, explanation of the results of the addition should be attempted in simple terms by assumption of a competition in the attack at one or other of the ethylenic carbon atoms of the acceptor, by distinction between a polar or a SET–radical combination mechanism (Scheme 3). For the latter mechanism the rate-determining step should then be established.

The observed trends for the free-energy linear correlation reaction constants are qualitatively in agreement with a polar mechanism, especially if rates are acknowledged to be determined by product development. Indeed, an anionic charge is being developed at the benzylic carbon when attack occurs at C-2, whereas an enolate forms on attack at C-3. The energy of the benzylic anion should then depend on the nature of the phenyl ring substituents, whereas the electron-withdrawing or releasing character of these would be immaterial for the development of the enolate anion. The value of the ρ reaction constant for the conversion of the acids is intermediate between the values of the constants of the 1,3- and 1,4-additions, a feature which fits with conversions occurring through competition between two different rate-determining steps, each of them leading to a different compound and each being subject to different substituent effects, as should happen in this polar mechanism.

The reaction constant $\rho=1.44$ here obtained for the 1,3-addition is lower than the value expected for generation of an anionic charge at the benzylic carbon. Reaction constants with absolute values well above 2 are usually reported for modification of charge at a carbon atom directly bound to a benzene ring.[20,21] However, the charged benzylic carbon resulting now from the polar 1,3-addition should be expected to be tightly coordinated to a lithium atom, a feature which should significantly reduce the substituent electronic effects and thus, the present result is not in contradiction with a polar mechanism. This lithium coordination has been put forward for the known selective ionization of the benzylic protons, instead of the protons α to carbonyl protons, on treatment of hydrocinnamic secondary amides with *sec*-butyllithium as base.[22]

When the SET–radical combination mechanisms are considered (Scheme 3, pathways c, d and e), the substituent effects cannot be taken separately, especially for the conversion of the starting acids and for the formation of the 1,4-adducts. If a SET–radical combination mechanism with a slow electron transfer occurs, the substituent effects found for the relative conversion rates of the cinnamic acids should be reflected on the rates of product formation and thus, the reaction constant for formation of 1,4-adducts should not be zero, unless substituent effects would be perfectly counterbalanced—a most unlikely circumstance. In contrast, a SET as a previous equilibrium cannot entirely be ruled out, as assumption of substituent effects in one step being counterbalanced in the other seem more feasible now. Indeed, the equilibrium constants of previous fast equilibria contribute to the observed rate constants and thus, the substituent effects found for the following rate-determining step cannot afford a reaction constant $\rho=0$ unless either the equilibrium constants are not influenced by substituent effects, or these are exactly counterbalanced in the second step. This might happen in the present case, where the electron transfer leads to an anion radical and thus a positive reaction constant should be expected. The following radical combination for the 1,4-addition does not neutralize the anionic charge, but disrupts the conjugation of the aromatic ring with the anionic chain and thus, a substituent effect of opposite sign could be expected. The value for the reaction constant found now for the 1,3-addition might be thought to



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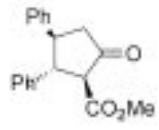

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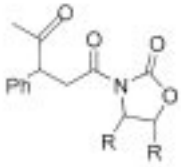

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fit with a SET leading to a delocalized radical anion (Scheme 3, path c), but it is certainly much higher than that reported for the reversible one-electron electrochemical reduction of methylthioesters of cinnamic acids against Hammett σ^- constants ($\rho \approx 0.2$).[23]

As for the side-products, adipic and cyclopentanones related to structures **10** or **11** would be expected from SET processes, but the observed structures **6–9** can be conveniently explained instead by polar additions.

Some further comments about the distinction between polar and SET mechanisms may be convenient here. Recent publications by Gajewski and by Holm discuss the vast amount of work done on the additions of magnesium and lithium organometallic reagents to aldehydes and ketones and stress the difficulties for the experimental distinction between polar and SET–radical combination mechanisms.[24,25] Thus, the conversion pathway is determined not only by the redox potentials of the organometallic reagent and the electrophilic acceptor, the ergonicity of the polar addition and steric effects, which may retard C—C bond formation, but also by reaction conditions, such as temperature. According to these publications butyllithium reagents are fairly readily oxidized to their corresponding radicals by transfer of one electron to carbonyl groups, but the exothermicity of the polar addition may render the latter pathway more favourable than the SET–radical combination process. Unfortunately, as far as we know, there are no equivalent studies on the 1,4-additions of organolithium reagents to unsaturated carboxylic acids or their derivatives. It is not feasible now to ascertain, for instance, to what extent the present acceptors may be reduced by butyllithium in a SET process and what is the exothermicity of the polar addition to the C-2 or C-3 atoms of the carboxyl- and phenyl-activated double bond of cinnamic acid.

Comparison of the present regioselectivity results with related processes and consideration of their mechanisms is rather puzzling, as exclusive 1,4-addition of the *tert*-butyllithium reagent to cinnamic acid would be advanced regardless of the polar or SET nature of its mechanism. On the one hand, phenyllithium is known to add to carbonyl groups through a two-electron C—C bonding process owing to its reluctance to be oxidized by one-electron transfer.[24] The same polar mechanism is most likely to be operative for the reaction of phenyllithium with cinnamic acids and esters, an addition which leads exclusively to 1,4-adducts.[4,5,9,16] On assumption then of a similar two-electron process for the addition of the *tert*-butyllithium reagent to cinnamic acid, only the 1,4-adduct would be expected, instead of the observed 1,4 and 1,3 mixture. On the other hand, there is ample experience indicating that radical anions generated by reduction of cinnamic systems tend to afford radical combination products through their C-3 carbons. Thus, cathodic and samarium(II) reductive reactions of cinnamic derivatives lead to 1,4-*homo*-coupling products, namely 3,4-diphenyladipic derivatives **10**, or their corresponding Dieckmann condensation cyclopentanones **11**.[23,26–28] Further, a 1,4-*hetero*-coupling of cinnamic amides and acetic anhydride, to give amides **12** under reductive electrochemically induced conditions, has also been reported.[29] Although these reductive and electrochemical conditions are not entirely comparable with the present additions, they suggest that only 1,4-adducts would again be obtained, should the easily reduced *tert*-butyllithium reagent add to cinnamic acid through a SET-radical coupling mechanism. The answer to this riddle is beyond the reach of the present study.

4. Conclusion

Study of the effect of reaction conditions on the regioselectivity of the addition of *tert*-butyllithium on the C=C double bond of cinnamic acid and competition experiments of addition to substituted cinnamic acids show that the addition of *tert*-butyllithium to cinnamic acids can be explained in a simple way by a polar addition mechanism, with competition between attack at C-3 and C-2 carbon atoms of the cinnamic lithium salts. However, a fast electron transfer followed by a rate-determining radical coupling may be possible as well.

5. Experimental

Gas chromatographic determinations were carried out with a ThermoQuest Trace 2130 gas chromatograph, with a FID detector, a 0.25 μm film DB-5 30 m capillary column and nitrogen as carrier gas. Introduction of sample at 230°C by splitless mode, detector at 310°C and a gradient program (5 min at 120°C, one 5°C/min ramp up to 200°C and 3 min hold time) were employed. Mass spectra were determined with VG Autospec or Trio 1000 spectrometers by electronic impact or chemical ionization. Tetrahydrofuran (THF) was distilled from blue sodium diphenylketyl immediately before use. All reactions were carried out under nitrogen atmosphere, using standard conditions for exclusion of moisture. The reaction temperature (−70°C) was achieved by cooling with a CO_2/acetone bath. Evaporation of solvents was carried out with a vacuum rotatory evaporator at 40°C. Cinnamic acids and 1.6 M *tert*-butyllithium in pentane were purchased from Aldrich. The concentration of the latter was established volumetrically with salicylaldehyde phenylhydrazone as 1.5 M.[30]

The methyl esters of the cinnamic acids **1** are well-known compounds and have been obtained now by esterification with diazomethane. The methyl esters of the 1,3- and 1,4-adducts have been previously described,[16] and prepared either with diazomethane or by selective esterification of the reaction mixtures with methanol, as already described.[16] Ethyl 3-phenylpropanoate has been prepared by esterification of hydrocinnamic acid with ethanol. ^1H and ^{13}C NMR spectra of common esters prepared now were in agreement with expectancy.

5.1. General procedure for addition of *tert*-butyllithium to cinnamic acids

tert-Butyllithium (1.5 M) in pentane (0.8 ml) was added dropwise over 3 min with the aid of a syringe to the stirred cinnamic acid (0.5 mmol) in THF (30 ml) at −70°C. The solution was stirred for 1 h at the same temperature, water (30 ml) was added, and the mixture extracted with hexane

(3×15 ml). The aqueous layer was acidified, under stirring and ice-water cooling, by slow addition of conc. hydrochloric acid and then extracted with ethyl acetate (4×15 ml). The joint organic layers were dried. Evaporation of the solvent gave a mixture of recovered starting acids and adduct carboxylic acids, whose weight was determined. An aliquot of the mixture was esterified with an ether solution of diazomethane; a known amount of ethyl 3-phenylpropanoate was added; the solution was diluted to a convenient volume and analysed by GLC.

5.2. General procedure for competition experiments of addition of *tert*-butyllithium to cinnamic acid (or *p*-methoxycinnamic acid) and a substituted cinnamic acid

The same procedure of addition was followed as above, except for the use of 0.5 mmol of both cinnamic acid **1a** and the substituted acid **1b**–**1d**.

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