

## Amlodipine Benzenesulfonate: A Mechanistic Investigation of Its Industrial Preparation via Detritylation of *N*-tritylamlopidine and Related NMR Studies\*

Borut Furlan,<sup>a</sup> Simona Golič Grdadolnik,<sup>b</sup> Stanko Hočvar,<sup>b</sup> Darko Kocjan,<sup>a</sup> Janez Levec,<sup>b</sup> Howard Maskill,<sup>c,\*\*</sup> Hana Navrátilová,<sup>d</sup> Jiří Pospíšil,<sup>d</sup> Milan Potáček,<sup>d</sup> Uroš Urleb,<sup>a</sup> and Janko Žmitek<sup>b</sup>

<sup>a</sup>*Lek Pharmaceuticals d.d., Verovškova 57, SI-1526 Ljubljana, Slovenia*

<sup>b</sup>*National Institute of Chemistry, Hajdrihova 19, SI-1000 Ljubljana, Slovenia*

<sup>c</sup>*Department of Chemical and Biological Sciences, School of Applied Sciences, University of Huddersfield, Queensgate, Huddersfield, UK*

<sup>d</sup>*Department of Organic Chemistry, Masaryk University of Brno, Kotlářská 2, CZ-61137 Brno, The Czech Republic*

RECEIVED JUNE 5, 2008; REVISED OCTOBER 1, 2008; ACCEPTED OCTOBER 6, 2008

**Abstract.** Kinetics and product analysis of detritylation of *N*-tritylamlopidine by benzenesulfonic acid in methanol, methanol-chloroform (volume ratio 9:1), ethanol, 2-propanol, and methanol/2-propanol (mole ratio 1:1) have been investigated by HPLC; amongst these reaction conditions are ones closely similar to those of one method of manufacturing amlodipine benzenesulfonate. Kinetics of detritylation of *N*-tritylamlopidine have also been investigated in methanol-*d*<sub>4</sub> by <sup>1</sup>H NMR spectroscopy and the agreement with the results by HPLC is good. The rate of detritylation increases with increasing concentrations of benzenesulfonic acid, and *p*-methoxy-substituents in the trityl group have been shown to lead to faster reactions. In methanol, the rate is hardly affected by 10 % (vol. fraction) chloroform. These studies relate to mechanistic investigations of acid-catalysed deaminations of methoxy-substituted tritylalkylamines, and Arrhenius activation parameters (*E*<sub>a</sub> and *A*) are similar indicating a common generic mechanism. Acid-catalysed *trans*-esterification has been shown by HPLC to accompany detritylation in methanol, and attendant protium-deuterium exchange in the methyl at C6 by reversible acid-catalysed iminium ion formation in the 4-aryl-1,4-dihydropyridine moiety of both *N*-tritylamlopidine and amlodipine has been investigated in deuteriated methanol by <sup>1</sup>H, <sup>13</sup>C, and <sup>15</sup>N NMR spectroscopy.

**Keywords:** kinetics, detritylation, mechanism, acid-catalysed deaminations

### INTRODUCTION

Amlodipine (**Aml**, Figure 1) is a potent and long-acting calcium channel blocker used as its benzenesulfonate salt (**Aml-Bz**, Figure 1) as an anti-ischaemic and anti-hypertensive agent.<sup>1</sup> In one manufacturing process,<sup>2</sup> the free base, **Aml**, is prepared by conventional methods, purified, then converted into the pharmaceutical (**Aml-Bz**) with benzenesulfonic acid (**BSA**) in a simple proton transfer reaction in ethanol. In another patented industrial procedure,<sup>3</sup> which purposefully avoids the formation and isolation of the free base, *N*-tritylamlopidine (**Tr-Aml**, Figure 1) is first synthesised in pure form with the *N*-tritylamino function in place. Then, in a single operation, the **Tr-Aml** is deprotected using **BSA** in methanol or ethanol to give the final product as the

salt directly (Scheme 1). Under the conditions of this reaction, the trityl electrofuge in the heterolysis of the protonated **Tr-Aml** is captured by the alcoholic solvent to give the trityl alkyl ether which is formed in quantitative yield. Unlike the corresponding cleavage of trityl alcohols,<sup>4</sup> this deprotection reaction involving conjugate acids of strongly basic amines is irreversible under the acidic conditions; the reaction also relates to the cleavage of trityl 2,2,2-trifluoroethyl ethers.<sup>5</sup>

We recently observed that the hydrogens of the methyl at C6 of the 4-aryl-1,4-dihydropyridine moiety of **Aml-Bz** in methanol/methanol-<sup>2</sup>H<sub>4</sub> mixtures undergo protium/deuterium exchange in the presence of an excess of **BSA**.<sup>6</sup> The most credible mechanism for this finding involves reversible hydronium ion addition to C5 to give an iminium cation which may be reversibly

\* Dedicated to Professor Zvonimir Maksić on the occasion of his 70<sup>th</sup> birthday.

\*\* Author to whom correspondence should be addressed. (E-mail: h.maskill@ncl.ac.uk; correspondence may be also addressed to SH, DK, or JŽ)

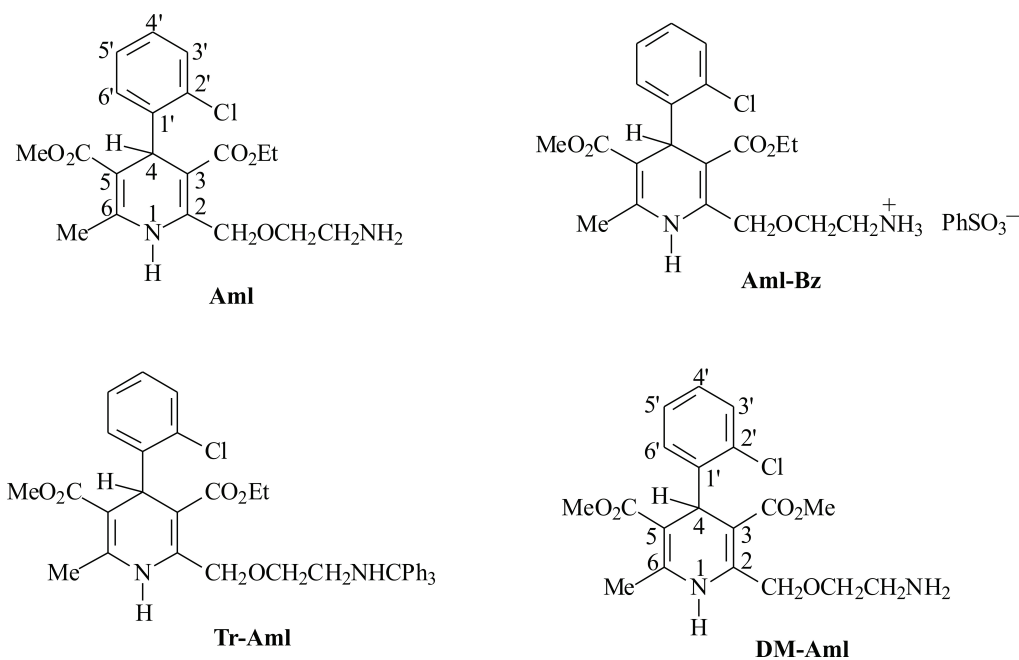


Figure 1. Structures.

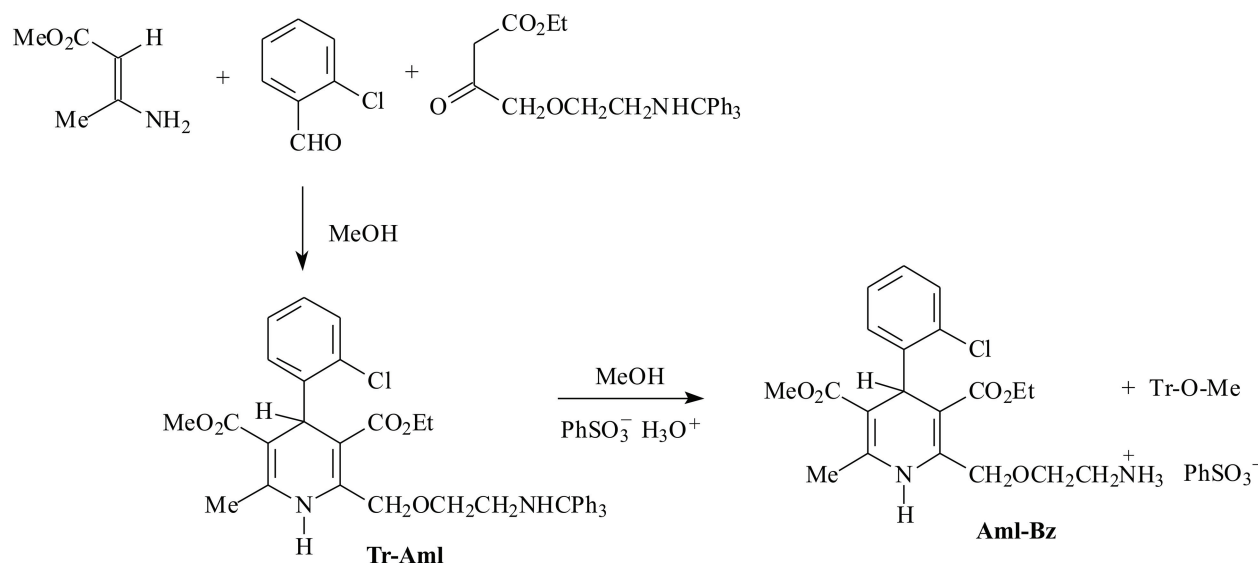
deprotonated from the methyl at C6 (Scheme 2). In support of this mechanism, the ratio of the intensities of the signals for C5 (104.1 ppm) and C6 (146.7 ppm) in the  $^{13}\text{C}$  spectrum of **Aml-Bz** changes appreciably in the presence of one equivalent of **BSA** indicating additional relaxation mechanisms for C5 in the presence of the excess of the acid.

The production of **Aml-Bz** by detritylation of **Tr-Aml** relates directly to investigations of solvolysis reactions in which substituted trityl cations have been liberated by heterolysis of  $\text{Tr}'\text{-N}$  bonds ( $\text{Tr}' =$  substituted trityl).<sup>7-10</sup> The ease of these cleavage reactions depends very much upon the molecular structure of the protected amine. The rates of cleavage of 4,4'-dimethoxytritylamines (**DMTrNHR**) and 4,4',4''-trimethoxytritylamines (**TMTTrNHR**) with  $\text{R} =$  alkyl are about  $10^6$  greater than when  $\text{R} = \text{H}$ . This effect is much greater than that of inserting up to three *para*-methoxy substituents into the trityl group of the parent  $\text{TrNH}_2$ .<sup>8,10</sup> Additionally, the reactions in water are affected by the ionic strength and are subject to specific acid catalysis.<sup>7,8</sup> This latter finding was remarkable since the actual substrate, the *N*-trityl-alkylammonium cation, has no basic site, and was explained by the intervention of ion-molecule pair intermediates.<sup>9,10</sup> However, the mechanistic investigations of the solvolytic reactions were generally carried out in dilute aqueous acidic solutions (typically,  $[\text{substrate}]_0 \approx 10^{-5} \text{ mol dm}^{-3}$  with  $[\text{H}_3\text{O}^+] \gg [\text{substrate}]_0$ ) under carefully controlled conditions at constant ionic strength and using *p*-methoxy-substituted trityl substrates. In contrast, the industrial process is carried out in methanol or ethanol at relatively high initial concentrations (typically  $0.8 \text{ mol dm}^{-3}$ ) of amlodipine pro-

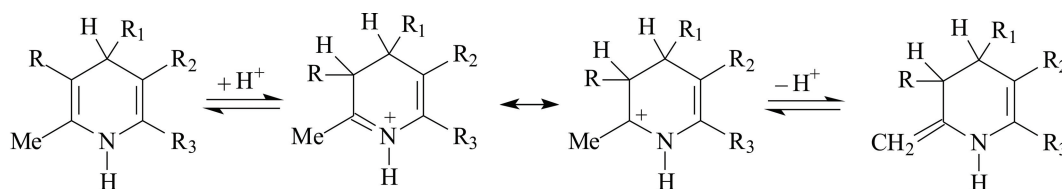
tected by the unsubstituted *N*-trityl group, and with the initial concentration of **BSA** similar to, or just slightly greater than, that of the substrate.<sup>3</sup>

We now report a mechanistic investigation of amlodipine and *N*-tritylamlopidine including product analytical and kinetics studies on the detritylation of the latter in methanol,  $\text{MeOH-CHCl}_3$  (vol. ratio 9:1), ethanol, 2-propanol, and methanol/2-propanol (mole ratio,  $r = 1:1$ ). The experimental conditions include ones designed to approximate the industrial process on the one hand and, on the other, to allow the solvent effect upon the industrial process to be investigated. The initial substrate concentrations (from 0.025 up to  $0.2 \text{ mol dm}^{-3}$ ) were too high to allow direct reaction monitoring by UV spectrophotometry so we used an HPLC method.<sup>11</sup> We have thus been able (i) to determine reaction parameters under conditions closely similar to those of the industrial process, and (ii) relate the results to the very substantial body of knowledge available in the literature regarding the formation of substituted trityl cations by C–N cleavage in dilute aqueous solution.

The kinetics results for detritylation of **Tr-Aml** in MeOH have been corroborated by an  $^1\text{H}$  NMR spectroscopic method in methanol- $d_4$ . In addition,  $^1\text{H}$ ,  $^{13}\text{C}$ , and  $^{15}\text{N}$  NMR studies of both **Tr-Aml** and **Aml** under acidic conditions in methanol are reported which cast new light on the lability of the hydrogens of the C6-methyl group arising from reversible formation of an iminium ion by hydrogen ion addition to C5 of the 1,4-dihydropyridine residue of **Aml** and **Tr-Aml**. This process under the acidic conditions, like the *trans*-esterification of the ethyl ester groups of **Aml** and **Tr-**



**Scheme 1.** Formation of *N*-tritylamlopidine and conversion into amlodipine benzenesulfonate and methyl trityl ether.



**Scheme 2.** Mechanism for hydrogen exchange in the methyl at C6 of Tr-Aml and Aml-Bz (see Figure 1 for identities of R-R<sub>3</sub>).

**Aml** in methanol identified by HPLC, accompanies the detritylation.

In addition to the new chemistry revealed, we believe these investigations provide a model for other investigators involved in mechanistic studies of organic reactions at the academic-industrial interface.

## METHODS AND RESULTS

### Product Analysis and Kinetics of Detritylation of *N*-tritylamlopidine by Reverse Phase HPLC<sup>11</sup>

HPLC conditions were identified which allowed complete resolution of **Tr-Aml**, **BSA**, **Aml** (or **Aml-Bz**), trityl alcohol (triphenylmethanol, **TrOH**), methyl trityl ether (**MeOTr**), 2-propyl trityl ether (**2-PrOTr**), and dimethyl amlodipine (**DM-Aml**) in single analyses. Calibration curves were constructed for **TrOH**, **MeOTr**, **2-PrOTr**, **Aml**, **Tr-Aml**, and **DM-Aml**.

*N*-Tritylamlopidine at  $[\text{Tr-Aml}]_0 = 0.200 \text{ mol dm}^{-3}$  was reacted with various equivalents of **BSA** in methanol at several temperatures, and in methanol/2-propanol (mole ratio,  $r = 1:1$ ) at 75 °C; periodic HPLC analyses allowed rate constants to be measured in each

case in the usual manner and these are given in Table 1. Application of the Arrhenius equation to results in MeOH at 45, 55, and 63 °C for  $[\text{BSA}]_0/[\text{Tr-Aml}]_0 = 1.1$  allowed calculation of  $E_a = 130 \text{ kJ mol}^{-1}$  and  $A = 8 \times 10^{16} \text{ s}^{-1}$  ( $R > 0.999$ ).<sup>12</sup> At completion in ethanol and in 2-PrOH (rates were not measured in these), **EtOTr** and **2-PrOTr** were formed in 100 % yields; in methanol and the mixed solvent, **MeOTr** was the only solvent-derived product (100 %), *i.e.* no **2-PrOTr** was detected in reactions of **Tr-Aml** in MeOH/2-PrOH (amount ratio 1:1). No **TrOH** was detected in any reactions although small yields of unidentified products were noted at short retention times; yields of **Aml** were typically over 80 % at completion in all three solvent systems.

In a further series of experiments, products and reaction rates were investigated in MeOH-CHCl<sub>3</sub> (vol. ratio, 90:10) with  $[\text{BSA}]_0/[\text{Tr-Aml}]_0$  in the range 0.95–1.5 and  $[\text{Tr-Aml}]_0$  in the range 0.025 to 0.1 mol dm<sup>-3</sup>. In these reactions at 59 °C, a low yield (up to about 4 %) of dimethylamlopidine (**DM-Aml**) was shown to form in addition to very much smaller yields of several unidentified products. Additionally, rates of the corresponding reactions of 4-methoxytrityl amlodipine (**MMTr-Aml**) and 4,4'-dimethoxytrityl amlodipine (**DMTr-Aml**) were measured in this solvent to explore

**Table 1.** HPLC kinetics results for detritylation of **Tr-Aml** in methanol and methanol:2-propanol (mole ratio 1:1);  $[\text{Tr-Aml}]_0 = 0.200 \text{ mol dm}^{-3}$ 

Solvent (temp. / °C)	$[\text{BSA}]_0 / [\text{Tr-Aml}]_0$	$10^4 k_{\text{exp}} / \text{s}^{-1}$
MeOH (45)	1.0	0.258
MeOH (45)	1.1	0.355 <sup>(a)</sup>
MeOH (45)	1.5	0.347
MeOH (55)	1.00	1.14
MeOH (55)	1.1	1.45 <sup>(a)</sup>
MeOH (55)	1.5	1.49
MeOH (63)	0.70	4.23
MeOH (63)	1.0	5.17
MeOH (63)	1.0 <sup>(b)</sup>	5.06 <sup>(b)</sup>
MeOH (63)	1.1	5.00 <sup>(a)</sup>
MeOH (63)	1.5	4.88
MeOH (63)	2.0	4.97
MeOH:2-PrOH (75)	1.1	4.9
MeOH:2-PrOH (75)	1.5	6.6
MeOH:2-PrOH (75)	2.2	6.7

<sup>(a)</sup> Using the Arrhenius equation with these three results,  $E_a = 130 (\pm 10) \text{ kJ mol}^{-1}$  and  $A = 8 (\pm 1) \times 10^{16} \text{ s}^{-1}$  ( $R > 0.999$ ),<sup>12</sup> interpolated values of  $k_{\text{exp}}$  at 50 and 59 °C are  $7.4 \times 10^{-5}$  and  $2.7 \times 10^{-4} \text{ s}^{-1}$ ; <sup>(b)</sup>  $[\text{Tr-Aml}]_0 = 0.104 \text{ mol dm}^{-3}$ .

the effect of methoxy substituents in the trityl residue. However, reactions of both of these compounds were too fast to follow by the HPLC method at 59 °C so were investigated at 45 and 35 °C; even at these temperatures only approximate rate constants were determinable from estimated half-lives for the decomposition of the substrate and formation of products. Results are given in Table 2.

*Kinetics of Detritylation of N-tritylamlopidine and Protium-deuterium Exchange in the C6-CH<sub>3</sub> in Amlodipine and N-tritylamlopidine in Methanol-<sup>2</sup>H<sub>4</sub> by <sup>1</sup>H NMR Spectroscopy<sup>6</sup>*

Deuterium-protium exchange in the C6-CH<sub>3</sub> in **Tr-Aml** with **BSA** was observed by recording <sup>1</sup>H spectra of solutions in methanol-d<sub>4</sub> with  $[\text{BSA}]_0 / [\text{Tr-Aml}]_0 = 1.5$  and 3.0 at 30 min intervals over 4 h at 25 °C. Under these conditions, the intensity of the C6-CH<sub>3</sub> signal ( $\delta = 2.28 \text{ ppm}$ ) diminishes at a readily measured rate as the CH<sub>3</sub> becomes CH<sub>2</sub>D, CHD<sub>2</sub>, and CD<sub>3</sub> (Figure 2, left hand side). Concurrent with this exchange process, the intensity of the CH<sub>3</sub> of the C3-CO<sub>2</sub>CH<sub>2</sub>CH<sub>3</sub> group of **Tr-Aml** at  $\delta = 1.05 \text{ ppm}$  diminishes much more slowly as **Tr-Aml** is detritylated (Figure 2, right hand side); the signal for the corresponding methyl in **Aml** is at  $\delta = 1.15 \text{ ppm}$ . Simultaneous monitoring of the intensities of the signals at  $\delta = 2.28 \text{ ppm}$  and  $\delta = 1.05 \text{ ppm}$ , therefore, allows differentiation of the H/D exchange in the C6-Me and the detritylation process, and the rate constant for the former process could be measured (Table 3).

Detritylation of **Tr-Aml** at 50 °C in methanol-d<sub>4</sub> with  $[\text{BSA}]_0 / [\text{Tr-Aml}]_0 = 1.0, 1.1, 1.25, 1.5, 2.0$ , and

3.0 was monitored by recording <sup>1</sup>H spectra at 30 min. intervals over 24 h. At  $[\text{BSA}]_0 / [\text{Tr-Aml}]_0 = 1.0$ , the decreasing intensity of the CH<sub>3</sub> signal of the C3-CO<sub>2</sub>CH<sub>2</sub>CH<sub>3</sub> group at  $\delta = 1.05 \text{ ppm}$  for **Tr-Aml**, or the increase in its signal at  $\delta = 1.15 \text{ ppm}$  in **Aml**, allowed measurement of the rate constant for detritylation. Under these conditions (no excess acid), signals of the C6-

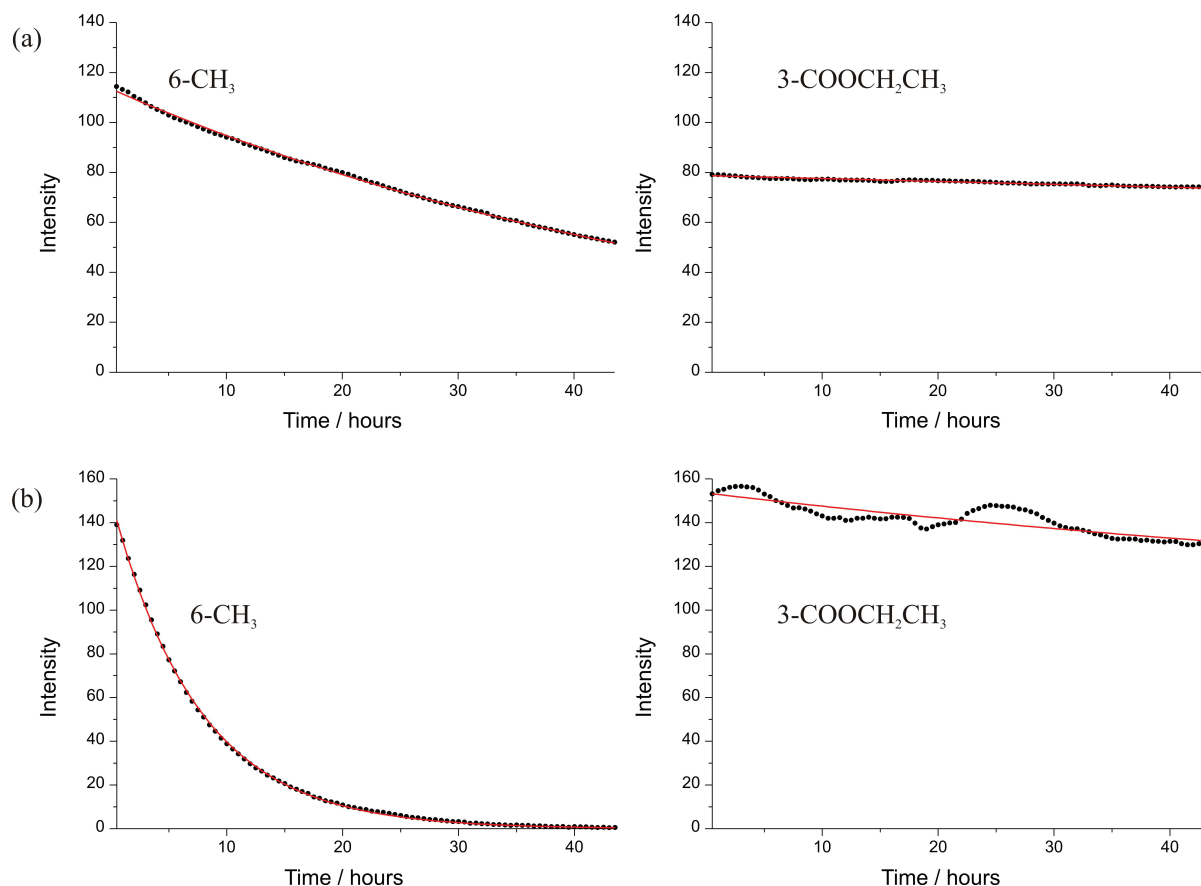
**Table 2.** HPLC kinetics results for detritylation of **Tr-Aml** in methanol : CHCl<sub>3</sub> (vol. ratio 9:1), 59 °C

$[\text{BSA}]_0 / [\text{Tr-Aml}]_0$	$[\text{Tr-Aml}]_0 / \text{mol dm}^{-3}$	$k_{\text{exp}} / \text{s}^{-1}$
0.95	0.025	$3.7 \times 10^{-4}$
1.0	0.025	$3.8 \times 10^{-4}$
1.05	0.025	$4.2 \times 10^{-4}$
1.5	0.025	$4.0 \times 10^{-4}$
0.95	0.05	$3.8 \times 10^{-4}$
1.0	0.05	$3.8 \times 10^{-4}$
1.05	0.05	$3.8 \times 10^{-4}$
0.95	0.075	$2.8 \times 10^{-4}$
1.0	0.075	$3.3 \times 10^{-4}$
1.05	0.075	$3.3 \times 10^{-4}$
0.95	0.10	$2.3 \times 10^{-4}$
1.0	0.10	$2.7 \times 10^{-4}$
1.05	0.10	$2.8 \times 10^{-4}$
1.0	0.025	$1 \times 10^{-5}$ , (a),(b)
1.0	0.025	$4.0 \times 10^{-5}$ , (c)
1.0	0.025	$2 \times 10^{-3}$ , (b),(d)
1.0	0.025	$5 \times 10^{-3}$ , (b),(e)
1.0	0.025	$3 \times 10^{-2}$ , (b),(f)
1.0	0.025	$> 0.1$ (b),(g)

<sup>(a)</sup> 35 °C, <sup>(b)</sup> approximate value based upon estimated half-life,

<sup>(c)</sup> 45 °C, <sup>(d)</sup> **MMTr-Aml** at 35 °C, <sup>(e)</sup> **MMTr-Aml** at 45 °C,

<sup>(f)</sup> **DMTr-Aml** at 35 °C, <sup>(g)</sup> approximate lower limit for **DMTr-Aml** at 45 °C.



**Figure 2.** Decreasing intensities (dots) and fitted curves (lines) of the  $^1\text{H}$  NMR signals due to the C6- $\text{CH}_3$  (left) and the methyl of C3- $\text{CO}_2\text{CH}_2\text{CH}_3$  (right) of **Tr-Aml** in methanol- $^2\text{H}_4$  at  $[\text{BSA}]_0/[\text{Tr-Aml}]_0 = 1.5$  (a), upper and 3.0 (b), lower, 25 °C.

$\text{CH}_3$  in **Tr-Aml** and **Aml** showed that the C6-methyl exchange processes are not significant (Figure 3) so changes in their intensities also correspond to the transformation of **Tr-Aml** into **Aml**. However, as soon as the **BSA** was in excess, the exchange process for **Aml** became evident (Figure 4); then, at larger excesses, the C6- $\text{CH}_3$  in **Tr-Aml** also showed exchange (Figure 5). Rate constants derived from these NMR results are also

collected in Table 3.

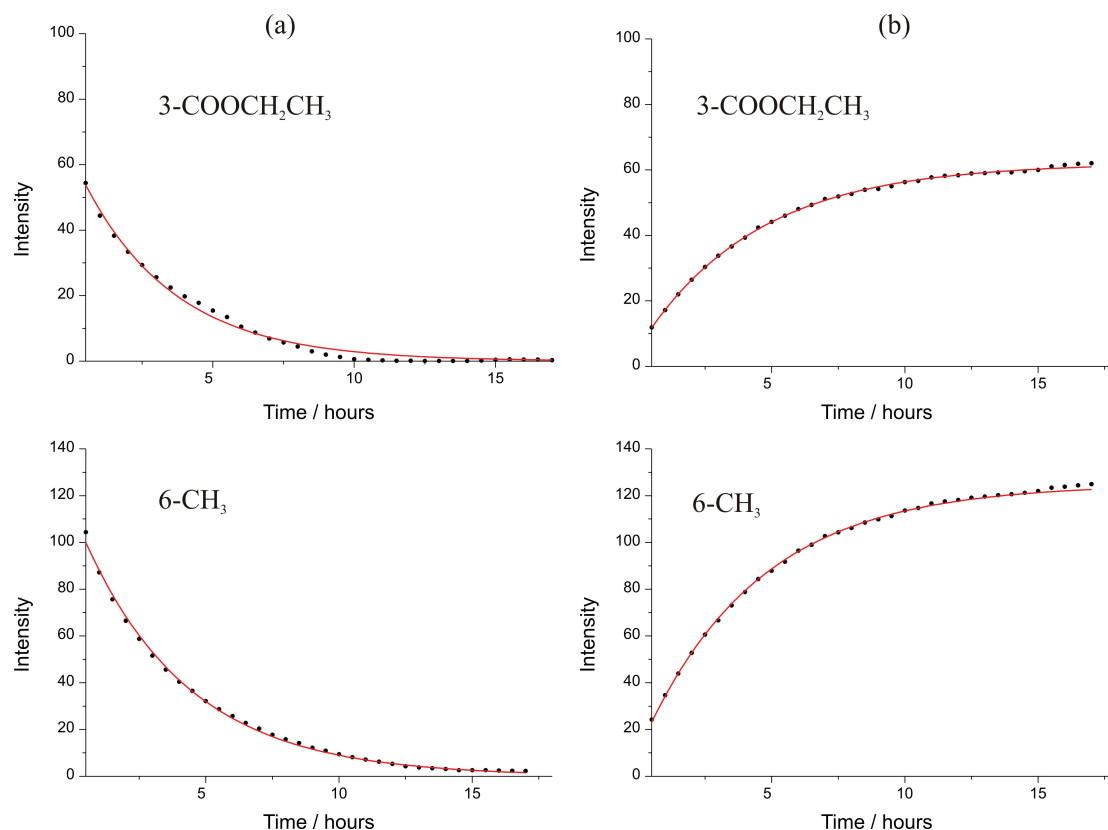
#### Further Investigation of Protonation Sites in **Tr-Aml** by $^{13}\text{C}$ NMR Relaxation Time Measurements

A series of  $^{13}\text{C}$   $T_1$  measurements on **Tr-Aml** in solution at mole ratios  $[\text{BSA}]_0/[\text{Tr-Aml}]_0 = 1.1, 1.5,$  and  $2.0$  were made. The values of the longitudinal relaxation times of  $^{13}\text{C}$  nuclei are presented in Table 4 (the esti-

**Table 3.** Rate constants for C6- $\text{CH}_3$  protium/deuterium exchange in *N*-tritylamlopidine and amlodipine, and for detritylation of *N*-tritylamlopidine with benzenesulfonic acid in methanol- $^2\text{H}_4$  at 50 °C <sup>(a)</sup>

$[\text{BSA}]_0/[\text{Tr-Aml}]_0$	$10^5 k_{\text{detril}}/\text{s}^{-1}$	$10^5 k_{\text{exch}}/\text{s}^{-1}$ in <b>Tr-Aml</b>	$10^5 k_{\text{exch}}/\text{s}^{-1}$ in <b>Aml</b>
1.5 <sup>(b)</sup>	-	0.5 <sup>(b)</sup>	-
3.0 <sup>(b)</sup>	-	3.7 <sup>(b)</sup>	-
1.0	6.3 (0.2)	Not observed	Not observed
1.1	6.3 (2.1)	Not observed	1.6 (2.1)
1.25	6.8 (1.1)	Not observed	1.4 (2.1)
1.5	8.7 (0.8)	Not observed <sup>(c)</sup>	2.8 (0.2)
2.0	8.3 (2.3)	7.1 (2.3)	10.2 (0.1)
3.0	8.7 (4.3)	8.5 (5.8)	9.8 (0.4)

<sup>(a)</sup>  $\chi^2$  values for curve fitting are shown in parentheses;  $[\text{Tr-Aml}]_0 = 0.051 \text{ mol dm}^{-3}$  in  $k_{\text{exch}}$  measurements and  $0.26 \text{ mol dm}^{-3}$  for  $k_{\text{detril}}$  measurements; <sup>(b)</sup> 25 °C, 25 mg of **Tr-Aml** in 0.75 ml of methanol- $\text{d}_4$ ; the values for detritylation were estimated to be more than 10 times smaller under these conditions; <sup>(c)</sup> The errors were too large to allow reliable extraction of  $k_{\text{exch}}$  for C6- $\text{CH}_3$  in **Tr-Aml** under these conditions.



**Figure 3.** Changing intensities (dots) and fitted curves (lines) of the  $^1\text{H}$  NMR signals due to the C6- $\text{CH}_3$  (lower) and the methyl of C3- $\text{CO}_2\text{CH}_2\text{CH}_3$  (upper) of **Tr-Aml** ((a), left) and **Aml** ((b), right) in methanol- $^2\text{H}_4$  at  $50^\circ\text{C}$  with  $[\text{BSA}]_0 = [\text{Tr-Aml}]_0$ .

mated accuracy of quoted  $T_1$  values is 10 %.) Increasing concentrations of **BSA** are seen to affect the relaxation times of  $^{13}\text{C}$  nuclei in several parts of the molecule.

#### $^{15}\text{N}$ NMR Measurements on **Aml** and **Aml-Bz**

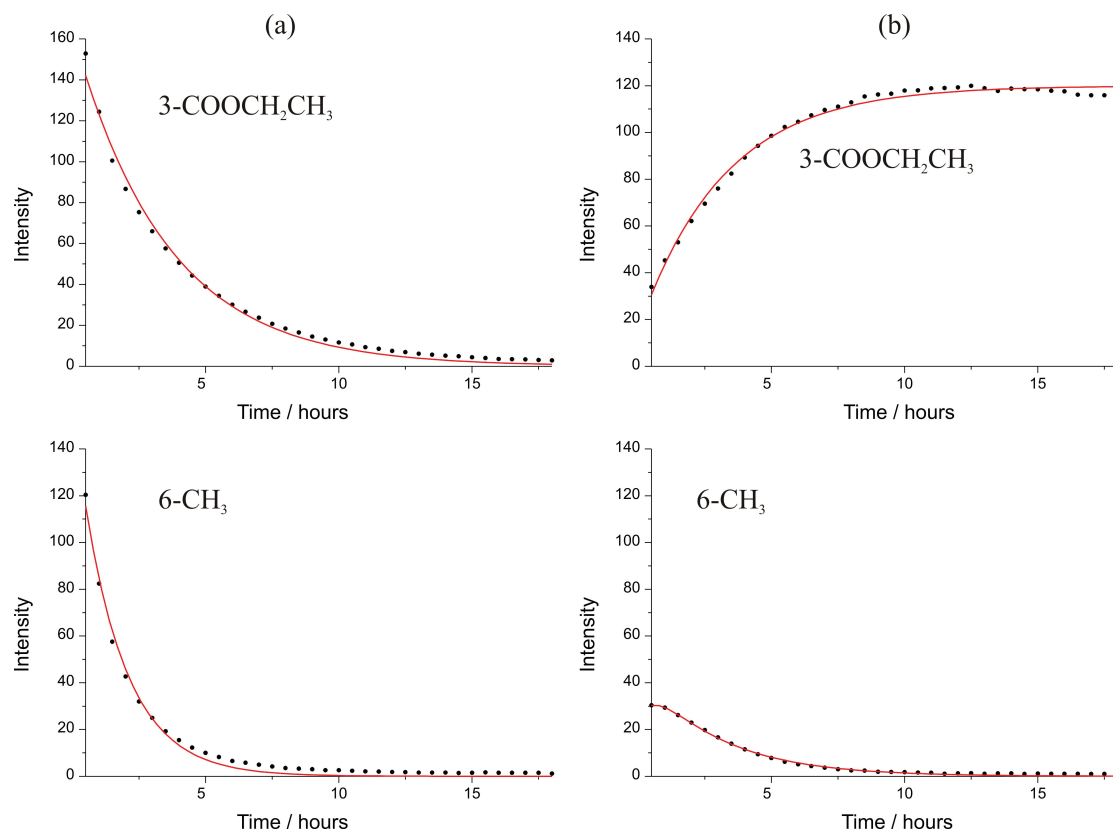
The  $^{15}\text{N}$  NMR spectrum of **Aml** in methanol- $\text{d}_4$  was re-

corded in the absence then in the presence of increasing proportions of **BSA**; chemical shifts are shown in Table 5. The two non-equivalent nitrogens of the free base were identified and the signal of the more basic one in the side chain at  $\delta^{15}\text{N} = 14.1$  ppm moves to greater values as **BSA** is added. The value corresponding to its

**Table 4.** Selected longitudinal relaxation times  $T_1$  and chemical shifts of  $^{13}\text{C}$  nuclei of **Tr-Aml** at  $25^\circ\text{C}$  <sup>(a)</sup>

Entry		$[\text{BSA}]_0 : [\text{Tr-Aml}]_0 =$			
		1:1.1	1:1.1	1:1.5	1:2.0
		$\delta / \text{ppm}^{(b)}$	$T_1$ relaxation time / s		
1	C2	146.39	3.0	2.3	1.8
2	C3	105.30	2.9	3.1	3.0
3	C4	38.56	0.73	0.61	0.74
4	C5	104.58	3.1	2.9	2.9
5	C6	146.68	2.2	2.6	2.9
6	2- $\text{CH}_2\text{O}$ -	69.55	0.42	0.38	0.38
7	-O- $\text{CH}_2$ - $\text{CH}_2$ -	67.24	0.40	0.32	0.30
8	-O- $\text{CH}_2$ - $\text{C}\text{H}_2$ -	47.95	0.46	0.34	0.28
9	3-CO	169.47	4.1	5.3	4.7
10	3- $\text{CO}_2\text{CH}_2\text{CH}_3$	61.59	1.5	1.4	1.1
11	3- $\text{CO}_2\text{CH}_2\text{CH}_3$	18.77	3.7	1.5	2.0
12	5-CO	169.78	4.0	4.1	4.2
13	5- $\text{CO}_2\text{CH}_3$	51.43	1.6	1.8	2.0
14	trityl- $\text{C}$	77.25	14.5	18.2	15.9
15	trityl- $\text{Ph}$	140.31	2.4	2.5	2.5
16	trityl- $\text{Ph}$	130.18	0.77	0.75	0.73
17	trityl- $\text{Ph}$	130.14	0.80	0.81	0.74

<sup>(a)</sup>  $[\text{Tr-Aml}]_0 = 0.063 \text{ mol dm}^{-3}$ ; see Figure 1 for atom numbering; <sup>(b)</sup> The chemical shifts (which refer to the residual signal of methanol- $\text{d}_4$  at 49.15 ppm) are for the 1:1.1 mole ratio but are not significantly different for other ratios.



**Figure 4.** Changing intensities (dots) and fitted curves (lines) of the  $^{15}\text{N}$  NMR signals due to the C6- $\text{CH}_3$  (lower) and the methyl of C3- $\text{CO}_2\text{CH}_2\text{CH}_3$  (upper) of **Tr-Aml** ((a), left) and **Aml** ((b), right) in methanol- $^2\text{H}_4$  at 50 °C with  $[\text{BSA}]_0/[\text{Tr-Aml}]_0 = 1.25$ .

complete protonation ( $\delta^{15}\text{N} = 24.8$  ppm) does not appreciably change further upon addition of further amounts of acid, and no signal at  $\delta = 14.1$  for the side-chain N of the free base **Aml** was detected in the spectrum of **Aml-Bz**. For comparison, the spectrum of a non-deuteriated sample was recorded,  $\delta^{15}\text{N} = 121.6$  (N1), which allowed the isotope effect on the chemical-shift (0.5–0.6 ppm, *ca.* 27 Hz at 500 MHz) and the one-bond H–N coupling constant ( $^1J_{\text{H,N}} = 97$  Hz) to be measured.

## DISCUSSION

### *Product Analysis and Kinetics by HPLC*

The deprotection of **Tr-Aml** with equal amounts or slight excesses of **BSA** in methanol (or ethanol) gives high isolated yields of pure **Aml-Bz** and essentially quantitative yields of **MeOTr** (or **EtOTr**); the concomitant *trans*-esterification we identified accounts to some degree for the less than quantitative yields of **Aml-Bz**. On the basis of the product analyses, our working hypothesis was that the mechanism of the acid-induced deprotection of **Tr-Aml** in methanol or ethanol, with or without small concentrations of cosolvents, is essentially the same as that of the deamination of *p*-methoxy-

substituted tritylamines and their *N*-alkyl analogues in aqueous acidic solution.<sup>7–10</sup>

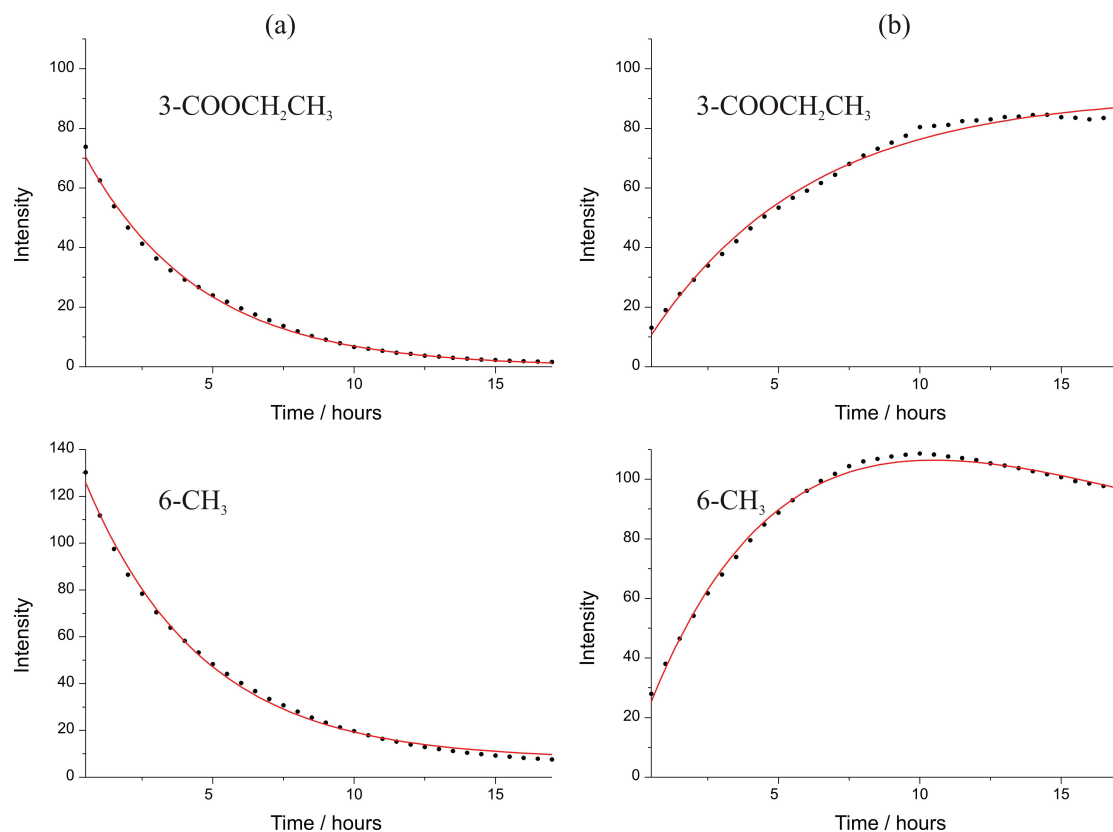
In trying to approximate the conditions of the industrial process, we did not investigate the detritylation over a wide range of  $[\text{BSA}]_0/[\text{Tr-Aml}]_0$ . Consequently, although the results in methanol (Table 1) show increased reactivity at higher ratios of  $[\text{BSA}]_0/[\text{Tr-Aml}]_0$ , our present results do not allow determination of separate rate constants for catalysed and uncatalysed reaction channels. However, we know from the more detailed results for 4,4'-dimethoxytritylamine (**DMTr-NH<sub>2</sub>**) and 4,4',4''-trimethoxytritylamine (**TMTrNH<sub>2</sub>**) that activation parameters are similar for uncatalysed ( $\Delta H^\ddagger = 97\text{--}105$  kJ mol<sup>-1</sup> and  $\Delta S^\ddagger = +15\text{--}21$  J K<sup>-1</sup> mol<sup>-1</sup>) and catalysed ( $\Delta H^\ddagger = 100\text{--}126$  kJ mol<sup>-1</sup> and  $\Delta S^\ddagger =$

**Table 5.**  $^{15}\text{N}$  chemical shifts,  $\delta$  / ppm<sup>(a)</sup> of **Aml** with **BSA** in methanol- $\text{d}_4$

Sample <sup>(b)</sup> ( <i>r</i> )	N1	Side chain N
<b>Aml</b>	121.1	14.1
<b>Aml + BSA (1:0.5)</b>	120.9	17.4
<b>Aml + BSA (1:1), <i>i.e.</i></b>	121.1	24.8
<b>Aml-Bz</b>		
<b>Aml + BSA (1:1.5)</b>	121.0	24.6

<sup>(a)</sup>  $^{15}\text{N}$  chemical shift reference is liquid  $\text{NH}_3$  ( $\delta = 0.0$  ppm);

<sup>(b)</sup> 30 mg of **Aml** in 0.50 ml methanol- $\text{d}_4$ .



**Figure 5.** Changing intensities (dots) and fitted curves (lines) of the  $^1\text{H}$  NMR signals due to the C6- $\text{CH}_3$  (lower) and the methyl of C3- $\text{CO}_2\text{CH}_2\text{CH}_3$  (upper) of **Tr-Aml** ((a), left) and **Aml** ((b), right) in methanol- $^2\text{H}_4$  at  $50^\circ\text{C}$  with  $[\text{BSA}]_0/[\text{Tr-Aml}]_0 = 3.0$ .

+19–85  $\text{J K}^{-1} \text{mol}^{-1}$ ) reaction channels of both compounds.<sup>8</sup> Consequently, we may legitimately compare numerical values of the empirical Arrhenius activation parameters ( $E_a$  and  $A$ ) derived from the composite rate constants,  $k_{\text{exp}}$ , of **Tr-Aml** at any arbitrary concentrations of **BSA** with values for catalysed and uncatalysed reactions of **DMTrNH<sub>2</sub>** and **TMTrNH<sub>2</sub>**. Results shown in Table 1 allow calculation of  $E_a = 130 \text{ kJ mol}^{-1}$  and  $A = 8 \times 10^{16} \text{ s}^{-1}$  ( $R > 0.999$ ) for the detritylation of **Tr-Aml** in methanol with  $[\text{BSA}]_0/[\text{Tr-Aml}]_0 = 1.1$ ; in spite of the excellent linearity of the plot of  $\ln(k_{\text{exp}}/\text{s}^{-1})$  against  $(\text{T/K})^{-1}$ , the reproducibility of individual rate constants and their modest precision lead to the conservative error limits shown below Table 1. The high value of  $E_a = 130 \text{ kJ mol}^{-1}$  compares with the arithmetic mean of values for catalysed and uncatalysed channels of **DMTrNH<sub>2</sub>** ( $120 \text{ kJ mol}^{-1}$ ) and the high value of  $A = 8 \times 10^{16} \text{ s}^{-1}$  compares with the geometric mean for catalysed and uncatalysed channels of **DMTrNH<sub>2</sub>** ( $1 \times 10^{16} \text{ s}^{-1}$ ),<sup>10</sup> as expected for reactions with closely similar mechanisms. These results are as anticipated for fragmentation of a cation with localised charge to give a transition structure in which the charge is dispersed. Dissociation of the tightly solvated tritylammonium cation with attendant shedding of solvent molecules

corresponds to an increase in entropy ( $A > 10^{13} \text{ s}^{-1}$ ) and a high enthalpy of activation.

Using the Arrhenius equation, we have estimated rate constants for detritylation of **Tr-Aml** at other temperatures as shown below Table 1. Comparison of the calculated result at  $59^\circ\text{C}$  in MeOH ( $2.7 \times 10^{-4} \text{ s}^{-1}$ ) with the experimental result in methanol- $\text{CHCl}_3$  (vol. ratio, 9:1) at  $59^\circ\text{C}$  ( $2.8 \times 10^{-4} \text{ s}^{-1}$ ) from Table 2 for  $[\text{Tr-Aml}]_0 = 0.1 \text{ mol dm}^{-3}$  and  $[\text{BSA}]_0/[\text{Tr-Aml}]_0 = 1.05$  indicates that the effect of a modest proportion of chloroform cosolvent is negligible. The same insensitivity to the effect of cosolvents was observed for cleavage of *p*-methoxy substituted *N*-tritylamines in water,<sup>10</sup> and attributed to lack of a change in charge in the transformation of reactant into transition structure.

Results in MeOH- $\text{CHCl}_3$  (vol. ratio, 9:1) at  $45^\circ\text{C}$  (Table 2) show that introduction of one *p*-methoxy-substituent into the trityl residue increases the rate constant for detritylation by a factor of 125; a second *p*-methoxy-substituent causes a smaller further rate enhancement (x 20) in line with the rate factors between **DMTrNH<sub>2</sub>** and **TMTrNH<sub>2</sub>** reported previously (x 11 and x 14 for uncatalysed and catalysed deamination channels in water at  $25^\circ\text{C}$ ).<sup>10</sup>



### NMR Experiments

The  $^1\text{H}$  NMR measurements allowed determination of rate constants for detritylation (Table 3). The result  $k_{\text{detr}} = 6.3 \times 10^{-5} \text{ s}^{-1}$  at 50 °C in methanol- $\text{d}_4$  with  $[\text{BSA}]/[\text{Tr-Aml}]_0 = 1.1$  is in excellent agreement with the value  $k_{\text{exp}} = 7.4 \times 10^{-5} \text{ s}^{-1}$  obtained by interpolation from our HPLC detritylation results at 45, 55, and 63 °C using the Arrhenius equation (see above). The NMR experiments also clearly show that the C6- $\text{CH}_3$  in both **Tr-Aml** and **Aml** undergoes acid-catalysed protium/deuterium exchange in methanol- $\text{d}_4$  at rates comparable with that of detritylation of **Tr-Aml**. This process has been attributed to formation of the iminium ion from the 1,4-dihydropyridine part of the amlodipine residue,<sup>6</sup> Scheme 2, and is appreciably faster in **Aml** than in **Tr-Aml**.

The most pronounced effects on longitudinal relaxation rates of nuclei with spin of one-half arise from the magnetic dipole relaxation interactions with other nuclei or with unpaired electrons. At the extreme narrowing condition, which is fulfilled for small molecules in media of low viscosity, the relaxation time becomes independent of frequency and the intramolecular dipole-dipole relaxation rate depends upon the inverse sixth power of the internuclear distance and the squares of the gyromagnetic ratios of the interacting nuclei.<sup>13</sup> We expect changes in longitudinal relaxation time ( $T_1$ ) of  $^{13}\text{C}$  nuclei when protonation/deuteration or protium/deuterium exchange of the compound occurs because, in the first case, the number and, in the second, the gyromagnetic ratios of interacting nuclei are changed.

The increasing values of  $T_1$  with increasing excesses of **BSA** for the C6 nucleus of **Tr-Aml** (Table 4, entry 5) can be attributed to the protium/deuterium exchange of 6- $\text{CH}_3$  group (the relaxation rate of the C6 nucleus decreases due to the significantly smaller gyromagnetic ratio of  $^2\text{H}$  compared with  $^1\text{H}$ ) which is caused by hydronium ion addition at C5 as shown in Scheme 2. At this stage, we cannot explain the decreasing relaxation times for the C2 and O- $\text{CH}_2$ - $\text{CH}_2$ - nuclei with increasing excesses of **BSA** (entries 1 and 8).

The  $^{15}\text{N}$  NMR measurements on **Aml** and **Aml-Bz** shown in Table 5 are essentially further aspects of product characterisation but also confirm the absence of **Aml** as the free base in methanol when the ratio  $[\text{BSA}]/[\text{Aml}]$  is unity or greater.

### CONCLUSION

Detailed product analyses by HPLC of the detritylation of *N*-tritylamlopidine under conditions designed to approximate an industrial method of production of amlodipine benzenesulfonate, and the similarities between

Arrhenius parameters of this reaction and those of cleavage of the substituted trityl group from *N*-tritylalkylamines in aqueous solution, indicate closely similar mechanisms. Both series involve acid catalysed cleavage of the Tr-N bond and the intermediacy of (substituted) trityl carbenium ions which suffer nucleophilic capture by the solvent. In the cleavage reaction of the tritylammonium cation to give the trityl carbenium, there is a redistribution of positive charge in the formation of the transition structure but no change of charge type hence no appreciable kinetic solvent effect is expected or found in the industrial process or the solvolytic reactions. The HPLC product analyses also established that a small extent of acid-catalysed methyl/ethyl exchange in the ethyl ester residue accompanies detritylation in methanol. The NMR experiments corroborate the HPLC kinetics results and additionally provide details of the acid-catalysed protium/deuterium exchange at C6- $\text{CH}_3$  of the 4-aryl-1,4-dihydropyridine moiety through reversible formation of an iminium ion in both **Tr-Aml** and **Aml** which accompanies (but does not interfere with) the detritylation.

### EXPERIMENTAL

#### Formation of *N*-tritylamlopidine and Conversion into Amlodipine Benzenesulfonate and Methyl Trityl Ether

Ethyl 4-(2'-(*N*-tritylamino)ethoxy)acetoacetate (79.5 kg, 92 % pure, 170 mol) was heated with equal amounts of methyl (*E*)-3-aminobut-2-enoate and 2-chlorobenzaldehyde in methanol under reflux for 15 hours. **BSA** (technical grade, 10 % excess over the other reactants) was added and the reaction mixture was allowed to cool. The precipitated methyl trityl ether was filtered off and dried (46.5 kg, 169 mol, 100 %; m.p. 91 °C, lit.<sup>14</sup> (a) 79–80 °C, (b) 81–83 °C;  $\delta^1\text{H}$  (300 MHz,  $\text{CDCl}_3$ , 22 °C) 3.1 (3H, s,  $\text{CH}_3$ ), 7.3–7.6 (15H, m,  $\text{CPh}_3$ ); *m/e* 274 ( $\text{M}^+$ ). Amlodipine benzenesulfonate (m.p. 197–203; lit.<sup>2</sup> 201.0 °C, lit.<sup>15</sup> 201–205 °C) was isolated from the filtrate in high yield and purified by two recrystallisations from methanol ( $\delta^1\text{H}$  (300 MHz,  $\text{CD}_3\text{OD}$ , 22 °C): 1.16 (3H, t,  $J = 7.1$  Hz), 2.32 (3H, s), 3.23 (2H, m), 3.58 (3H, s), 3.77 (2H, m), 4.04 (2H, m), 4.65 (1H, d,  $J = 14.3$  Hz), 4.77 (1H, d,  $J = 14.3$  Hz), 5.41 (1H, s), 7.08 (1H, td,  $J = 7.6$  Hz, 1.7 Hz), 7.16 (1H, td,  $J = 7.6$ , 1.3), 7.24 (1H, dd,  $J = 7.9$ , 1.3), 7.37–7.47 (4H, m), 7.81–7.86 (2H, m)).

#### NMR Experiments

$^{15}\text{N}$  NMR spectra were recorded on Bruker Avance DRX-500 and DPX-300 spectrometers using gradient-enhanced HMBC techniques.<sup>16</sup> The 2D spectra were acquired as data matrices (4096 x 600) with 8–32 transients accumulated per  $t_1$  increment with final digital

resolution better than 0.4 ppm in the  $^{15}\text{N}$  dimension.<sup>17</sup> Liquid nitromethane was used as a secondary external standard for the measurement in a coaxial system and its shift has been referenced to the  $^{15}\text{N}$  chemical shift of liquid  $\text{NH}_3$  ( $\delta = 0.0$  ppm).

Deuterium-protium exchange in the C6-Me was investigated using samples of **Tr-Aml** (25 mg) and **BSA** in the ratios 1:1.5 and 1:3.0 in methanol- $\text{d}_4$  (0.75 ml). After solutions had been prepared and left 4 h at 25 °C,  $^1\text{H}$  spectra were recorded at 30 min intervals at 25 °C on a Varian UNITY+ 300MHz spectrometer.

Detritylation of **Tr-Aml** was observed using the same instrument by recording  $^1\text{H}$  spectra of 1:1, 1:1.25, 1:1.5, 1:2, and 1:3 mole ratios of **Tr-Aml** (10 mg) and **BSA** in methanol- $\text{d}_4$  (0.6 ml) at 50 °C after solutions had been first prepared and left at room temperature for 24 h.

Longitudinal relaxation times ( $T_1$ ) of  $^{13}\text{C}$  nuclei were measured on a Varian INOVA 600 MHz spectrometer at 25 °C. Samples of **Tr-Aml** (28.6 mg) were dissolved in methanol- $\text{d}_4$  (0.7 ml) containing 1.1, 1.5, and 2.0 mole equivalents of **BSA**. The  $^{13}\text{C}$  chemical shifts were assigned by observation of one-bond  $^{13}\text{C}$ - $^1\text{H}$  correlations in HSQC spectra and long-range  $^{13}\text{C}$ - $^1\text{H}$  correlations in HMBC spectra. The  $T_1$  relaxation times were measured by the Non-selective Inversion-Recovery  $T_1$  method. Three different arrays of variable delay were used to optimize the measurement of short, medium, and long relaxation times. The variable delays (expressed in seconds) were: (0.0125, 0.05, 0.1, 0.3, 0.6, 1.2), (0.0125, 0.05, 0.2, 0.8, 3.2, 12.8), and (0.8, 3.2, 6.4, 12.8, 25.6) for short, medium, and long relaxation times, respectively.

#### Kinetics Experiments by HPLC

All kinetics experiments by this method were carried out in a 50 ml glass flat-bottomed three-necked thermostatted batch reactor fitted with a condenser, magnetic stirrer (600 rpm), thermometer, and Hamilton digital syringe (to allow samples for analysis to be withdrawn). The whole was wrapped in aluminium foil to prevent photochemically-induced reactions and dry nitrogen was passed through the reaction solution to prevent oxidation. The temperature of a reaction was maintained constant ( $\pm 0.02$  °C) by a Lauda ultra-thermostat.

#### HPLC Analysis

A Hewlett-Packard 1100 series liquid chromatograph fitted with a diode array detector (220 nm) was used with a SymmetryShield RP 18 column (150 x 4.6 mm, particle size 5  $\mu\text{m}$ , thermostatted at 30 °C) and a 78:22 acetonitrile-aqueous phosphate buffer (20 mmol  $\text{dm}^{-3}$ ,  $\text{pH} = 6.75$ ) mobile phase (1.0 ml  $\text{min}^{-1}$ ). The sample loop was 20  $\mu\text{L}$  and samples were diluted 400 times in the mobile phase for analysis. Calibration curves were

constructed from standard solutions of authentic samples in the mobile phase in the range 0.005–0.32 mg  $\text{ml}^{-1}$ ; only that for **Tr-Aml** was linear.

#### Description of a Typical Kinetic Experiment in MeOH:CHCl<sub>3</sub> (Vol. Ratio 90:10)

Standard solutions of **Tr-Aml** in  $\text{CHCl}_3$  (10.00 ml) and **BSA** in MeOH (30.00 ml) were prepared such that, upon mixing, a final solution of the required composition would be obtained; they were equilibrated at the required reaction temperature. The **BSA** solution was added to the thermostatted reactor, stirring was started, then immediately the **Tr-Aml** solution was quickly added; the moment of addition of the **Tr-Aml** was taken as time = 0. Samples of the reaction were withdrawn on a logarithmic timescale over at least 4 half-lives and diluted into the HPLC mobile phase in 2 ml HPLC vials according to the initial composition of the reaction mixture. All samples from a single kinetic run were analysed together (auto-sampler) by HPLC after a calibration check. Analysis results for reactants and products were first presented as amount concentration-time data then transformed into logarithmic first-order plots. In this manner, kinetics for **Tr-Aml** were measured at temperatures in the range 45–63 °C, and for its monomethoxy derivative at 45 °C; the reaction of the dimethoxy analogue was too fast even at this temperature to allow reliable measurement of the rate constant but an estimate of the half-life ( $< 0.1$  min) indicates a value  $> 7$   $\text{min}^{-1}$ . Rate constants for **Tr-Aml**, **MMTr-Aml**, and **DMTr-Aml** were also estimated at 35 °C from half-lives.

#### REFERENCES

1. The Merck Index, 14th edition, 2006, Monograph number: 00491.
2. Pfizer process: EP 0 244 944 B1, 1987.
3. LEK process: (a) MeOH as solvent, EP 0 599 220 B1, 1993; (b) EtOH as solvent, US patent 7,153,970 B2, 2006.
4. J. Crugeiras and H. Maskill, *Can. J. Chem.* **77** (1999) 530–536; J. Crugeiras and H. Maskill, *J. Chem. Soc., Perkin Trans. 2* (2000) 441–445.
5. M. Canle, L. I. Demirtas, H. Maskill, and M. Mishima, *J. Phys. Org. Chem.* (2008), in press.
6. D. Kocjan, *Acta Chim. Slov.* **45** (1998) 355–361; D. Kocjan and J. Žmitek, *8th Blue Danube Symposium on Heterocyclic Chemistry*, Bled, 2000, Book of Abstracts, p. 94.
7. C. Bleasdale, B. T. Golding, W. H. Lee, H. Maskill, J. Riseborough, and E. Smits, *J. Chem. Soc., Chem. Commun.* (1994) 93–94.
8. M. C. Lopez, J. C. Martinez, I. Demirtas, H. Maskill, and E. Stix, *Org. React.* **31** (1997) 71–77.
9. J. Crugeiras and H. Maskill, *J. Chem. Soc., Perkin Trans. 2* (1998) 1901–1907.
10. M. Canle L., I. Demirtas, and H. Maskill, *J. Chem. Soc., Perkin Trans. 2* (2001) 1748–1752.
11. T. W. Bentley, *Investigation of reaction mechanisms by product*

- studies in: H. Maskill (Ed.), *The investigation of organic reactions and their mechanisms*, Blackwell, Oxford, 2006, Chapter 2, pp. 18–45.
12. H. Maskill, *The Physical Basis of Organic Chemistry*, Oxford University Press, Oxford, 1985.
13. A. Carrington and A. D. McLachlan, *Introduction To Magnetic Resonance*, Chapman and Hall, London, 1967; A. E. Derome, *Modern NMR Techniques for Chemistry Research*, Pergamon Press, Oxford, 1987.
14. (a) D. J. Chadwick, *J. Chem. Soc., Perkin Trans. 1*, (1983) 93–102; (b) M. B. Gazizov, *Russ. J. Gen. Chem.* **75** (2005) 1325–1326.
15. Patent, WO 2003043635 A1, 2003.
16. G. E. Martin and C. E. Hadden, *J. Nat. Prod.* **63** (2000) 543–585.
17. R. Marek, O. Humpa, J. Dostal, J. Slavik, and V. Sklenar, *Magn. Reson. Chem.* **37** (1999) 195–202.

---

## SAŽETAK

### Amlodipin benzenesulfonat: mehanistički studij njegove industrijske pripreve detritilacijom *N*-tritolamlopidina i NMR studije

Borut Furlan,<sup>a</sup> Simona Golič Grdadolnik,<sup>b</sup> Stanko Hočevar,<sup>b</sup> Darko Kocjan,<sup>a</sup> Janez Levec,<sup>b</sup> Howard Maskill,<sup>c</sup> Hana Navrátilová,<sup>d</sup> Jiří Pospíšil,<sup>d</sup> Milan Potáček,<sup>d</sup> Uroš Urleb<sup>a</sup> i Janko Žmitek

<sup>a</sup>*Lek Pharmaceuticals d.d., Verovškova 57, SI-1526 Ljubljana, Slovenia*

<sup>b</sup>*National Institute of Chemistry, Hajdrihova 19, SI-1000 Ljubljana, Slovenia*

<sup>c</sup>*Department of Chemical and Biological Sciences, School of Applied Sciences, University of Huddersfield, Queensgate, Huddersfield, UK*

<sup>d</sup>*Department of Organic Chemistry, Masaryk University of Brno, Kotlářská 2, CZ-61137 Brno, The Czech Republic*

Kinetika i analiza produkata detritilacije *N*-tritolamlopidina s benzensulfonskom kiselinom u metanolu, metanol:kloroformu (volumni omjer 1:1), etanolu, 2-propanolu, i metanol:2-propanolu (molni omjer 1:1) proučavane su pomoću HPLC metode. Među ovim reakcijama su one koje su slične metodi proizvodnje amlodipin benzenesulfonata. Kinetika detritilacije *N*-tritolamlopidina također je proučavana u metanolu- $d_4$  pomoću  $^1\text{H}$  NMR spektroskopije i u dobrom je skladu s HPLC rezultatima. Brzina detritilacije povećava se s povećanjem koncentracije benzensulfonske kiseline, dok *p*-metoksi-supstituenti na tritolnoj skupini vode do brže reakcije. U metanolu je brzina djelomično pod utjecajem 10 % (vol. udjel) kloroforma. Ove studije povezane su s mehanističkim proučavanjima kiselinom-katalizirane deaminacije metoksi-supstituiranih tritolalkilamina, pa su Arrheniusovi aktivacijski parametri ( $E_a$  i  $A$ ) slični, što potkrepljuje postojanje istog mehanizma. Uz pomoć HPLC-a pokazano je da kiselinom-katalizirana *trans*-esterifikacija prati detritilaciju u metanolu, a prateća proton-deuterij izmjena na metilnoj skupini C6 atoma prilikom kiselinom-kataliziranog reverzibilnog stvaranja iminium iona u 4-aril-1,4-dihidropiridinskom dijelu *N*-tritolamlopidina i amlodipina je istraživana u deuteriranom metanolu pomoću  $^1\text{H}$ ,  $^{13}\text{C}$  i  $^{15}\text{N}$  NMR spektroskopije.