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Asymmetric photodeconjugation of ammonium ene-carboxylates: temperature effects and evidence for the α-carbon of the dienolic species as a latent trigonal centre

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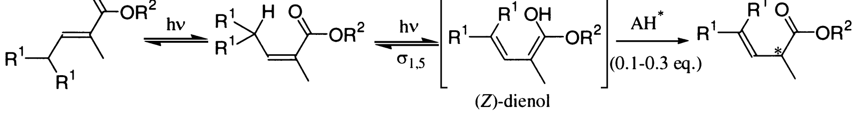
Abstract

The diastereoselective photodeconjugation of CH_2Cl_2 solutions of enantiopure ammonium ene-carboxylates was studied and the results compared with those of the enantioselective photodeconjugation of ene-esters in the presence of catalytic amounts of chiral aminoalcohols. We have observed a significant entropic effect and shown that a C-β control of the selectivity is operative in the asymmetric protonation of the photodienolic species. © 2000 Elsevier Science Ltd. All rights reserved.

1. Introduction

Enantioselective protonation of prostereogenic enolic species is an attractive route for the preparation of optically active carbonyl compounds.[1] One of our contributions in this area applies the photochemical generation of an enolic species in an aprotic solvent by either: (i) a Norrish type II rearrangement of a conjugated unsaturated ester producing a transient dienol which was selectively protonated in the presence of catalytic amounts of a chiral aminoalcohol AH*[2] (Scheme 1) or (ii) a Norrish type II cleavage from a trisubstituted arylketone allowing the formation of a simple enol which led to the optically active ketone under similar conditions[3] (Scheme 2).



Scheme 1. Enantioselective photodeconjugation of α,β-unsaturated esters

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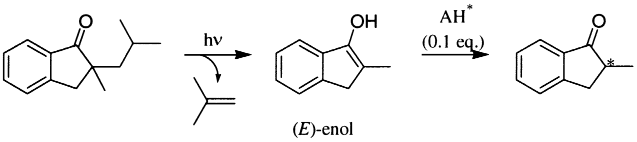
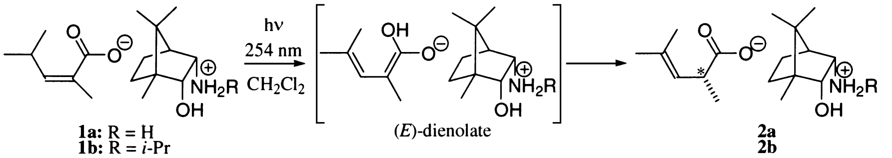


Scheme 2. Enantioselective tautomerization of arylenols

During the photochemical step, the enolic species were formed as a single geometrical isomer,[4] *Z* for the dienol and *E* for the arylenol. Whatever the configuration of the enol linkage, we have observed the same facial selectivity in using the same chiral protic source AH*.[2,3] Since Duhamel's group developed the concept of the latent trigonal centre relative to enantioselective reactions of *Z*- and *E*-enol species with electrophiles,[6,7] this aspect has received relatively few applications in asymmetric protonations although the methodology is well documented.[1] Many investigations avoided the problem of *Z*,*E*-isomerism either by starting from cyclic enolates[8] or by using stereoselective methods to prepare an enolate with a determined geometry.[9] However some of the investigations, starting from enriched *Z*- or *E*-enolates, displayed opposite[10] or the same[11] enantiofacial preference, while enhanced selectivities have been observed[12] starting from enolates of undetermined configuration. Meticulous studies reported by Fehr's group[13] have shown that, for the asymmetric protonation of enolates of similar structure, α- or β-control is operative, apparently depending on the electronic properties of the groups carried by the α-carbon. Although *E*- and *Z*-enolates may exhibit different enantiofacial selectivities due to two diastereomeric transition states for their respective protonation, examination of the results starting from the geometrical isomers will allow us to define the half region of the enol, α or β, that is responsible for the chiral discrimination. Here we report the effects of temperature and of the geometry of the intermediate dienol produced in the course of asymmetric photodeconjugation reactions.

2. Results and discussion

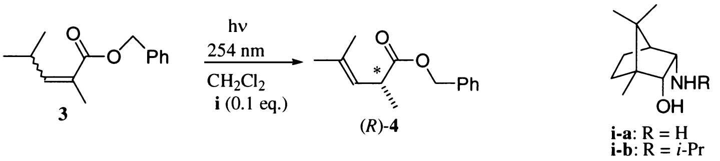
The comparison between the protonation of *Z*- and *E*-photodienolic species was carried out by studying the photodeconjugation, in solution, of the ammonium carboxylates **1** (Eq. (1)). The results were compared with the previous study of the photodeconjugation of benzylesters[2] **3** (Eq. (2), Scheme 1). Substrates **1** and **3** have the same acyl part; thus, the transient dienolic species have the same β-substituents and, respectively, the *E*- or *Z*-geometry. For **1** the ammonium group is linked to an isoborneol moiety since the corresponding free aminoalcohols **i** afforded the best selectivities when used in the asymmetric protonation of photodienols[2b,c] (Eq. (2), *ee* up to 42% with **i**–**a** and 97% with **i**–**b**).



(1)

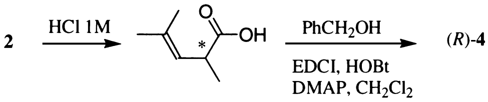
1a: R = H
1b: R = *i*-Pr

2a
2b



(2)

Furthermore, such an auxiliary does not bear any chromophore absorbing at 254 nm and is thus suitable under our photochemical conditions. As far as the photochemistry of ammonium carboxylates is concerned, the *E*,*Z*-photoisomerization of conjugated unsaturated compounds has been previously studied in the solid state and there is one example of a Norrish type II reaction.[14] The carboxylate functional group has been used as the chiral auxiliary in photochemical stereoselective reactions[15] rather than as the photosensitive group. In our case, it played both roles. The salts **1a** and **1b** formed between the conjugated acid[16] and an equimolecular amount of the aminobornanol[17] **i–a** or **i–b** were isolated, recrystallized and then dissolved in dichloromethane. The resulting solutions (8×10^{-3} M) were deoxygenated and irradiated at 254 nm for 6 h. The new ammonium salts **2** were directly transformed into benzyl esters for enantioselectivity determinations: after hydrolysis of **2** in aqueous hydrochloric acid, the residual acid was reacted with benzyl alcohol in the presence of DMAP (dimethylaminopyridine), EDCI (1-[3-dimethylaminopropyl]-3-ethylcarbodiimide hydrochloride) and HOBt (hydroxybenzotriazole)[18] (Eq. (3)).



(3)

The temperature effects were analyzed between +10 and –46°C, this relatively narrow range being due to the following observations: (i) at room temperature, partial photolysis of the halogenated solvent (dichloromethane) led to the formation of HCl[19] which did not permit the isolation of **2**; and (ii) at low temperature, precipitation of the salt took place and the photodeconjugation reaction proceeded at least in part in the solid state.[20,21]

From the results presented in Table 1, it appears that the major configuration of the deconjugated product is (*R*) as for our previous studies starting from the benzyl ester[2] (Eq. (2)). The observed selectivity was fair with **1a**, and increased strongly with **1b**, these results being similar to those of Eq. (2) where **i–a** and **i–b** were used, respectively.[2a,c] The Eyring-plots corresponding to the deconjugation of the carboxylates are presented in Fig. 1 (graphs a and b) and compared with our previous results starting from **3**[2c] (graphs a′ and b′). As expected from the principle of isoinversion,[22] each system showed two linear correlations intersecting at an inversion point. This point has the dimension of temperature, is called T_{inv}[22] and corresponds to the values of –7°C for **1a** and –9°C for **1b**; at temperatures lower than T_{inv}, the selection is under enthalpic control for both systems **1a** and **1b**. For **1a**, at temperatures higher than T_{inv}, the slope of the line and the enthalpic difference are both zero (Table 2) and the selectivity is no longer controlled by the temperature. The selectivity was entirely determined by the remaining entropic term. In contrast, for **1b** an abrupt change in dominance is observed at T_{inv} and the entropic contribution becomes dominant, while the enthalpy disfavoures the formation of the major stereoisomer. The importance of the entropic factor in selective reactions has been recently underlined.[23]

The values calculated for T_{inv} also represent the relationship $\delta\ \Delta\Delta H^{\ddagger}/\delta\ \Delta\Delta S^{\ddagger}$ and can be considered as near to the characteristic isoinversion temperature T_i of the system.[22,24] The existence

Table 1
Photodeconjugation of **1**

t °C	Yield[a] (%)	*ee*[b] (%)	Yield[a] (%)	*ee*[b] (%)
	1a → (*R*)-**4**	of **4**	**1b** → (*R*)-**4**	of **4**
10	60	17	58	56
0	59	16	62	49
-10	62	17	61	40
-20	55	27	60	50
-30	62	32	57	66
-40	60	40	61	79
-46	60	45	65	85

[a] Overall isolated yield for the 3 steps (Eqs. 1 and 3).

[b] Determined from optical rotation values: $[\alpha]_D^{20}$ (CH_2Cl_2) = -92 for enantiopure (*R*)-**4**, estimated from different samples, the enantiomeric excess of which had been evaluated by NMR in presence of Eu(hfc)$_3$.[16]

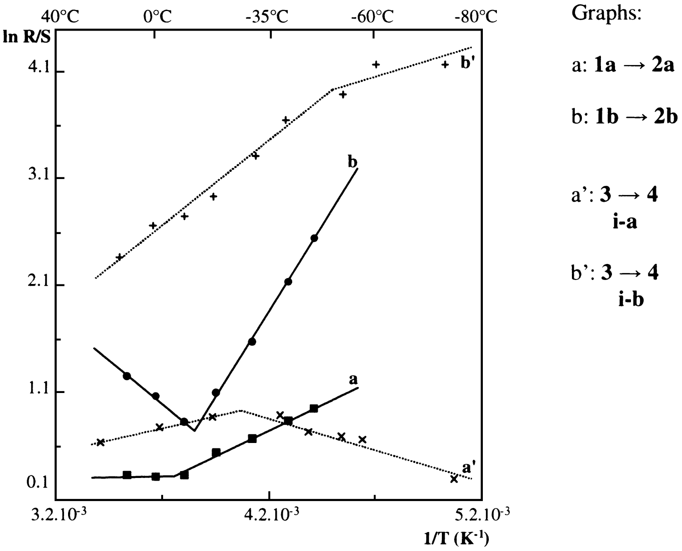


Figure 1. Photodeconjugation of **1** and **3**, Eyring diagrams

Table 2
Activation parameters

T	**1a → 2a**		**1b → 2b**	
	ΔΔH≠ kJ. mol^{-1}	ΔΔS≠ J. mol^{-1}. K^{-1}	ΔΔH≠ kJ. mol^{-1}	ΔΔS≠ J. mol^{-1}. K^{-1}
T>Tinv	0	2.8	13	56.6
T<Tinv	-8.3	-28.4	-27.3	-95.9

of T_{inv} or T_i (which in fact represents the average of the T_{inv}'s) in selective chemical processes has received several explanations. It can indicate the occurrence of two levels of selectivity in a two step reaction mechanism, which entails the changes in dominance between the activation parameters.[22,25] It can also imply a shift in the rate determining step of the reaction.[26] However this is not compatible with the abrupt changes observed in our case, especially in curve b.[25] Finally it can also be a sign of a phase modification and correspond to a transition between two different solvation clusters of the solute. The value of T_{inv} is then strongly dependent on the solvent.[27]

The results with esters and carboxylates present some differences. The two sets of graphs show opposite trends in the slopes of curves and a much lower entropic contribution in the reactions of the esters. Moreover, we observe for the carboxylates, a minimum of selectivity at T_{inv}, which is unusual.[28] The isoinversion temperature corresponding to the photodeconjugation of carboxylates (around –10°C) is different from that for the esters (–55°C). That suggests different mechanisms in the protonation step, rather than a transition phase[27] since the same solvent is used in both cases. The differences could be due to the presence of the ionized carboxylate species, compared to the non-dissociated ester-complexes.[2a,c] Such an explanation would also be compatible with the entropic effect being more important in the former case, even in non-polar dichloromethane.

However, each dienolic species with *Z*- or *E*-configuration leads to the same (*R*) enantiomer; according to the principle of the latent trigonal centre,[6,7] the selection control is then attributable to the β-carbon. At this stage, it seems inappropriate to propose a complete mechanistic explanation of the selectivity which takes account of the steric and electronic effects[29] as well as the equally important entropic parameters.[23] Nevertheless, we have shown that the protonation of the dienolates is a stepwise process like that of dienols, without presuming the nature of the proton source. Indeed, the acidic ammonium group could be operative in the protonation step of the dienolates, rather than the hydroxylic function invoked in the case of the dienols.[2] This assumption leads to the transition states presented in Fig. 2. The *E*-geometry and the *S-cis* conformation of the dienolate arise from the geometry required for γ-H abstraction by the excited carboxylate. Obviously, no major interaction can be detected from the α-part of the dienolate. If

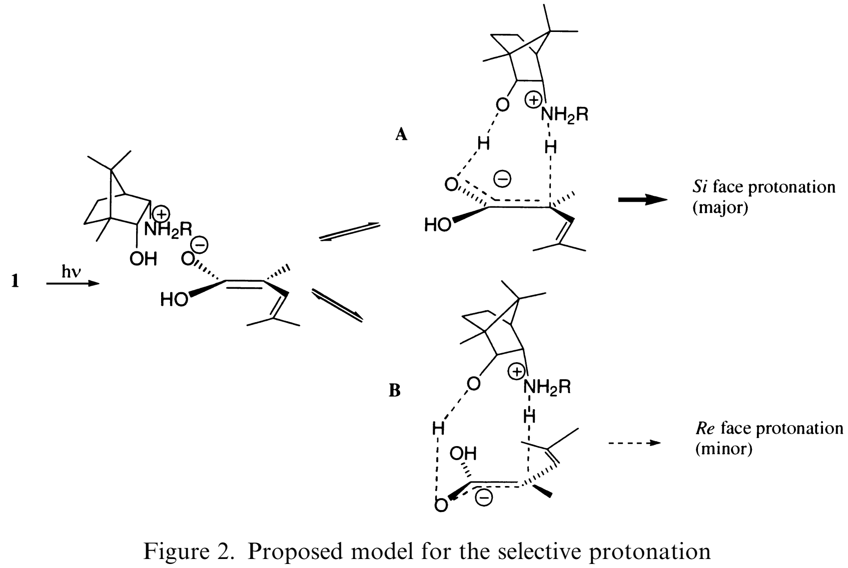


Figure 2. Proposed model for the selective protonation

we assume that the dienolate is protonated by the ammonium group, it moves perpendicularly to the dienolate plane allowing the formation of the second level selection intermediates **A** or **B**, the interconversion between **A** and **B** taking place through a reversible pathway. The differences in *Si*- or *Re*-face protonation appear in the steric interactions arising from the β-substituents of enolic species; however some other factors, in particular entropy, have to be taken into account to make better models of these transition states.

3. Experimental

3.1. General

^{1}H NMR spectra (250 MHz) were recorded on a Bruker AC 250 spectrometer in $CDCl_3$ as solvent; optical rotations were measured on a Perkin–Elmer Model 241 polarimeter. Silica gel Merck 60 $PF_{254+366}$ and 0.040–0.063 mm were, respectively, used for preparative TLC and flash chromatography. Dichloromethane was distilled from CaH_2 under an argon atmosphere prior to use. Starting materials were synthesized as previously described for the carboxylic acid[16] and the aminoalcohols.[17]

3.2. Main spectral characteristics of 1

(1′*R*,2′*R*,3′*S*,4′*S*) (2′-hydroxy-1′,7′,7′-trimethylbicyclo[2.2.1]heptan-3′)-ammonium 2,4-dimethyl-2-pentenoate **1a**: 99%; ^{1}H NMR: 0.93 (15H, m, C*H*$_3$-1′,7′,7′,5,6); 1.18 (1H, m); 1.42 (1H, m); 1.57 (1H, m); 1.83 (3H, s, C*H*$_3$ -2); 1.85–1.99 (2H); 3.07 (1H, m, C*H*-4); 3.54 (1H, dd, *J*=9.1 and 4.5, *H*-3′); 3.91 (1H, d, *J*=9.1, *H*-2′); 5.30 (1H, d, *J*=9.5, *H*-3); 6.1 (4H, O*H* and $^+$N*H*$_3$).

(1′*R*,2′*R*,3′*S*,4′*S*) (*N*-*i*-propyl-2′-hydroxy-1′,7′,7′-trimethylbicyclo[2.2.1]heptan-3′)-ammonium 2,4-dimethyl-2-pentenoate **1b**: 98%; ^{1}H NMR: 0.93 (15H, m, C*H*$_3$-1′,7′,7′,5,6); 1.2–1.45 (2H); 1.29 (3H, d, *J*=6.5, C*H*$_3$-*i*-Pr); 1.39 (3H, d, *J*=6.5, C*H*$_3$-*i*-Pr); 1.65 (1H, m); 1.84 (4H, m); 1.85 (3H, s, C*H*$_3$-2); 2.05 (1H, m); 3.01 (1H, sept, *J*=6.5, C*H*-*i*-Pr); 3.16 (1H, m, C*H*-4); 3.50 (1H, dd, *J*=9.1 and 4.2, *H*-3′); 4.06 (1H, d, *J*=9.1, *H*-2′); 5.31 (1H, d, *J*=9.5, C*H*-3); 8.6 (3H, O*H* and $^+$N*H*$_2$).

3.3. Photolysis experiments

A dichloromethane solution (50 mL) of the substrate **1** (0.4 mmol) was poured into quartz tubes, degassed with argon and placed in a temperature controlled ethanol bath; the irradiations were realised for 6 h with an OSRAM H.N.S. 10 lamp. Then, the solution was acidified by HCl 1 M and the organic layer washed with brine, dried over $MgSO_4$ and concentrated under vacuum. The crude acid was used for the next step without further purification.

3.4. Benzyl 2,4-dimethyl-3-pentenoate[16]

The esterification experiments were carried out in dichloromethane solution (1 mL) containing the crude deconjugated acid (0.4 mmol), benzyl alcohol (43 mg, 0.4 mmol), EDCI (119 mg, 0.4 mmol), HOBt (54 mg, 0.4 mmol) and DMAP (3 mg, 0.02 mmol). After stirring for 16 h, the solution was diluted with CH_2Cl_2, washed with brine, dried ($MgSO_4$), evaporated under reduced pressure and the residue purified by flash chromatography or preparative TLC (petroleum ether:ethyl acetate = 97:3).

Acknowledgements

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