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1,2- vs 1,4-Regioselectivity of Lithiated Phenylacetonitrile toward α,*β*-Unsaturated Carbonyl Compounds. 2. Relation between the Regioselectivity and the Structure of the Species in Solution

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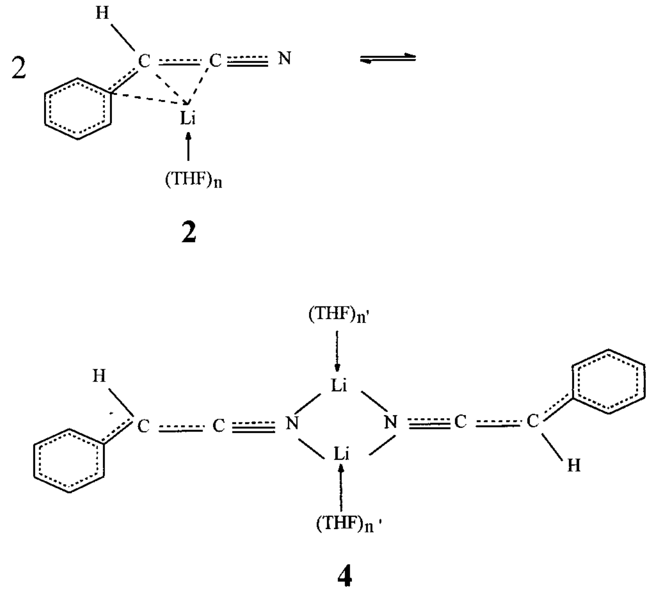
In THF and THF−toluene media, the reaction of lithiated phenylacetonitrile (**1**) with benzylideneacetone (**5**), at low temperature, led to the same ratio of 1,2- and 1,4-adducts after 5 or 30 min of reaction time. The concentrations of the monomeric bridged ion pair **2** preferentially formed in THF and of the dimer of ion pairs **4** predominating in media that favor association such as THF−toluene solvent mixtures were measured from the IR-integrated intensities of the *ν* (C≡N) bands. These concentrations were quantitatively related to the concentrations of the 1,2- and 1,4-adducts, respectively. All these results evidence the kinetic control of this reaction. Intermediate complexes that take into account the peculiar geometries of the monomer **2** and the dimer **4** are proposed to interpret the different regioselectivities observed with **5**. This study is extended to cyclic α-enones and cinnamaldehyde. Similar trends hold for the former, while cinnamaldehyde always leads to 1,2-addition. The formation of intermediate complexes allows us to rationalize the cinnamaldehyde behavior but is insufficient to explain the 1,4-addition with cyclic α-enones lying in an s-trans conformation.

Introduction

Carbanions α to nitriles are useful reagents for C−C bond formation in organic synthesis. The study of the regioselectivity of the reaction of these carbanions toward α-enones was extensively studied by our group and others.[1,2] It was shown that different parameters such as structures of the anionic species and α-enone, medium, temperature, concentration, and added salts play an important role in the 1,2- vs 1,4-addition. Lithiated phenylacetonitrile (**1**) afforded 1,2- or 1,4-addition depending on the experimental conditions.[2] Such was also the case for lithiated cyanohydrin ethers,[3] cyanosilyl ethers[4] and phosphonitriles.[5] On the other hand, lithiated 3-pyridylacetonitrile[2a] and (*N*,*N*-dimethylamino)phenylacetonitrile[6] gave 1,4-addition essentially.

For a better understanding of the structural parameters of the anionic species that may control the 1,2- vs 1,4-regioselectivity, we have performed IR, NIR FT-Raman, and ^{13}C NMR spectroscopic studies of lithiated phenylacetonitrile (**1**) in THF, THF-hexane, and THF−toluene. We have shown that only two species are in equilibrium in these media: a monomeric lithium-bridged ion pair **2** and a dimeric lithium ion pair **4**[7] (Scheme 1).

Scheme 1



In THF, monomeric species predominates at $C = 0.25$ M while dimeric species increases as the amount of hexane or toluene in THF solution increases. Our preliminary results have shown[2a] a change of the 1,2/1,4 ratio, from 95/5 in THF down to 8/92 in THF−hexane (50/50 v/v) in the case of the reaction of **1** with benzylideneacetone **5** at $C = 0.25$ M at −80 to −90 °C.

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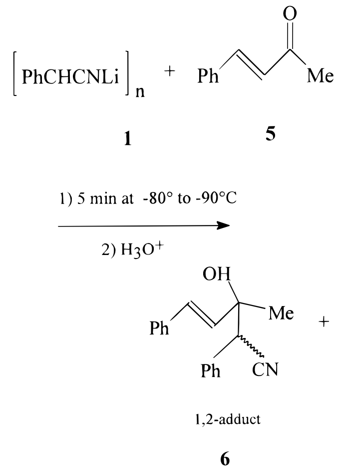
Table 1. Study of the Reaction of Lithiated Phenylacetonitrile 1[a] with Benzylideneacetone (5) at −80 to −90 °C. Influence of Solvent, Concentration *C*, and Reaction Time on the 1,2- vs 1,4-Regioselectivity

entry	solvent v/v	concentration *C* of **1**[c]	reaction time (min)	yield[b] (%)			1,2/1,4 ratio
				S_M	1,2	1,4	
1	THF	0.06	5	9	89	2	97/3
2	THF	0.12	5	6	89	5	95/5
3	THF	0.12	30	6	88	6	94/6
4	THF	0.25	5	6	87	7	93/7
5	THF	0.25	30	5	89	6	93/7
6	THF	0.5	5	18	74	8	91/9
7	THF	0.5	30	18	72	10	88/12
8	THF−toluene 70/30	0.25	5	38	46	16	75/25
9	THF−toluene 50/50	0.25	5	41	32	27	54/46
10	THF−toluene 50/50	0.25	30	46	28	26	51/49
11	THF−toluene 30/70	0.25	5	32	22	46	32/68

[a] The base used was 1.2 equiv of 1 M LHMDS in THF. [b] Yield (%) determined by ^{1}H NMR integration of the methyl signals. S_M: unreacted **5**. [c] The concentration is given in mol L^{-1}.

Scheme 2



Herein, we examine the 1,2- vs 1,4-regioselectivity of the reaction of **1** with **5** in THF, in a range of concentrations $C = 0.06{-}0.5$ M at low temperature. We also extend this study to different THF−toluene media at $C = 0.25$ M. To check the formation of 1,2- and 1,4-adducts under kinetic control, this reaction is carried out at different times. The correlation between the concentrations of 1,2- and 1,4-adducts at −80 to −90 °C in all these media and those of the species present in solution and determined by IR at room temperature is reported. The temperature difference between the reactivity experiments and IR is discussed. The influence of the aggregation state of **1** on the 1,2- vs 1,4-regioselectivity is generalized to various α,β-unsaturated carbonyl compounds. The diastereoselectivity of the reaction of **1** with all these compounds is described. The results are interpreted in terms of "intermediate complexes" involving either a monomeric or a dimeric species.

(1) Regioselectivity Study. (1-1) Reaction of 1 with Benzylideneacetone (5). 1,2- and 1,4-Adduct Formation (Scheme 2). LHMDS (1 M, 1.2 equiv) in THF solution was added to 1 equiv of phenylacetonitrile (**1**) in THF under argon at 20 °C, the concentrations being $C = 0.06$, 0.12, 0.25, and 0.5 M. After being stirred for 30 min, the solution was cooled at −80 to −90 °C and 1 equiv of benzylideneacetone (**5**) was added. The reaction medium was stirred during 5 or 30 min at −80 to −90 °C and then quenched by slow addition of 2 M HCl aqueous solution to limit a too fast temperature increase. After the usual workup, the crude product was analyzed by ^{1}H NMR. In some cases an internal standard was used. The allylic alcohol **6** (1,2-adduct) and γ-cyano ketone **7** (1,4-adduct) were previously described.[2c,d]

The results concerning the influence of solvent, concentration, and reaction time on the 1,2- vs 1,4-regioselectivity of the reaction of **1** with **5** at −80 to −90 °C are presented in Table 1. In THF, after 5 min of reaction, a 87−89% yield of 1,2-adduct is observed for concentration values of 0.06, 0.12, and 0.25 M, which falls to 74% at $C = 0.5$ M (Table 1, entries 1, 2, 4, and 6). Conversely, a small increase of 1,4-addition is registered, reaching a 8% yield at $C = 0.5$ M.

By adding toluene to THF solutions: 30, 50, and 70% (Table 1, entries 8, 9, and 11) the proportion of 1,4-adduct varies from 16 up to 46% after 5 min of reaction. Thus, in THF−toluene mixtures, 1,4-addition depends on the percentage of added toluene to THF solutions. The same results are obtained after 30 min of reaction either in THF (Table 1, entries 3, 5, and 7 compared to 2, 4, and 6, respectively) or in THF−toluene medium 50/50 v/v (Table 1, entries 9 and 10). These observations evidence the stability of 1,2- and 1,4-adducts at −80 to − 90 °C in all these media, during the above-mentioned reaction times.

Influence of the Temperature. Chabanel has reported[8] that the dimerization equilibrium of LiSCN monomeric ion pairs is entropy driven and slightly temperature dependent. To get an insight into the equilibrium between monomeric and dimeric species of lithiated phenylacetonitrile (**1**), when the temperature is lowered from 20 to −80 or −90 °C, we have compared the ^{13}C chemical shifts of $C_{1'}$ and $C_{6'}$ atoms of **1** at 20 °C ($C = 0.25$ M) in THF−HMPA 35/65 v/v, THF, and THF−toluene 30/70 v/v with those at − 90 °C in THF solution (Table 2). From the integrated molar absorption coefficients previously measured[7] by IR, we have determined the monomer and dimer concentrations in THF and THF−toluene solutions at 20 °C. The ^{13}C chemical shifts of the monomer δ_m and dimer δ_d are thus calculated at 20 °C (Table 2) from a molar fraction equal to 0.89 for the monomeric species in THF and to 0.81 for the dimeric species in THF−toluene 30/70 v/v. These values confirmed the noticeable high-frequency shift of $C_{1'}$ and $C_{6'}$ atoms when going from the free anion (THF−HMPA) to the monomer (THF) and to the dimer (THF−toluene). The experimental ^{13}C chemical shifts observed at − 90 °C in THF are at a lower frequency than the calculated

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Table 2. Experimental ^{13}C NMR Chemical Shifts of $C_{1'}$ and $C_{6'}$ of 1 (C = 0.25 M) at 20 °C for the Free Anion, the Monomer, the Dimer, and at −90 °C for the Monomer. Comparison with the Calculated Shifts of the Monomer and Dimer at 20 °C

solvent v/v	δ^a	$\delta C_{1'}$	$\delta C_{6'}$
THF−toluene 30/70	exp^b	150.3	114.5
THF	exp^b	144.3	112.0
THF	exp^c	139.6	110.4
THF−HMPA 35/65	exp^b	134.3	107.5
THF	calcd $\delta_m{}^d$	143.0	111.5
THF−toluene 30/70	calcd $\delta_d{}^d$	152.1	115.2

[a] δ are given in ppm downfield from TMS. [b] δ at 20 °C. [c] δ at −90 °C. [d] Calculated from a molar fraction equal to 0.89 for the monomeric species in THF and to 0.81 for the dimeric species in THF−toluene 30/70 v/v[7]at 20 °C.

ones δ_m for the monomeric species at 20 °C in THF: 3.4 ppm for $C_{1'}$ and 1.1 ppm for $C_{6'}$. These values are too large to be assigned to a simple temperature effect that is usually of the order of 10^{-3} ppm per degree.[9] Similar variations were observed when going from the monomer to the free anion, 8.7 and 4.0 ppm, respectively. The dependence of the ^{13}C data with temperature indicates a strengthening of the cation solvation at low temperature, reducing its polarization effect on the anion.

We may thus conclude that the equilibrium between monomeric and dimeric species (which is entropy driven with probably a small positive enthalpy value) is shifted in THF at − 90 °C toward the monomeric species, the molar fraction of the monomeric species varying from 0.89 to 1. This small influence of the temperature on the equilibrium justifies the further correlation between the concentration of the species at 20 °C measured by IR with those of the 1,2- and 1,4-adducts formed at −80 to −90 °C in the same media.

IR Concentration Measurements. We have determined the concentrations of the species **2** (C_m) and **4** (C_d) in THF at C concentrations in the range 0.06−0.5 M, as previously described,[7] following the method proposed by Chabanel and Paoli.[8a] As shown for LiSCN,[8a] the IR bandwidth may increase with concentration. We have thus performed this study with a more elaborate treatment of the spectra of **1** involving the sum of four components at 2090 and 2083 cm^{-1} for **2**, and 2072 and 2058 cm^{-1} for **4**. The integrated intensity of each band was measured for concentrations: C = 0.5, 0.4, 0.25, 0.24, 0.20, 0.12, 0.10 and 0.06 M, the bandwidth increasing slightly with concentration. The ratio of the integrated intensities of ν_{as} (2058 cm^{-1}) over ν_s (2072 cm^{-1}) bands of the dimer was found equal to 5.2 ± 1 in the concentration range 0.5−0.12 M; this ratio is in agreement with a small distortion of the quasi centrosymmetric dimer, which leads to a small activity of the ν_s mode in IR. On the other hand, the ratio of the integrated intensities of the bands at 2090 and 2083 cm^{-1} of the monomer was equal to 1.82 ± 0.2 in the same concentration range, indicating a strong intensity exchange through a Fermi resonance with a combination or overtone mode. We have thus considered A_m as the sum of the integrated intensities of the bands at 2090 and 2083 cm^{-1} and A_d as the integrated intensity of the band at 2058 cm^{-1}. The variations of A_m/lC versus A_d/lC are shown in Figure 1. In the concentration range 0.12−0.5 M (Figure 1, points 1−6) a quasilinear variation was observed as shown previously for THF−toluene and THF−hexane media (ref 7, Figure 4). This is not the case at lower concentrations (Figure 1, points 7−9). The ratio of the integrated intensities of the dimer ν_{as}/ν_s falls down to 3.5 and 2 ± 0.5 at C = 0.1 M and 0.06 M, respectively. These results suggest that, at concentrations smaller than 0.12 M, another species appears with a ν(C≡N) mode around 2072 cm^{-1}. This species is probably a lithiated linear monomeric ion pair, whose ν(C≡N) wavenumber is as expected close to that of the dimeric species.[7]

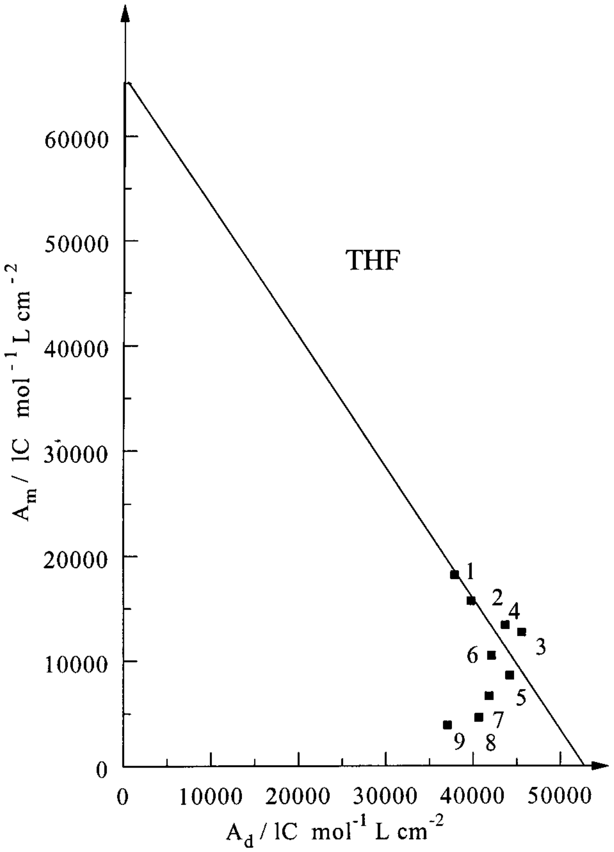

Figure 1. Diagram for the determination of the integrated molar absorption coefficients of the monomeric species **2** and of the dimeric species **4** in THF solution.[7] Concentrations C in mol L^{-1} are for the following points: 1, 0.5; 2, 0.4; 3, 0.25; 4, 0.24; 5, 0.20; 6, 0.12; 7, 0.10; 8, 0.06; 9, 0.06.

The concentrations C_m of the bridged monomer **2** and C_d of the dimer **4** were calculated from ϵ_m and ϵ_d (part I, eq 6) as previously described.[7] ϵ_m and ϵ_d were determined from the intersections of the straight line with the axis (Figure 1). The C_m and C_d values are presented in Table 3.

We have calculated the apparent equilibrium constant[8a] $K_{app} = C_d/C^2{}_m$ at concentrations varying from 0.5 to 0.06 M (Table 3). The equilibrium constant $K = K_{app}\gamma_d/\gamma_m{}^2$ involves the activity coefficients γ_m and γ_d of the monomer and dimer, respectively. Taking into account the accuracy of the measurements and neglecting the possible variation of these coefficients, we may consider K as constant in the concentration range 0.5−0.12 M. This is in favor of an equilibrium between only bridged monomers and dimers. The fact that the sum $C_m + 2C_d$ (Table 3) is equal to the total concentration C, in the above concentration range, is also in agreement with this single equilibrium.

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Table 3. Determination of the Concentrations C_m of 2 and C_d of 4 from the IR Integrated Intensities A_m and A_d of the ν(C≡N) Bands in THF at Different Concentrations and Comparison with the Concentrations $C_{1,2}$ and $C_{1,4}$ of the Adducts Formed with 5

C^a	point no.	$C_m{}^b$	$C_d{}^b$	$C_m + 2C_d$	$K_{app}{}^c$	$C_{1,2}{}^d$	$C_{1,4}{}^d$	$C_{1,2} + C_{1,4}$
0.50	1	0.363	0.070	0.503	0.53	0.365	0.045	0.410
0.40	2	0.305	0.048	0.401	0.51			
0.25	3	0.218	0.024	0.266	0.50	0.220	0.016	0.236
0.24	4	0.201	0.025	0.251	0.62			
0.20	5	0.161	0.016	0.193	0.62			
0.12	6	0.102	0.008	0.118	0.77	0.106	0.007	0.113
0.10	7	0.080	0.005	0.090	0.78			
0.06	8	0.047	0.002	0.051	0.90	0.053	0.001	0.054
0.06	9	0.042	0.002	0.046	1.13			

[a] Concentrations are given in mol L^{-1}. [b] $C_m = A_m/l\epsilon_m$ and $C_d = A_d/l\epsilon_d$, where ϵ_m and ϵ_d are deduced from eq 6 as in ref 7, from the intersections of the straight line with the axis in Figure 1. [c] $K_{app} = C_d/C_m{}^2$ is given in mol^{-1} L. [d] $C_{1,2}$ and $C_{1,4}$ are deduced from the yields reported in Table 1, after 5 min of reaction time.

At concentrations lower than 0.12 M, the increase of K_{app} is probably due to the low accuracy of the measurements and to the variation of activity coefficients. The comparison of the total concentration C with the calculated sum $C_m + 2C_d$ confirms the presence of another species.

In THF–toluene and THF–hexane solvent mixtures at $C = 0.25$ M, the concentrations C_m and C_d were calculated from the integrated intensities of the ν(C≡N) bands of the monomer **2** (2090 cm^{-1}) and dimer **4**[7] (ν_{as} = 2058 cm^{-1}) and presented in Table 4. There is an excellent correlation between the calculated $C_m + 2C_d$ value and that of the total concentration C, confirming the presence of an equilibrium between only monomers and dimers, as shown previously.[7]

Correlation between Concentrations C_m and C_d and 1,2- and 1,4-Adducts Respectively. In THF at different concentrations C, the concentrations of the 1,2-adduct ($C_{1,2}$) and of the 1,4-adduct ($C_{1,4}$) obtained by reacting **1** with **5** at −80 to −90 °C during 5 min are presented in Table 3. They were calculated from the corresponding yields reported in Table 1. Tables 1 and 3 indicate a good correlation between the concentrations of the monomeric species C_m and $C_{1,2}$. From Table 1, it appears also that the yield of the highly predominant 1,2-adduct remains constant after 5 and 30 min of reaction. This result is in line with a kinetic control of the 1,2-process.

In THF–toluene and THF–hexane media at $C = 0.25$ M, the concentrations $C_{1,2}$ and $C_{1,4}$ of the 1,2- and 1,4-adducts are reported in Table 4. They were calculated from the corresponding yields presented in Table 1 for THF–toluene media and ref 2b for THF–hexane media. The variations of $C_{1,2}$ and $C_{1,4}$ as a function of C_m and C_d, respectively, are presented in Figures 2 and 3. Figure 2 shows a linear correlation between C_m and C_d and $C_{1,2}$ and $C_{1,4}$, respectively, in THF–toluene media with a slope of 1. This implies that, at low temperature, the reaction of the monomeric species **2** and of the dimeric species **4** with **5**, respectively, is much faster than their interconversion. Consequently, these processes take place under kinetic control. This one was also confirmed by the stability of the 1,2- and 1,4-adducts at −80 °C after 30 min of reaction time in THF–toluene 50/50 v/v (Table 1, entry 10).

In THF–hexane media (Figure 3), the correlation between C_m and C_d and $C_{1,2}$ and $C_{1,4}$, respectively, fits well only at low concentrations in hexane (18%). At higher concentrations of hexane (up to 50%), $C_{1,4}$ is higher than expected from C_d whereas $C_{1,2}$ is lower than expected from C_m. This result may be explained by the insolubility of the monomer **2** when the temperature decreases.

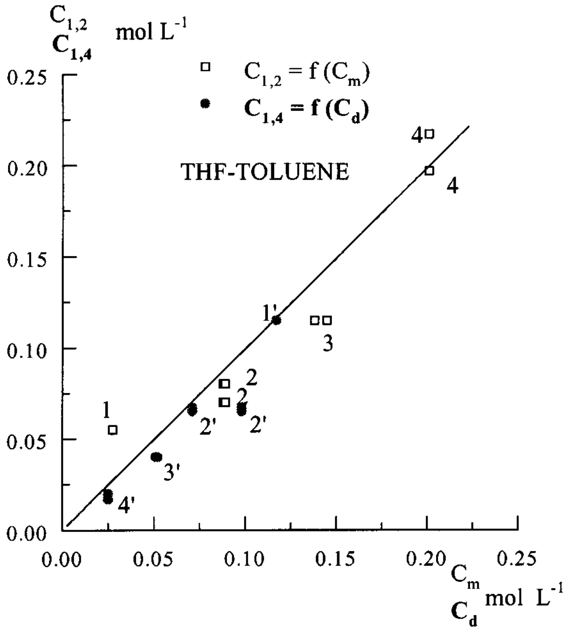


Figure 2. Correlation between the concentrations $C_{1,2}$ of the 1,2-adduct and C_m of the monomeric species **2** (points 1–4, Table 4) and correlation between the concentrations $C_{1,4}$ of the 1,4-adduct and C_d of the dimeric species **4** (points 1′–4′, Table 4) in THF–toluene media (C = 0.25 mol L^{-1}). $C_{1,2}$ and $C_{1,4}$ are determined from Table 1. C_m and C_d are measured from A_m, A_d and ϵ_m, ϵ_d (Table 4).

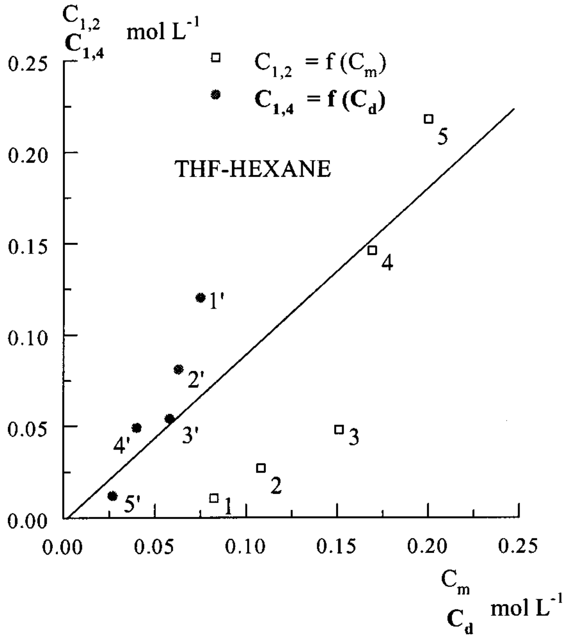


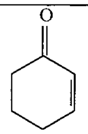
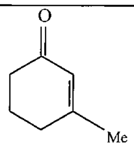
Figure 3. Correlation between the concentrations $C_{1,2}$ of the 1,2-adduct and C_m of the monomeric species **2** (points 1–5, Table 4) and correlation between the concentrations $C_{1,4}$ of the 1,4-adduct and C_d of the dimeric species **4** (points 1′–5′, Table 4) in THF–hexane media (C = 0.25 mol L^{-1}). $C_{1,2}$ and $C_{1,4}$ are taken from ref 2b. C_m, C_d are measured from A_m, A_d and ϵ_m, ϵ_d (Table 4).

Table 4. Determination of the Concentrations[a] C_m of 2 and C_d of 4 from the IR-Integrated Intensities A_m and A_d of the $\nu(C{\equiv}N)$ Bands in THF-Toluene and THF-Hexane Media and Comparison with the Concentrations $C_{1,2}$ and $C_{1,4}$ of the Adducts Formed from 5 at $C = 0.25$ M

solvent v/v	point no.	C_m	$C_{1,2}$	point no.	C_d	$C_{1,4}$	$C_m + 2C_d$	$C_{1,2} + C_{1,4}$
THF−toluene								
30/70	1	0.027	0.055	1′	0.117	0.115	0.261	0.170
50/50	2	0.088	0.080	2′	0.098	0.067	0.284	0.147
		0.088	0.070		0.098	0.065	0.284	0.135
		0.089	0.080		0.071	0.067	0.231	0.147
		0.089	0.070		0.071	0.065	0.231	0.135
70/30	3	0.138	0.115	3′	0.052	0.040	0.242	0.155
		0.145	0.115		0.051	0.040	0.247	0.155
100	4	0.201	0.197	4′	0.025	0.020	0.251	0.217
		0.201	0.217		0.025	0.017	0.251	0.234
THF−hexane								
50/50	1	0.082	0.011	1′	0.075	0.120	0.232	0.131
60/40	2	0.108	0.027	2′	0.063	0.081	0.234	0.108
70/30	3	0.151	0.048	3′	0.058	0.054	0.267	0.102
82/18	4	0.169	0.146	4′	0.040	0.049	0.249	0.195
100	5	0.200	0.218	5'	0.027	0.012	0.254	0.230

[a] C_m, C_d, $C_{1,2}$, and $C_{1,4}$ are given in mol L^{-1}.

Table 5. Reactivity of 1 toward α,β-Unsaturated Carbonyl Compounds[a]

Base (1.2 eq.)	Solvent v/v	PhCH=CH-CO-Me 1,2/1,4 ratio Yield %[b] [d.r] 1,2[c] [d.r.] 1,4[c]	 1,2/1,4 ratio Yield % [d.r.] 1,2 [d.r.] 1,4	 1,2/1,4 ratio Yield % [d.r.] 1,2 [d.r.] 1,4	PhCH=CH-CHO 1,2/1,4 ratio Yield % [d.r.] 1,2 [d.r.] 1,4
LHMDS	THF	93/7[d] 94 [41/59] [70/30]	53/47 98 [65/35] [57/43]	71/29 81 [55/45] [32/68]	>98/2 95 [84/16] -
LHMDS	THF-toluene 30/70	32/68 68 [58/42] [76/24]	33/67 83 [59/41] [40/60]	10/90 64 [37/63] [33/67]	>98/2 56 [86/14] -
n-BuLi	THF-hexane 50/50	8/92[d] 53 [60/40] [66/34]	<2/98 77 - [34/66]	12/88 55 [62/38] [44/56]	>98/2 63 [64/36] -

[a] C = 0.25M ; 5 minutes of reaction time at - 80° to -90°C.

[b] Yield % determined by ^{1}H NMR, the complement to 100% being starting materials.

[c] Diastereomeric ratios [d.r.] measured by ^{1}H NMR.

[d] See reference 2b.

The difference between the sum $C_{1,2} + C_{1,4}$ and C, reported in Table 4, is due to unreacted benzylideneacetone (**5**) and seems to indicate that the dimer reacts with only one molecule of **5**.

(1-2) Generalization of the Reaction of 1 with Other α,β-Unsaturated Carbonyl Compounds. The reaction of **1** with 2-cyclohexen-1-one, 3-methyl-2-cyclohexen-1-one, and cinnamaldehyde was carried out in THF, THF−toluene 30/70 v/v, and THF−hexane 50/50 v/v at $C = 0.25$ M, the temperature being kept at −80 to −90 °C during 5 min, as described above. After the reaction medium was quenched by 2 M HCl aqueous solution, the 1,2- and 1,4-adducts previously reported[2,10] were characterized by ^{1}H NMR of the crude products. The results are shown in Table 5.

Several points concerning the regioselectivity of these reactions can be outlined:

In THF medium, the 1,2/1,4 ratio falls from 95/5 with **5** down to 53/47 and 71/29 with cyclic α-enones; nevertheless, the 1,2-adduct remains the major product.

In THF−toluene and in THF−hexane solvent mixtures, the 1,4-addition predominates with all α-enones, as we already noticed for **5**.

Cinnamaldehyde leads to the 1,2-adduct whatever the medium is, THF, THF−toluene, or THF−hexane.

The yields of the reactions performed in media that favor association are generally lower than those obtained in THF medium for α-enones as well as for cinnamaldehyde. Although the kinetic control is not ascertained in the case of these α-enones, we also envisaged that monomeric species are responsible for the 1,2-adducts, whereas dimeric species give the 1,4-adducts.

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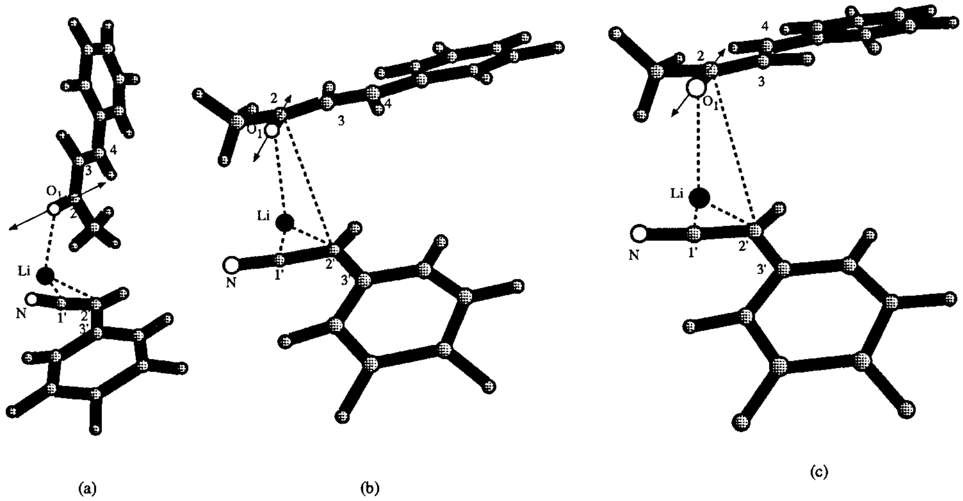

Figure 4. Models constructed for the intermediate complexes between benzylideneacetone (**5**) and the lithium-bridged monomer **2** using the molecular geometry of **5** and the calculated structure of **2**. The following fixed parameters for the intermolecular distances and angles are used: (a) the Li^+ cation is coordinated to the oxygen lone pair of **5** in the s-trans conformation with the parameters $O_1Li = 2.08$ Å, $LiO_1C_2 = 120°$, $O_1LiC_{2'} = 110°$, which are kept constant in all schemes; (b) and (c) **5** in the s-cis or s-trans conformation is rotated around the C_2O_1 axis until its plane is almost parallel to that of the phenylacetonitrile anion. The distances and angles are as follows: (b) $C_2C_{2'}$ ~3.6 Å; $C_{2'}C_2O_1$ ~73°; $C_{2'}C_{4'}$ ~4.5 Å; (c) $C_{2'}C_2$ ~3.6 Å; $C_{2'}C_2O_1$ ~73°; $C_{2'}C_4$ ~5.4 Å.

(2) Diastereoselectivity Study. A poor diastereoselectivity was observed with α-enones for both 1,2- and 1,4-adducts in the media studied at $C = 0.25$ M (Table 5). With cinnamaldehyde, a higher diastereoselectivity, about 85/15, was obtained in THF and THF–toluene solutions. For both benzylideneacetone and cinnamaldehyde, the diastereoselectivity was not modified by diluting the THF solution from $C = 0.25$ M to $C = 0.06$ M. A significant improvement of the diastereoselectivity was reported when the reaction of PhCHCNLi was performed with aldehydes bearing a bulky secondary or tertiary substituent[11,12] at low concentration ($C = 0.025$ M). In the cases we have studied, there is no clear relationship between the degree of aggregation of **1** and the diastereoselectivity observed at $C = 0.25$ M and $C = 0.06$ M.

(3) Intermediate Complex Models. Assuming an early transition state on the reaction pathway,[13] a qualitative approach of the reactants is proposed using geometric models.

Intermediate complexes between either the bridged monomeric **2** or the dimeric ion pair **4** are involved, allowing the oxygen lone pair and the lithium p orbital interactions in the carbonyl plane of the benzylideneacetone (**5**) in an s-cis or s-trans conformation. The O_1Li distance was set equal to 2.08 Å (sum of the ionic radius of Li and of the van der Waals radius of O_1).[14] The formation of one of the diastereomers is shown in Figures 4a and 5a, **5** being represented only in an s-trans or in an s-cis conformation.

A simple rotation around the CO_1 axis brings the planes of **5** and of the carbanion parallel and leads for each complexe to two approaches related to the s-cis or s-trans conformation of **5** (Figures 4b,c and 5b,c). In the case of the 1,2-addition, both the $C_{2'}C_2$ distance (~3.6 Å) and the $C_{2'}C_2O_1$ angle (~73°) allow the development of a favorable $C_{2'\pi^*}$ interaction, whatever the s-cis or s-trans conformation of **5** (Figure 4b,c). These models are quite similar to the transition structures calculated by ab initio methods for the reaction of monomeric methyllithium with formaldehyde.[13] On the other hand, only the approach using **5** in an s-cis conformation (Figure 5b) is in agreement with a C_4 attack, leading to 1,4-addition, the shortest distance being the $C_{2'}C_4$ one (~3.9 Å). This is no longer the case when **5** is in an s-trans conformation, the $C_{2'}C_4$ distance (~5.7 Å) being not the shortest one. In the same way, the simple models proposed for **5** are not valid for 2-cyclohexen-1-one and 3-methyl-2-cyclohexen-1-one lying in an s-trans conformation. Nevertheless, the exclusive 1,2-addition observed with cinnamaldehyde in THF–toluene and THF–hexane media may also imply dimeric species. If its conformation is assumed to be s-trans, the model shown in Figure 5c may account for the 1,2-regioselectivity ($C_{2''}C_2$ ~4.5 Å). The low 1,2-adduct yield fits well with this hypothesis. The intermediate complexes presented in Figure 5b,c and involved in these processes may lead to open dimers via the breakup of one LiN bond. Such open dimers are described in ab initio calculations of the reaction of solvated dimeric methyllithium with formaldehyde.[13,15]

Conclusion

In THF, and in media that favor association, such as THF–toluene solvent mixtures, the reaction of benzylideneacetone (**5**) with lithiated phenylacetonitrile (**1**) proceeds under kinetic control: the concentrations of 1,2- and 1,4-adducts are directly related to the concentrations of monomeric **2** and dimeric **4** species, respectively. In THF, the monomeric bridged ion pair **2** leads to predominately 1,2-addition with α,*β*-unsaturated carbonyl compounds. High 1,4-regioselectivity is evidenced with

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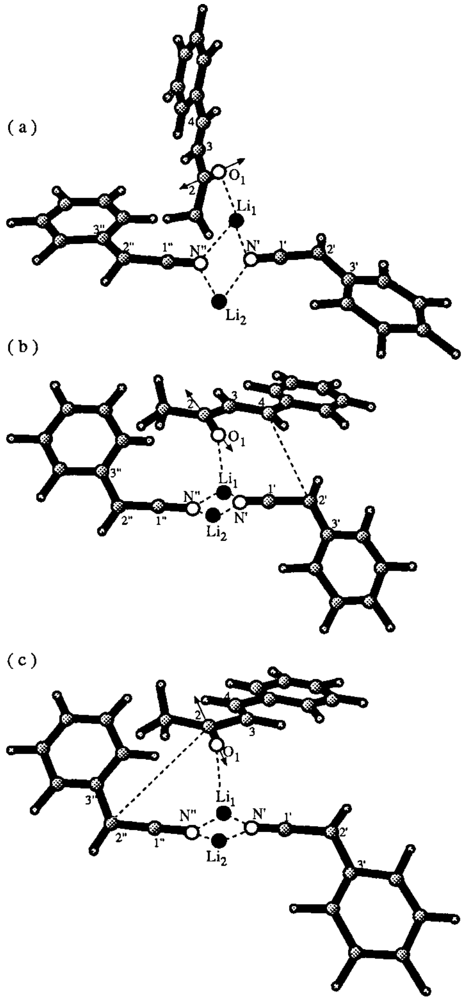

Figure 5. Models constructed for the intermediate complexes between benzylideneacetone (**5**) and the dimer **4** using the molecular geometry of **5** and the X-ray data[7] of the dimer. The following fixed parameters, for the intermediate distances and angles are used: (a) the Li^+ cation is coordinated to the oxygen lone pair of **5** in the s-cis conformation with the parameters $O_1Li = 2.08$ Å, $LiO_1C_2 = 120°$, $O_1LiC_2 = 110°$, which are kept constant in all schemes; (b) and (c) **5** in the s-cis or s-trans conformation is rotated around the C_2O_1 axis, until its plane is almost parallel to that of the phenylacetonitrile anion. The distances and angles are the following: (b): $C_{2'}C_4 \sim 3.9$ Å; $C_{2'}C_4C_3 \sim 124°$; $C_{2'}C_2 \sim 5.2$ Å; $C_{2'}C_2O_1 \sim 65°$; $C_{2''}C_2 \sim 4.5$Å; $C_{2''}C_2O_1 \sim 80°$; $C_{2''}C_4 \sim 6.5$ Å; $C_{2''}C_4C_3 \sim 47°$; (c): $C_{2''}C_2 \sim 4.5$ Å; $C_{2''}C_2O_1 \sim 80°$; $C_{2''}C_4 \sim 6.2$ Å; $C_{2''}C_4C_3 \sim 62°$; $C_{2'}C_2 \sim 5.2$ Å; $C_{2'}C_2O_1 \sim 65°$; $C_{2'}C_4 \sim 5.7$ Å; $C_{2'}C_4C_3 \sim 41°$.

α-enones in media that favor association, while only 1,2-regioselectivity is observed with cinnamaldehyde whatever the media is. The formation of intermediate complexes is proposed and may satisfactorily account for the different regioselectivities observed either with the monomeric bridged ion pair **2** or with the dimeric aggregate **4** in the case of **5**. The intermediate complex model between **4** and cinnamaldehyde in an s-trans conformation also allows us to explain the 1,2-regioselectivity observed. However, the 1,4-adducts obtained with 2-cyclohexen-1-ones are more difficult to interpret.

Experimental Section

Tetrahydrofuran was distilled from sodium benzophenone and kept under argon. Toluene was distilled over CaH_2 and hexane over P_2O_5. Phenylacetonitrile, 2-cyclohexen-1-one, 3-methyl-2-cyclohexen-1-one, and cinnamaldehyde are Janssen products and were distilled prior to use. LHMDS (1 M in THF) and *n*-Buli (1.6 M in hexane) are Aldrich commercial solutions.

IR spectra were scanned using a Perkin-Elmer 983 spectrometer at 3 cm^{-1} resolution. The CaF_2 cell thickness was 0.0037, 0.0052, or 0.0096 cm depending on the concentration of the solutions. The preparation of the anion solutions and the filling of the cells were performed at 20 °C under argon in a glovebag.[2a] The different concentrations of the solutions ($C = 0.5$, 0.4, 0.25, 0.24, 0.20, 0.12, 0.10 M) were obtained directly and also by dilution of the parent solution.

^1H NMR spectra were recorded on a Bruker AM 250 spectrometer, the solvent being $CDCl_3$ or C_6D_6.

^{13}C NMR spectra were recorded on a Bruker AM 250 or 400 spectrometer as in ref 2.

A typical procedure for addition of lithiated phenylacetonitrile (**1**) to benzylideneacetone (**5**) (Table 1) follows. In a 50 mL oven-dried three-necked round-bottomed flask fitted with a rubber septum, a thermometer, and a mechanical stirrer was placed under argon phenylacetonitrile (3 mmol for $C = 0.5$ and 0.25 M; 2 mmol for $C = 0.12$ M; 1 mmol for $C = 0.06$ M) in the required amount of solvent (THF or THF-toluene) so that the final concentration of **1** in the solution was 0.5, 0.25, 0.12, or 0.06 M after addition of base and of **5**. The anion was formed by adding dropwise at room temperature via a well-dried syringe purged with argon 1.2 equiv of 1M LHMDS in THF under stirring. After 30 min, the reaction mixture was cooled between −80 and −90 °C. A stoichiometric amount of benzylideneacetone (**5**) dissolved in 0.5 mL of solvent was added dropwise via a dried syringe to the stirred solution between −85 and −90 °C during 1 min. The reaction medium was then stirred during the times indicated in Table 1 and then quenched with an aliquot amount of 2 M HCl aqueous solution (5 mL for 3 mmol of **5**, for instance) added slowly dropwise via a syringe in order to limit the temperature increase of the reaction medium.

It is very important to quench the reaction medium very slowly, especially at $C = 0.5$ M in THF, otherwise less 1,2-adduct and more starting materials were found. This quenching step is crucial for the reproduction of the results. The choice of the hydrolyzing agent is also important as this reaction takes place in heterogeneous conditions. Poorer yields were obtained with 1 M HCl (10 mL for 3 mmol of **5**) or saturated NH_4Cl (5 mL for 3 mmol of **5**) aqueous solutions.

The cooling bath was removed after complete addition of HCl, and the reaction mixture was diluted at room temperature with 30 mL of ether. The combined organic layers were washed three times with 30 mL of brine and then dried over anhydrous $MgSO_4$. In some cases, benzyl benzoate was added as internal standard in equimolecular amounts to determine the yield of 1,2- and 1,4-adducts **6** and **7**, respectively. The solvents were removed under reduced pressure to afford an oil that was examined by ^1H NMR in $CDCl_3$. The yields were determined by integration of the signals of methyl protons of **5**−**6** and **7** (altogether 100%) or by integration of these same signals relative to the methylene protons of the benzyl benzoate standard. The yields reported in Table 1 are close to those determined with the internal standard. About 10% of products were lost during extraction. 1,2- and 1,4-adducts were previously described.[2c]

The generalization of the reaction of **1** with other α,*β*-unsaturated carbonyl compounds, shown in Table 5, was achieved as above. The reactions were carried out at $C = 0.25$ M during 5 min between −80 and −90 °C to provide the corresponding adducts that were already described. [2c,d,10]

The ^1H NMR spectra of the products obtained from 2-cyclohexen-1-ones were run in C_6D_6, allowing a better splitting of the α to CN protons on which integration was performed. With cinnamaldehyde, the analysis was realized in $CDCl_3$ as above.

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