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A mechanistic study of the ammonolysis of alkyl acetoacetates in water. Formation of 1,5-dimethyl-2,6,9-triaza-bicyclo[3.3.1]nonane-3,7-dione as the main product

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Abstract—Ammonolysis of alkyl acetoacetates with 15% NH_3 in water at room temperature initially lead to formation of alkyl β-aminocrotonates which slowly converted into 1,5-dimethyl-2,6,9-triaza-bicyclo[3.3.1]nonane-3,7-dione as the main product. © 2002 Published by Elsevier Science Ltd.

1. Introduction

We have presented evidence in favor of an enol mechanism to explain the rapid alkaline hydrolysis of ethyl acetoacetate in water and the first-order kinetics observed when a dilute equimolar (1.0×10^{-4} M) solution of ester and HO^- is allowed to react at room temperature.[1] The mechanism first involves the establishment of base catalyzed keto–enol equilibrium, via the enolate anion, between the ester and enols $CH_3C(OH){=}CHCO_2Et$ and $CH_3COCH{=}C(OH)OEt$. Of these enols, only the latter is reactive toward nucleophylic addition of water, in the rate-determining step, to form the dipolar ion $CH_3C(O^-){=}CHC(OH)_2O^+(H)Et$, whose breakdown losing EtOH leads to the products.

In this work, we have investigated the ammonolysis in water of ethyl and methyl acetoacetates and have found that an enol mechanism, analogous to the one proposed for the alkaline hydrolysis of ethyl acetoacetate, explains the various experimental facts, characteristic of the reaction.

2. Results and discussion

2.1. Study of the products formed in the ammonolysis reaction

In order to determine the nature of the organic product or products formed in the ammonolysis reaction, we treated $CH_3COCH_2CO_2Me$ with excess aqueous 15% NH_3 at room temperature. After about 20 min abundant white crystals had formed whose analysis showed that they corresponded to methyl β-aminocrotonate **6a** (Scheme 1). After initial formation of the white crystals, the mixture was left standing at room temperature. After 4 weeks, the reaction mixture had turned into a yellow aqueous solution. After water and NH_3 were taken off in vacuum, a brown syrupy solid formed, which was washed with methanol. White crystals were obtained after the washings. This white solid was identified as 1,5-dimethyl-2,6,9-triaza-bicyclo[3.3.1]-nonane-3,7-dione **10** on the basis of its IR, ^1H, ^{13}C NMR and mass spectra, X-ray crystallographic analysis and confirmed with the spectroscopic and analytical data reported by Shim and co-workers.[2] From the reaction mixture, we isolated another solid. This solid corresponded to a pure compound that appears to be another heterocycle different from **10**, **12** and **14** (Schemes 2 and 3). We are at present attempting to determine its structure.

Mechanistically, we believe that, **6a** formed as shown in Scheme 1 and that conversion of **6a** into heterocycle **10** took place via intermediates **5a**, **7a**, **8a** and **9** (Scheme 1). For the conversion of methyl acetoacetate into aceto-

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Keywords: acetoacetates; ammonolysis; enol mechanism; β-aminocrotonates; heterocycles.

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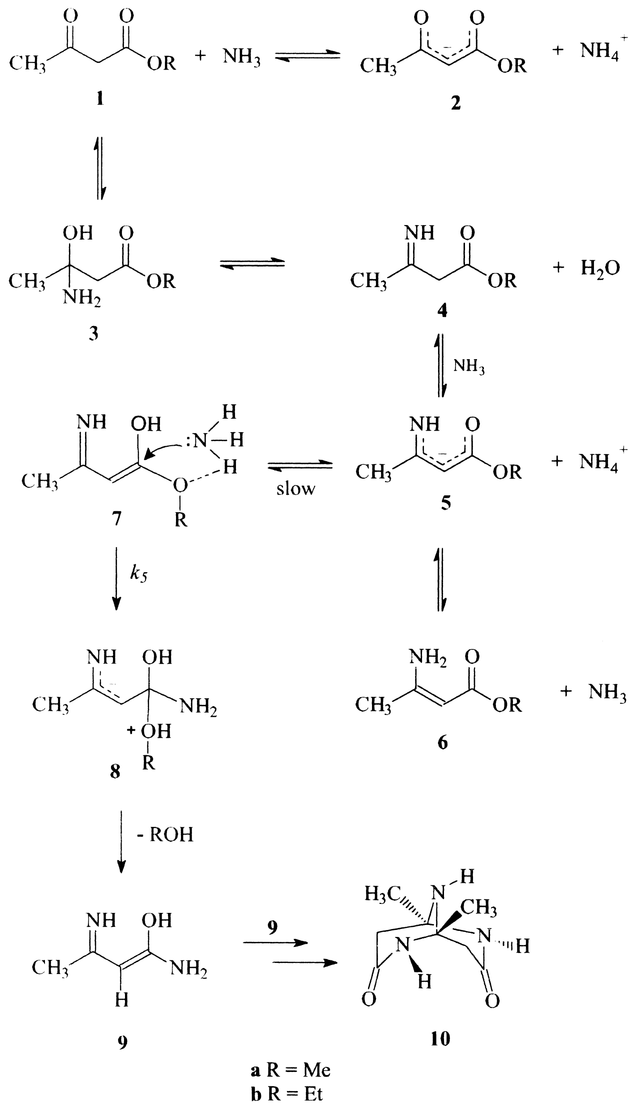


Scheme 1. Mechanistic sequence proposed for the ammonolysis in water of alkyl acetoacetates **1a**,**b** at room temperature, leading to the formation of heterocycle **10**.

acetamide, García and co-workers treated the ester with 2% ammonia in dioxane in the presence of *Candida antarctica* lipase.[3] These authors found that enamino esters such as **6** (Scheme 1) are not adequate substrates for the enzymatic reaction, since, when they were treated with excess NH_3 in the presence of the enzyme, no reaction took place. In this case, the lipase-catalyzed ammonolysis took a different path than in our reaction. Presumably the ammonolysis took place only at the ester group.

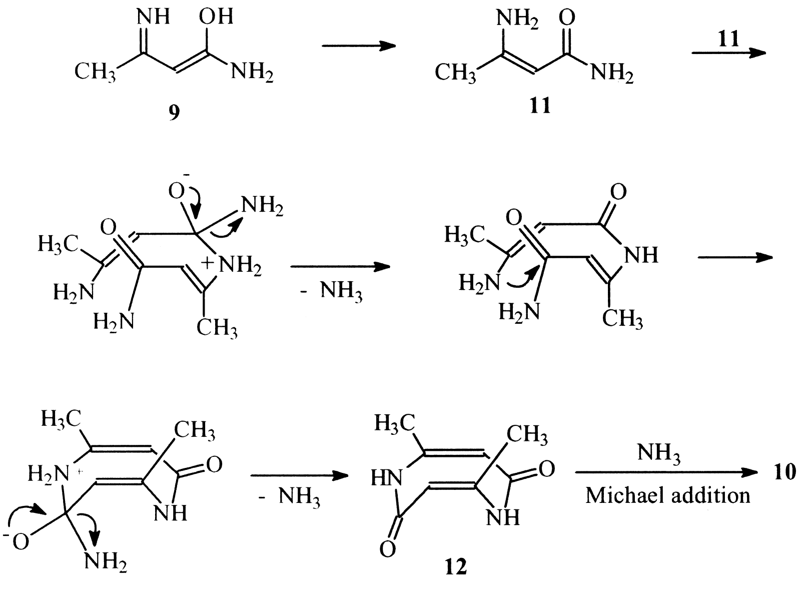
2.2. Kinetic study of the ammonolysis reaction

Ammonolysis reactions were carried out by mixing equal volumes of aqueous NH_3 and $CH_3COCH_2CO_2Et$ where a large excess of ester was used. Each reaction was monitored by measuring the decreasing NH_3 and enolate concentrations at time intervals. The NH_3 concentrations were measured by a potentiometric method and the enolate concentrations were measured by UV spectrometry.

The following facts were observed during the course of the reactions:

At the start a very fast and substantial drop in the NH_3 concentration occurred. As seen in Table 1, for one of the experiments, as soon as the NH_3 and ester solutions were mixed (time 0.0), the NH_3 concentration dropped from 2.32×10^{-4} to 2.5×10^{-5} M (89% disappearance of NH_3). Initially, we thought that the disappearance of NH_3 was due to its very fast conversion into acetoacetamide. However, work up of the reaction mixture at the start, showed that no product had formed at all and that the only organic compound present was unreacted ethyl acetoacetate **1b**. Another possibility for a fast consumption of NH_3 is via a rapid acid–base reaction between the ester and NH_3 (Scheme 4).

For this reaction, its equilibrium constant can be evaluated



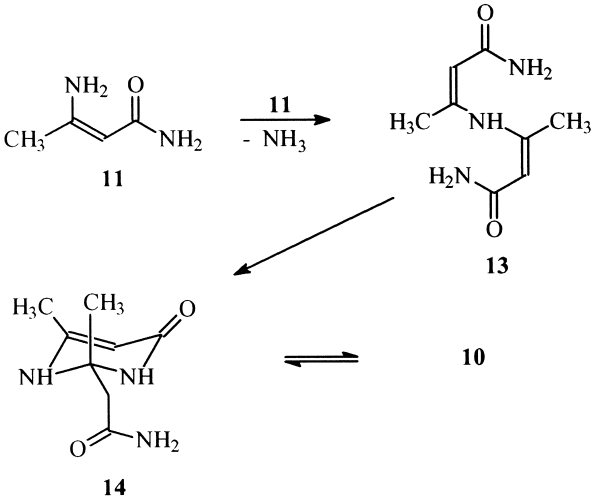
Scheme 2. Stepwise formation of heterocycle **10** via proposed intermediate **12**.

as follows:

$$\frac{[\text{enolate}](\text{NH}_4^+)}{[\text{ester}][\text{NH}_3]} = K = \frac{K_a K_b}{K_W} = 0.036$$

where K_a is the acidity constant for $CH_3COCH_2CO_2Et$, pK_a=10.7[4], K_b the basicity constant for NH_3=1.8×10^{-5} and K_w is the water constant=1.0×10^{-14}.

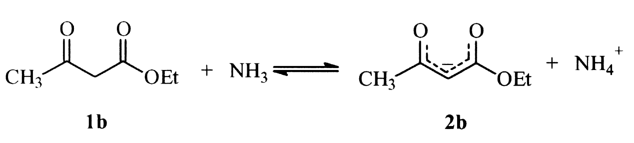
Assuming that the above equilibrium was established at once as soon as the reagents were mixed, the calculated hypothetical equilibrium constant is 0.087, a value 2.4 times larger than the expected 0.036. This indicated that the sudden initial decrease in NH_3 concentration possibly occurred because the ester and NH_3 reacted very fast to form imine **4b** (Scheme 1). This view is reinforced by the facts described below.



Scheme 3. Formation of heterocycle **10** according to Shim and co-workers.

Table 1. Ammonolysis in water of 0.0200 M $CH_3COCH_2CO_2Et$ with 2.32×10^{-4} M NH_3 at room temperature

Time (min)	$[NH_3]$ (M)	[Enolate] (M)
0.0	2.5×10^{-5}	1.0×10^{-4}
2.5	1.9×10^{-5}	1.0×10^{-4}
5.0	1.7×10^{-5}	9.9×10^{-5}
10.0	1.4×10^{-5}	9.4×10^{-5}
15.0	1.2×10^{-5}	8.9×10^{-5}
20.0	1.1×10^{-5}	8.5×10^{-5}
25.0	1.0×10^{-5}	8.1×10^{-5}
30.0	8.7×10^{-6}	7.7×10^{-5}



Scheme 4.

A plot of $\ln[NH_3]$ versus time for the experiment described in Table 1 showed that after the initial fast drop in NH_3 concentration, a sloping straight line was obtained from time 10 to 30 as expected from the pseudo-first-order reaction. Furthermore, when for each point at times 10, 15, 20, 25 and 30, the pK_a for $CH_3COCH_2CO_2Et$ was calculated from the experimental data, a value of 10.7 was obtained (Table 2). This result indicated that from time 10 to 30, the equilibrium between ester and enolate had been established. Between time 0 and 10, the system moved toward the establishment of the ester–enolate equilibrium (Scheme 1), as seen from the pK_a values in Table 2.

Three reactions between excess $CH_3COCH_2CO_2Et$ and NH_3 in water were run. In all these reactions, we observed an initial fast drop in NH_3 concentration as seen from their plots of $\ln[NH_3]$ versus time. After about time 10, straight lines were obtained whose slopes correspond to the k_{obs} values measured (Table 3). The results shown in Table 3 indicate that for these reactions the rate law is first order in NH_3 and zero order in ester. To explain this rate law, we considered that the rate of formation of the dipolar ion **8b** is:

Table 3. Ammonolysis in water of $CH_3COCH_2CO_2Et$ at room temperature

$[\text{Ester}]_{\text{init.}}$	$[NH_3]_{\text{init.}}$	k_{obs} (min^{-1})
0.100	3.5×10^{-3}	0.024
0.050	6.9×10^{-4}	0.022
0.020	2.3×10^{-4}	0.025

$$\text{rate} = k_5[\mathbf{7b}][NH_3]$$

Since **7b** is a reactive, unstable species whose concentration at all times after time 10 is very small and approximately constant, we have:

$$\text{rate} = k_5[\mathbf{7b}][NH_3] = k_{obs}[NH_3]$$

This last equation shows that the kinetics for the reaction is first-order in NH_3 and zero order in ester as determined experimentally.

2.3. Mechanism for the formation of the heterocycle

Although Shim and co-workers[2] prepared heterocycle **10** via

Table 2. Ammonolysis in water of 0.0200 M $CH_3COCH_2CO_2Et$ with 2.32×10^{-4} M NH_3 at room temperature (pK_a=10.7[4], for each point the charge balance $[\text{enolate}]+[OH^-]=[NH_4^+]+[H^+]$ is maintained)

Time (min)	[Enolate] (M)	$[NH_3]$ (M)	$[OH^-]$ (M)	$[NH_4^+]$ (M)	$[H^+]$ (M)	Calculated pK_a
0.0	1.0×10^{-4}	2.5×10^{-5}	4.3×10^{-6}	1.0×10^{-4}	2.5×10^{-9}	10.9
5.0	9.9×10^{-5}	1.7×10^{-5}	3.0×10^{-6}	1.0×10^{-4}	3.3×10^{-9}	10.8
10.0	9.4×10^{-5}	1.4×10^{-5}	2.6×10^{-6}	9.7×10^{-5}	3.8×10^{-9}	10.7
15.0	8.9×10^{-5}	1.2×10^{-5}	2.4×10^{-6}	9.1×10^{-5}	4.2×10^{-9}	10.7
20.0	8.5×10^{-5}	1.1×10^{-5}	2.3×10^{-6}	8.8×10^{-5}	4.4×10^{-9}	10.7
25.0	8.1×10^{-5}	1.0×10^{-5}	2.2×10^{-6}	8.3×10^{-5}	4.6×10^{-9}	10.7
30.0	7.7×10^{-5}	8.7×10^{-6}	2.0×10^{-6}	7.9×10^{-5}	5.0×10^{-9}	10.7

Table 4. Other crystal and refinement data of compound **10**

Diffractometer	Enraf-Nonius CAD4
Crystal dimensions (mm^3)	0.2×0.2×0.15
Scan technique	$\omega/2\theta$
Data collected	(0, −14, −13) to (10, 14, 12)
Unique data	2198
Observed reflections $F_o>4(\sigma(F_o))$	1497
Decay	<1%
R_{int} (%)	0.03
R	0.045
$wR2$	0.124
Maximum shift/error	0.0
Computing structure solution	SHELXS-97[6]
Computing structure refinement	SHELXL-97[5]

Table 5. Fractional atomic coordinates and equivalent isotropic displacement parameters (Å^2)

	x	y	z	U_{eq}
O12	0.07890(14)	0.20475(12)	−0.00249(12)	0.0248(3)
O13	0.00643(14)	0.28989(11)	−0.53806(11)	0.0204(3)
N9	0.05608(16)	0.52440(14)	−0.21399(13)	0.0167(3)
C3	0.0674(2)	0.29677(16)	−0.07905(15)	0.0177(4)
N2	0.19874(16)	0.34281(14)	−0.12164(13)	0.0183(3)
C1	0.19969(19)	0.44696(16)	−0.21679(15)	0.0166(4)
C8	0.1933(2)	0.39495(16)	−0.36059(16)	0.0185(4)
C7	0.0257(2)	0.34841(16)	−0.42835(15)	0.0171(4)
N6	−0.10078(17)	0.37524(13)	−0.36964(13)	0.0171(3)
C5	−0.09361(19)	0.45112(15)	−0.24386(15)	0.0159(4)
C4	−0.0934(2)	0.36374(16)	−0.12363(16)	0.0174(4)
C10	−0.2427(2)	0.53608(16)	−0.26840(17)	0.0208(4)
C11	0.3551(2)	0.52299(17)	−0.16980(17)	0.0220(4)

intermediate **14** by thermolysis of β-aminocrotonamide as shown in Scheme 3, we believe that under our mild reaction conditions heterocycle **10** is formed via intermediate **12**, from a double Michael addition of NH_3 on **12**, as shown in Scheme 2. Under our reaction conditions, we did not detect intermediate **14**, while Shim separated it as a stable compound from the reaction mixture.

2.4. X-Ray crystallographic analysis for compound 10

Single crystal of $C_8H_{13}N_3O_2$, are at 123 K, monoclinic, space group $P2_1/n$ (No. 14), with a=8.3070(2) Å, b=10.7160(3) Å, c=10.0490(3) Å, β=101.507(2) Å, V= 876.56(4) Å^3, Z=4, D_c=1.388 g/cm^3, μ(Mo Kα)= 0.102 mm^{-1}. The structure was refined on F^2. A summary of crystal and refinement data is given in Table 4. The cell dimensions were refined by least-squares fitting the θ values of 25 reflections with θ range of 1.0–27.88°. The ring H atoms were added at calculated positions. The H atoms treated with a riding model with SHELXL97 defaults,[5] (C–H, 0.96–0.97 Å and N–H, 0.86 Å) were not refined (Tables 5 and 6, Fig. 1).

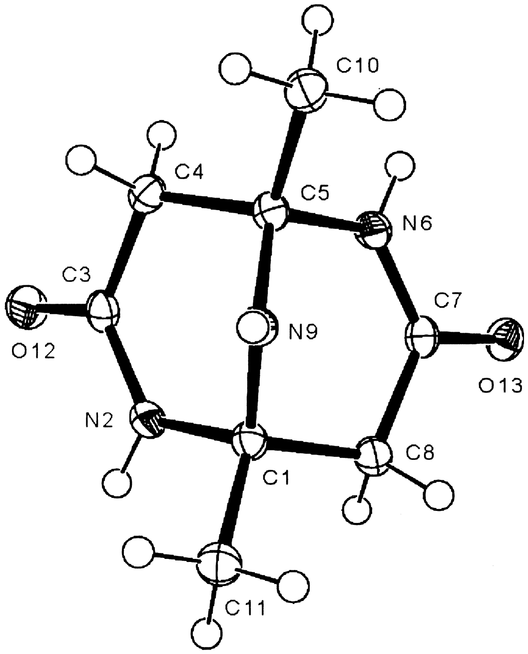


Figure 1. Ortep-3 view[7] of compound **10** with the atom labeling. Thermal ellipsoids are shown at 50% probability, except for H atoms which are represented by spheres of arbitrary size.

Table 6. Geometric parameters of compound **10**

O12–C3	1.243(2)	O13–C7	1.2506(19)	N9–C5	1.451(2)
N9–C1	1.458(2)	C3–N2	1.343(2)	C3–C4	1.504(2)
N2–C1	1.471(2)	C1–C11	1.520(2)	C1–C8	1.540(2)
C8–C7	1.508(2)	C7–N6	1.335(2)	N6–C5	1.494(2)
C5–C10	1.517(2)	C5–C4	1.528(2)		
C5–N9–C1	111.03(13)	O12–C3–N2	121.44(16)	O12–C3–C4	121.16(15)
N2–C3–C4	117.37(14)	C3–N2–C1	126.58(14)	N9–C1–N2	107.99(12)
N9–C1–C11	109.67(14)	N2–C1–C11	108.61(13)	N9–C1–C8	110.42(12)
N2–C1–C8	109.38(14)	C11–C1–C8	110.71(13)	C7–C8–C1	113.55(13)
O13–C7–N6	121.62(15)	O13–C7–C8	120.54(14)	N6–C7–C8	117.81(14)
C7–N6–C5	126.10(14)	N9–C5–N6	110.95(12)	N9–C5–C10	110.32(13)
N6–C5–C10	107.19(12)	N9–C5–C4	107.60(12)	N6–C5–C4	109.20(13)
C10–C5–C4	111.60(13)	C3–C4–C5	112.88(13)		
O12–C3–N2–C1	176.96(15)	C4–C3–N2–C1	−5.2(2)	N6–C5–C4–C3	73.14(16)
C5–N9–C1–N2	−55.51(15)	C5–N9–C1–C11	−173.70(12)	C10–C5–C4–C3	−168.53(13)
C5–N9–C1–C8	64.03(16)	C3–N2–C1–N9	23.4(2)	N2–C3–C4–C5	16.9(2)
C3–N2–C1–C11	142.22(16)	C3–N2–C1–C8	−96.84(18)	N9–C5–C4–C3	−47.38(17)
N9–C1–C8–C7	−43.04(19)	N2–C1–C8–C7	75.66(17)	C7–N6–C5–C4	−101.09(18)
C11–C1–C8–C7	−164.69(14)	C1–C8–C7–O13	−171.19(15)	O12–C3–C4–C5	−165.22(14)
C1–C8–C7–N6	10.9(2)	O13–C7–N6–C5	−175.93(15)	C7–N6–C5–N9	17.3(2)
C8–C7–N6–C5	2.0(2)	C1–N9–C5–N6	−50.06(16)	C7–N6–C5–C10	137.85(16)
C1–N9–C5–C10	−168.69(12)	C1–N9–C5–C4	69.35(15)		

3. Conclusions

Results from our work show that ammonolysis in water of alkyl acetoacetates at room temperature does not lead to the formation of acetoacetamide as could be expected. Instead alkyl β-aminocrotonates form as kinetically controlled products which then convert slowly into a mixture of at least two heterocycles of which the main product is 1,5-dimethyl-2,6,9-triaza-bicyclo[3.3.1]nonane-3,7-dione. Ammonolysis of methyl acetoacetate catalyzed by *C. antarctica* lipase lead to the formation of acetoacetamide.

4. Experimental

4.1. Materials

All chemicals were of the highest possible purity available. Solutions for the kinetic studies were prepared daily in distilled water.

4.2. Instruments

A UV–visible Shimadzu UV-160A spectrophotometer was used for the spectrometric measurements. An Orion AE940 ion analyzer equipped with a NH_3 electrode and a reference electrode was used to measure NH_3 concentrations in the standard solutions. A digital Schött–Gerate CG 820 pH meter equipped with a Schött–Gerate H61 combined electrode was used for the potentiometric measurements. The ^1H and ^{13}C NMR spectra were recorded on a Varian Gemini 200 instrument, chemical shifts (δ) are reported in ppm relative to internal tetramethylsilane, DMSO-d_6 and D_2O as solvent. Silica gel plates (Merck F_{254}) were used for analytical TLC. The IR spectra were taken in a FT-IR ATI MATTSON spectrophotometer. The mass spectrum was taken on a Varian Model MAT MS-311 spectrometer at 70 eV.

4.3. Determination of λ_{max} and ε_{max} for the enolate of $CH_3COCH_2CO_2Et$ in water at room temperature

The enolate ion of 1,3-dicarbonyl compounds absorb strongly in the UV in the 270–300 nm region.[8] An aqueous 0.250 M KOH and 2.28×10^{-5} M $CH_3COCH_2CO_2Et$ solution displays maximum absorption at 273 nm due to the complete conversion of the ester into enolate ion, as calculated from the $pK_a=10.7$ for the ester.[4]

The formation of the enolate was accomplished by mixing 50.0 mL of aqueous 0.500 M KOH with 50.0 mL of aqueous 4.55×10^{-5} M $CH_3COCH_2CO_2Et$. Aliquots were poured into 1 cm UV cells and readings of absorbance A at 273 nm were taken every 5 min during 100 min. A plot of $\ln A$ versus time gave a straight line with intercept −0.693 and slope −0.00334.

$$\varepsilon_{max} = \frac{A_0}{[\text{enolate}]_0} = \frac{e^{-0.693}}{2.28\times10^{-5}} = 2.19\times10^4$$

4.4. Determination of enolate concentrations in the ammonolysis of $CH_3COCH_2CO_2Et$ in water at room temperature

After mixing the aqueous NH_3 and ester solutions, absorbance readings were taken at time intervals during 30 or 60 min. Enolate concentrations were calculated as shown:

$$[\text{enolate}] = \frac{A}{\varepsilon_{max}}$$

4.5. Calibration curve of $\ln[NH_3]$ versus potential

Several aqueous NH_3 standard solutions of appropriate concentrations were prepared. The NH_3 concentration of each solution was determined using the Orion ion analyzer. For each solution, its potential (mV) was measured. A plot of $\ln[NH_3]$ versus potential gave a straight line with intercept −15.54 and slope −0.0498.

4.6. Determination of NH_3 concentrations in the ammonolysis of $CH_3COCH_2CO_2Et$ in water at room temperature

After mixing the aqueous NH_3 and ester solutions, potential readings were taken at time intervals during 30 or 60 min. NH_3 concentrations were determined from the calibration curve.

4.7. Determination of $NH_4^+$and OH^- concentrations in the ammonolysis of $CH_3COCH_2CO_2Et$ in water at room temperature

NH_4^+originates from the reaction of $CH_3COCH_2CO_2Et$ with NH_3 and from the reaction of NH_3 with water. $[OH^-]$ and $[NH_4^+]$ for each point were calculated from the following equation:

$$\frac{[NH_4^+][OH^-]}{[NH_3]} = \frac{\{[\text{enolate}] + [OH^-]\}[OH^-]}{[NH_3]} = K_b = 1.8\times10^{-5}$$

4.7.1. Determination of the products formed in the ammonolysis of $CH_3COCH_2CO_2Et$ in water at room temperature. 8.56 g (0.0738 mol) of $CH_3COCH_2CO_2Me$ was added to 50 mL 15% aqueous NH_3. After 20 min, an abundant white solid had formed. The solid was filtered off, washed with water and dried at room temperature. It amounted to 7.94 g of a product identified as methyl β-aminocrotonate **6a** (94% yield, mp 81.2–83°C) on comparison with an authentic sample of the compound obtained from Aldrich.[9]

10.53 g (0.0908 mol) of $CH_3COCH_2CO_2Me$ was added to 50 mL 15% aqueous NH_3. After formation of the white solid, the mixture was left standing at room temperature. TLC showed that methyl β-aminocrotonate was converting into products. After 4 weeks, the conversion was complete and the reaction mixture was a yellow solution. After water and NH_3 were taken off in vacuum, a brown syrupy solid formed which was washed with methanol. 1.93 g of white crystals were obtained after the washings and corresponded to 1,5-dimethyl-2,6,9-triaza-bicyclo[3.3.1]nonane-3,7-dione **10**. 23% isolated yield, mp, 198.0–198.2°C [197–198]; IR (KBr, cm^{-1}): 3282 [3280], 3198 [3179], 1662 [1660], 1508 [1510], 1396 [1400]; ^{1}H NMR (DMSO-d_6): δ 1.28 (s, 6H, 1- and 5-CH_3) [1.28 (s, 6H)], 2.19 (s, 4H, 4- and 8-CH_2) [2.15 (s, 4H)], 3.55 (s, 1H, 9-NH) [3.45 (s, 1H)], 8.01 (s, 2H, 2- and 6-NH) [7.89 (s, 2H)]; ^{1}H NMR (D_2O): δ 1.39 (s, 6H, 1- and 5-CH_3) [1.52 (s, 6H)], 2.42 (s, 4H, 4- and 8-CH_2) [2.53 (s, 4H)]; ^{13}C NMR (DMDO-d_6): δ 28.1 (1- and 5-CH_3), 44.5 (4- and 8-C), 65.7 (1- and 5-C), 168.0 (3-and 7-CO); ^{13}C NMR (D_2O): δ 26.2, 42.4, 65.7, 170.1; MS *m/z* (%): 184 (96, M+1), 183 (100, M^+) [183], 166 (8, $M-NH_3$). Signals in square brackets correspond to those reported by Shim and co-workers.[2] The overall yield of **10** is higher than 23% since we detected more of this product mixed with other products in the methanolic washings.

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