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Asymmetric protonation of enolic species: dramatic increase in the selectivity with temperature and unexpected Eyring diagram[1]

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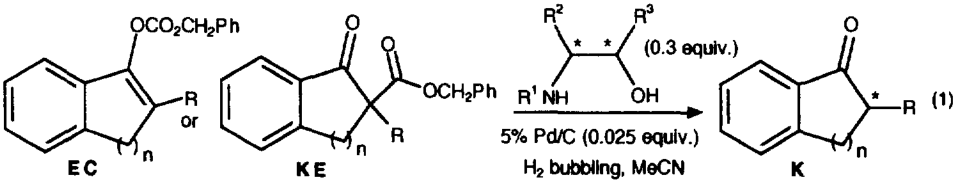
Abstract: The palladium-induced cleavage of β-ketosters and enol carbonates derived from α-alkylated 1-indanones and 1-tetralones in the presence of (+)-*endo*-2-hydroxy-*endo*-3-aminobornane led to (*R*)-α-alkylated indanones and tetralones with a large increase in the enantioselectivity (up to 38–40%) when the reaction temperature was raised from 21 to 45–70°C. Thus, enantiopure 2-methyl-1-indanone was obtained at 52°C. More than one inversion temperature has appeared in plotting the corresponding Eyring diagrams. © 1997 Elsevier Science Ltd. All rights reserved.

Great efforts during the last few years have been devoted to the synthesis of optically active carbonyl compounds by enantioselective protonation of prochiral enol species.[2–7] The reactions have been generally carried out in a range of temperatures from −40 to −100°C since it has been shown that lowering the reaction temperature of the protonation step resulted usually in a clear increase in the enantioselectivity.[3–5] Nevertheless, few inverse *ee*/t°C correlations have been reported for such reactions[4–7], relatively important *ee* modifications being thus observed solely for low temperatures.[8]

In the course of our studies related to this topic, we have described the palladium-mediated formation of optically active ketones (**K**) from either prochiral enol carbonates (**EC**)[9] or racemic β-ketoesters (**KE**) in the presence of substoichiometric amounts of various enantiopure β-aminoalcohols[10–12] (Eq. 1). The reactions were mainly carried out at room temperature. A decrease in the reaction temperature slowed down the rate of the transformation and sometimes afforded lower enantiomeric excesses (*ee*'s). The drop in the *ee* seems to be due to the increase of the reaction time since slow racemisation of the ketone has been observed under these experimental conditions.[10,12]



Recently, we have been very surprised to observe that in some cases, the increase in the reaction temperature induced impressively higher *ee*'s of the resulting ketones. These gratifying results are reported here.

The process has been particularly studied in the range of +20 to +80°C, using indanone (**EC 5** and **KE 5**) and tetralone (**EC 6** and **KE 6**) derivatives, (+)-*endo*-2-hydroxy-*endo*-3-aminobornane (**A**, 0.3 equiv.),[13,14] 5% palladium on charcoal as metal catalyst (0.025 equiv.),[15] acetonitrile as solvent and continuous bubbling of hydrogen (Eq. 1, Scheme 1). The reactions were followed by TLC and led to the complete consumption of the substrate; isolated chemical yields were between 72 and 96%.

The experimental results (Tables 1–6 in the Experimental part) are summarized in Figure 1 where *ee*'s are plotted versus reaction temperatures.

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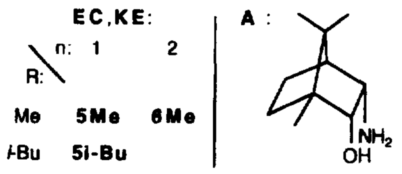


Scheme 1.

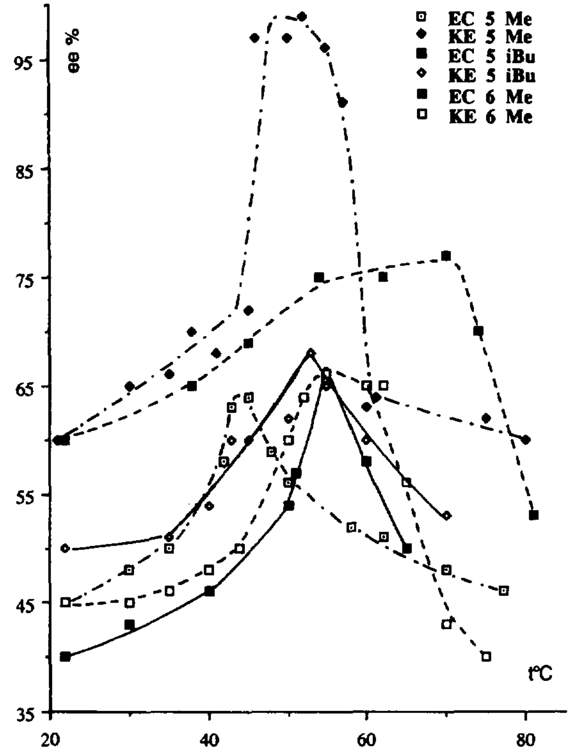


Figure 1. Influence of the reaction temperature on the enantiomeric excesses of **K 5Me**, **K 6Me** and **K 5i-Bu** obtained from **EC 5Me**, **EC 6Me**, **EC 5i-Bu**, **KE 5Me**, **KE 6Me** and **KE 5i-Bu**.

All the curves present relatively similar shapes with maximum *ee*'s reached between 45 and 70°C. The reaction of the ketoester **KE 5Me** exemplified particularly the effect of temperature: the increase in temperature from 21 to 52°C induced a jump of more than 39% *ee* and led to **K 5Me** as its pure (*R*) form. As **K 5Me** was obtained in a high yield, a simple kinetic resolution of the starting ketoester is ruled out.[16]

These unexpected results were analyzed according to the modified Eyring formalism[17] (Tables 1–6 in the experimental part, Figs 2–4).

It appears that plotting Ln (*R*/*S*) versus 1/T led to two approximately straight lines only when **EC 6Me** was the starting material (Figure 3). In this case, the inversion point (T_{inv})[18] corresponds to an inversion in dominance of enthalpy and entropy in the enantioselective steps. Three linear correlations at least could be deduced from the diagrams corresponding to the five other substrates: each of them contains i) a T_{inv} with characteristics similar to the above one and ii) other T_{inv}'s which correspond to

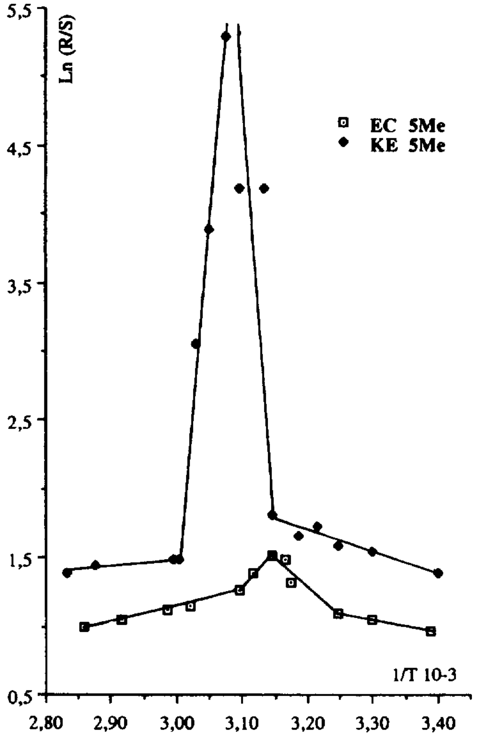


Figure 2. Eyring diagram for the formation of **K 5Me** from **EC 5Me** and **KE 5Me**.

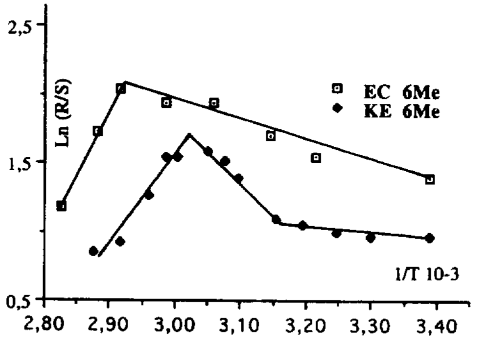


Figure 3. Eyring diagram for the formation of **K 6Me** from **EC 6Me** and **KE 6Me**.

changes of $\Delta\Delta H^{\neq}/\Delta\Delta S^{\neq}$ relationships without inversion in dominance. The diagram obtained from **KE 5Me** (Figure 2) is particularly noteworthy since it presents a very strong increase in selectivity of the process in a narrow temperature range.

The discrimination steps of the present reactions are more complex than those of the protonation of photoenols arising from the photodeconjugation of prochiral α,β-unsaturated esters at low temperature as analyzed before.[19] We have previously supposed that the palladium-launched reactions of each **EC/KE** pair would produce the same enolic species which would afford the optically active **K** through development of diastereoselective interactions with the aminoalcohol in the course of the protonation

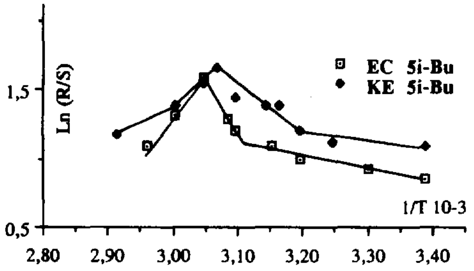
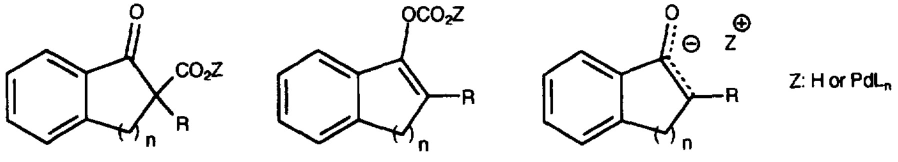
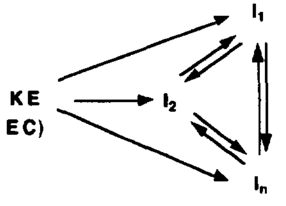


Figure 4. Eyring diagram for the formation of **K 5i-Bu** from **EC 5i-Bu** and **KE 5i-Bu**.



Scheme 2.

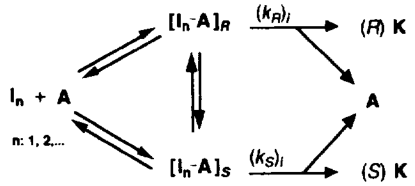


Scheme 3.

step.[10,11] Indeed, it appears now that the shapes of the curves of the Eyring diagrams corresponding to the formation of each **K**, depend on the nature of the starting substrate **EC** or **KE** (Figs 2–4). Consequently, the selective pathways leading to **K** from either **EC** or **KE** present some differences.

In considering the results reported here, we now propose that there is more than one species (noted $\mathbf{I}_n$, n=1, 2,...) developing interactions with **A** in the discrimination steps. The palladium-induced cleavage of the benzyl–oxygen bond could lead to various plausible $\mathbf{I}_n$'s such as those indicated in Scheme 2.[20] Some of them are produced from different reactive pathways and could be in equilibrium (Scheme 3). Each $\mathbf{I}_n$ could react with **A** to lead to the two diastereomeric intermediates $[\mathbf{I}_n\text{-}\mathbf{A}]_R$ and $[\mathbf{I}_n\text{-}\mathbf{A}]_S$ whose rearrangement would deliver preferentially (*R*) **K** or (*S*) **K** respectively (Scheme 4). The *ee* of **K** would result from the concentrations of the various $[\mathbf{I}_n\text{-}\mathbf{A}]$ in the medium and of the rates of their rearrangement into **K**.[21]

The distribution ratio of $\mathbf{I}_n$ would be depend on both the nature of the starting substrate and the reaction conditions, especially temperature. Furthermore, as there are kinetic relationships between the concentrations of $\mathbf{I}_n$ and $[\mathbf{I}_n\text{-}\mathbf{A}]$, the enantioselectivity produced from these cascade reactions of **EC** and **KE**, which involve deprotection, decarboxylation and enantioselective protonation, depends on many limiting factors. Consequently, complex Eyring diagrams are produced and the methodology developed by Scharf's group to determine an isoinversion temperature is unexploitable in the present study.



Scheme 4.

Table 1. Palladium-induced transformation of **EC 5Me** into **K 5Me** in MeCN under bubbling of hydrogen in the presence of **A** at various reaction temperatures

t°C	Time, h	Yield %	*ee* %[a]	10^{-3} 1/T	R/S	Ln(R/S)
22	2.5	72	45[b]	3.390	73/27	0.969
30	0.33	87	48[c]	3.300	74/26	1.046
35	0.33	72	50[c]	3.247	75/25	1.099
42	0.42	90	58[c]	3.175	79/21	1.325
43	1	90	63[d]	3.165	81.5/18.5	1.483
45	0.33	78	64[c]	3.145	82/18	1.516
48	0.58	92	59[c]	3.115	79.5/20.5	1.386
50	0.45	80	56[d]	3.096	78/22	1.266
58	1	82	52[b]	3.021	76/24	1.153
62	1	81	51[b]	2.985	75.5/24.5	1.126
70	1	79	48[b]	2.915	74/26	1.046
77	0.33	75	46[c]	2.857	73/27	0.995

[a] (*R*) configuration attributed to the main enantiomer from comparison of the specific rotation with literature data.[1]

[b] *ee* determined from polarimetry comparisons.[1]

[c] *ee* determined from HPLC using a Chiralcel OB-H column.

[d] *ee* determined from HPLC using a Chiralcel OD column.

Although it is premature to make further comments about these enantioselective reactions, this report exemplifies an impressive, unexpected large increase in the enantioselectivity with temperature in the course of an asymmetric protonation reaction and furthermore leads us to suspect a correlation between the number of T_{inv} determined from the Eyring diagram and the number of intermediates implied in the selective events.

Experimental part

Typical experimental procedure

A round-bottom flask containing the β-ketoester **KE 6Me** (50 mg, 0.0177 mmol) in dry, distilled acetonitrile was heated at the desired temperature in an oil-bath. Then were added **A** (9 mg, 0.3 equiv.) and 5% palladium on charcoal (18 mg from Engelhard Company — Ref. 5011, 0.025 equiv. of Pd). A slow stream of hydrogen was immediately bubbled into the solution for the time indicated in Table 5. At the end of the reaction time, the solvent was evaporated under reduced pressure. The residue was purified by flash-chromatography eluting with petroleum ether/EtOAc (90/10).

Determination of the enantiomeric excesses

The specific rotations of (*R*) **K 5Me**[22] and (*S*) **K 6Me**[23,24] have been reported. These literature values have been used for an initial estimation of *ee*'s. A large part of the *ee*'s were determined from ^{1}H NMR in the presence of $Eu(hfc)_3$ and/or HPLC using a chiral column from Daicel as indicated in Tables 1–6.

Two chiral columns have been used at room temperature with UV detection at 254 nm:

Chiralcel OD; eluant, isopropanol/hexane: 2/98.

Table 2. Palladium-induced transformation of **EC 6Me** into **K 6Me** in MeCN under bubbling of hydrogen in the presence of **A** at various reaction temperatures

t°C	Time, h	Yield %	*ee* %[a]	10^{-3} 1/T	R/S	Ln (R/S)
22	0.75	67	60[b]	3.390	80/20	1.386
38	1	84	65[b]	3.215	82.5/17.5	1.551
45	2.3	88	69[c]	3.145	84.5/15.5	1.696
54	0.66	80	75[d]	3.058	87.5/12.5	1.946
62	0.4	76	75[c]	2.985	87.5/12.5	1.946
70	0.4	90	77[c]	2.915	88.5/11.5	2.041
74	0.41	92	70[c]	2.882	85/15	1.735
81	0.41	82	53[c]	2.825	76.5/23.5	1.180

[a] (*R*) configuration attributed to the main enantiomer from comparison of the specific rotation with literature data.[1]

[b] *ee* determined from HPLC using a Chiralcel OD column.

[c] *ee* determined from polarimetry comparisons.[1]

[d] *ee* determined from ^{1}H NMR in the presence of Eu(hfc)$_3$.

Table 3. Palladium-induced transformation of **EC 5i-Bu** into **K 5i-Bu** in MeCN under bubbling of hydrogen in the presence of **A** at various reaction temperatures

t°C	Time, h	Yield %	*ee* %[a]	10^{-3} 1/T	R/S	Ln(R/S)
22	4	78	40[b]	3.390	70/30	0.847
30	1	80	43[b]	3.300	71.5/28.5	0.920
40	1	74	46[b]	3.195	73/27	0.995
44	0.6	91	50[b]	3.154	75/25	1.099
50	0.5	80	54[b]	3.096	77/23	1.208
51	0.5	82	57[b]	3.086	78.5/21.5	1.295
55	0.42	96	66[b]	3.049	83/17	1.586
60	0.5	84	58[b]	3.003	79/21	1.325
65	0.5	82	50[b]	2.959	75/25	1.099

[a] (*R*) configuration attributed to the main enantiomer from circular dichroïsm studies (see above).

[b] *ee* determined from HPLC using a Chiralcel OD column.

For **K 5Me**; flow rate: 0.7 ml/min; retention time, (*R*) enantiomer: 8.6 min, (*S*) enantiomer: 9.8 min.

For **K 6Me**; flow rate: 0.5 ml/min; retention time, (*R*) enantiomer: 14.4 min, (*S*) enantiomer: 13.1 min.

For **K 5i-Bu**; flow rate: 0.5 ml/min; retention time, (*R*) enantiomer: 8.7 min, (*S*) enantiomer: 7.5 min.

Chiralcel OB-H; eluant: isopropanol/hexane, 10/90.

For **K 5Me**; flow rate: 0.8 ml/min; retention time, (*R*) enantiomer: 12.8 min, (*S*) enantiomer: 8.9 min.

Attribution of the absolute configuration of the stereogenic centers

The absolute configuration of the stereogenic center of the main enantiomer of **K 5Me** and **K 6Me** has been attributed from comparisons with literature data.[22,23] The (*R*) configuration has been attributed to the main enantiomer of **K 5i-Bu** from comparison of the Cotton effects[24] observed in its circular dichroism spectrum with those of **K 5Me**.

Table 4. Palladium-induced transformation of **KE 5Me** into **K 5Me** in MeCN under bubbling of hydrogen in the presence of **A** at various reaction temperatures

t°C	Time, h	Yield %	*ee* %[a]	10^{-3} 1/T	R/S	Ln(R/S)
21	3.5	90	60[b]	3.401	80/20	1.386
30	0.5	81	65[b]	3.300	82.5/17.5	1.551
35	0.75	83	66[c]	3.247	83/17	1.586
38	0.83	80	70[c]	3.215	85/15	1.735
41	0.5	92	68[c]	3.185	84/16	1.658
45	0.58	90	72[c]	3.145	86/14	1.815
46	0.5	79	97[c]	3.135	98.5/1.5	4.185
50	0.5	88	97[c]	3.096	98.5/1.5	4.185
52	0.58	86	> 99[c]	3.077	> 99.5 / < 0.5	5.293
55	0.58	86	96[c]	3.049	98/2	3.892
57	0.58	92	91[b]	3.030	95.5/4.5	3.055
60	1	91	63[b]	3.003	81.5/18.5	1.483
61	0.5	89	64[c]	2.994	81.5/18.5	1.483
75	0.58	78	62[c]	2.874	81/19	1.450
80	0.75	80	60[b]	2.833	80/20	1.386

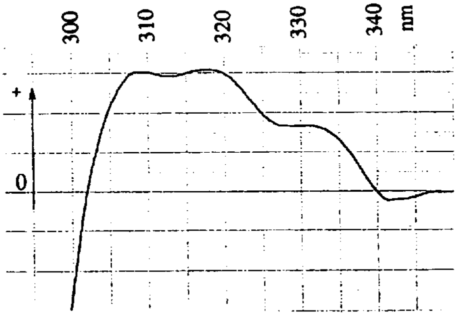
[a] (*R*) configuration attributed to the main enantiomer from comparison of the specific rotation with literature data.[1]
[b] *ee* determined from HPLC using a Chiralcel OB-H column.
[c] *ee* determined from HPLC using a Chiralcel OD column.

Table 5. Palladium-induced transformation of **KE 6Me** into **K 6Me** in MeCN under bubbling of hydrogen in the presence of **A** at various reaction temperatures

t°C	Time, h	Yield %	*ee* %[a]	10^{-3} 1/T	R/S	Ln(R/S)
22	4	74	45[b]	3.390	72.5/27.5	0.969
30	2	80	45[c]	3.300	72.5/27.5	0.969
35	2	80	46[c]	3.247	73/27	0.995
40	1.5	78	48[c]	3.195	74/26	1.046
44	1	80	50[c]	3.155	75/25	1.099
50	1	82	60[c]	3.096	80/20	1.386
52	1	79	64[c]	3.077	82/18	1.516
55	0.75	84	66[c]	3.049	83/17	1.586
60	0.75	79	65[c]	3.003	82.5/17.5	1.551
62	0.75	84	65[c]	2.985	82.5/17.5	1.551
65	0.75	81	56[b]	2.959	78/22	1.266
70	0.75	75	43[c]	2.915	71.5/28.5	0.920
75	0.75	78	40[c]	2.874	70/30	0.847

[a] (*R*) configuration attributed to the main enantiomer from comparison of the specific rotation with literature data.[1]
[b] *ee* determined from ^{1}H NMR in the presence of Eu(hfc)$_3$.
[c] *ee* determined from polarimetry comparisons.[1]

CD spectrum of K 5Me (66% *ee*) in MeCN (2.4 mg/ml, sensitivity: 10. 10^{-6}):



CD spectrum of K5i-Bu (60% *ee*) in MeCN (2 mg/ml, sensitivity: 5. 10^{-6}):

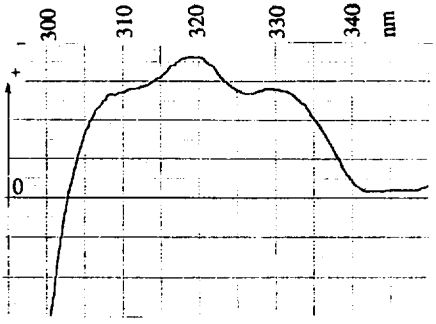


Table 6. Palladium-induced transformation of **KE 5i-Bu** into **K 5i-Bu** in MeCN under bubbling of hydrogen in the presence of **A** at various reaction temperatures

t°C	Time, h	Yield %	*ee* %[a]	10^{-3} 1/T	R/S	Ln(R/S)
22	4.5	81	50[b]	3.390	75/25	1.099
35	4	79	51[b]	3.247	75.5/24.5	1.126
40	0.75	70	54[b]	3.195	77/23	1.208
43	0.5	82	60[b]	3.165	80/20	1.386
45	0.8	82	60[b]	3.145	80/20	1.386
50	0.5	76	62[b]	3.096	81/19	1.450
53	0.5	90	68[b]	3.067	84/16	1.658
55	0.42	91	65[b]	3.049	82.5/17.5	1.551
60	0.5	84	60[b]	3.003	80/20	1.386
70	0.5	88	53[b]	2.915	76.5/23.5	1.180

[a] (*R*) configuration attributed to the main enantiomer from circular dichroïsm studies (see above).
[b] *ee* determined from HPLC using a Chiralcel OD column.

*Optical rotation of **K 5i-Bu***

For a sample having 66% *ee* and (*R*) configuration, $[\alpha]_D=-47$ (c =0.44, CH_2Cl_2).

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14. We have to point out that the purity of **A** has to be carefully checked before its use. This compound can contain small amounts of diastereoisomers which are strongly deleterious to the enantioselectivity of the process. The presence of these impurities is easily detected by ^{1}H NMR (signals between 3.06 and 3.40 ppm). These impurities are selectively removed by refluxing the mixture in aqueous 6M HCl for 24 h as previously described.[13].
15. 5% Pd/C Ref. 5011 from Engelhard Company was used for this work. This catalyst has a surface area of 1100 m^2/g and contains 50% of water. The carbon type of this catalyst is activated wood (Technical informations from Engelhard Company). For the importance of the nature of the catalyst for these reactions, see ref. 11 and 12.
16. A dynamic kinetic resolution of the ketoester under our experimental conditions seems to be unlikely. For a review on dynamic kinetic resolution processes, see: Ward, R.S. *Tetrahedron: Asymmetry* **1995**, *6*, 1475.
17. For a stimulating review, see: Buschmann, H.; Scharf, H.D.; Hoffmann, N.; Esser, P. *Angew. Chem. Int. Ed. Engl.* **1991**, *30*, 477.
18. For the definition of T_{inv}, see ref. 17. Note however that on p. 483-§5, the german/english translation has led to a printing mistake. The sentence "We describe the temperature at the isoinversion point as the..." has to be read as "We describe the temperature at the inversion point as the...".
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20. Ammonium salts of the β-ketoacids and ammonium enolates formed by reaction with **A** could also be considered at this level but they are included in the species noted **[I_n-A]** in the following.
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