Crystal Structure, Thermal Behaviour, Protonation and Mass Spectroscopic Studies of Racemic 4-[1-(2,3-Dimethylphenyl)-ethyl]-1*H*-imidazole Hydrochlorides

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The crystal structure, thermal behaviour, mass spectrum and protonation of 4-[1-(2,3-dimethylphenyl)ethyl]-1*H*-imidazole (medetomidine) hydrochloride have been investigated. The title compound crystallizes in both hydrated and anhydrous forms, and their structures have been determined by three-dimensional *X*-ray structure analysis. The crystals of the anhydrous form are monoclinic and those of the hydrated form (containing one hydrate water molecule) are triclinic with unit-cell dimensions: $a = 23.861(9)$, $b = 7.721(4)$, $c = 22.037(9)$ Å, $\beta = 140.20(4)°$, $Z = 8$, and space group $C2/c$, and $a = 7.841(4)$, $b = 8.380(3)$, $c = 12.743(6)$ Å, $\alpha = 93.66(3)$, $\beta = 102.90(3)$, $\gamma = 116.85(3)°$, $Z = 2$, and space group $P\bar{1}$, respectively. Thermal decomposition of the title compound has been interpreted from the TG, DTG and DSC curves with the help of mass spectrometry. Medetomidine hydrochloride monohydrate decomposes in four stages. The first is dehydration at 45–100 °C, the second is evaporation of HCl and medetomidine base at 200–320 °C, and the third and fourth are decomposition at 340–570 °C. The protonation constant is 7.04 in aqueous 0.1 M $NaClO_4$ (25 °C).

In an earlier paper we reported crystal structure, protonation and thermal behaviour of 4-(2,3-dimethylbenzyl)-1*H*-imidazole (detomidine) hydrochloride monohydrate, a new drug developed by the Farmos-Group, Ltd. (Domosedan®).[1] This study was undertaken to characterize various chemical properties of a new original drug compound, structurally similar to detomidine, *viz.* 4-[1-(2,3-dimethylphenyl)ethyl]-1*H*-imidazole (medetomidine) hydrochloride, developed also by the Farmos-Group.[2]

Medetomidine is one of the most potent and selective α_2-adrenoceptor agonists known today and at very low concentrations is able to activate α_2-adrenoceptors both in the central and peripheral nervous systems.[3] Thus, medetomidine is, for example, very effective as a sedative–analgesic agent and it has been developed to facilitate the treatment of dogs and cats in animal clinics (Domitor® by Farmos-Group Ltd.).[4]

Medetomidine has a chiral center in its structure and thus has two optical isomers. In the present study the racemic mixture of these isomers was investigated. The study on the pure *R* and *S* isomers is in progress.

Experimental

Preparation of the compound. Medetomidine hydrochloride was prepared according to a procedure described in the literature.[2]

Structure determination. Unit-cell parameters and intensity data for medetomidine hydrochloride,

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Table 1. Crystal data and experimental parameters.

Compound	$C_{13}H_{17}ClN_2$	$C_{13}H_{19}ClN_2O$
Space group	C_2/c	$P\bar{1}$
a/Å	23.861(9)	7.841(4)
b/Å	7.721(4)	8.380(3)
c/Å	22.037(9)	12.743(6)
α/°	90	93.66(3)
β/°	140.20(4)	102.90(3)
γ/°	90	116.85(3)
V/Å^3	2598.8	715.0
Z/Å^3	8	2
D_c/g cm^{-3}	1.21	1.18
D_m /g cm^{-3}	^{m}cm^{-3}	1.21
μ(MoK_α)/cm^{-1}	2.7	2.6
FW	236.8	254.8
F(000)	1008	272
Crystal size/mm	0.3×0.2×0.1	0.5×0.4×0.3
Data collection	ω-scan	ω-scan
Radiation	μ(MoK_α)	μ(MoK_α)
Scan range	$4° < 2\theta < 46°$	$4° < 2\theta < 48°$
Scan rate/° min^{-1}	2–30	2.5–30
Refl. meas.	1911	2241
Used in analysis	946 [$I>2\sigma(I)$]	1351 [$I>3\sigma(I)$]
R ($=\Sigma\|\|F_o\|-\|F_c\|\|/\Sigma\|F_o\|$	0.050	0.048
R_w ($=[\Sigma w(\|F_o\|-\|F_c\|)^2/\Sigma wF_o^2]^{1/2}$)	0.036	0.047

$C_{13}H_{17}ClN_2$, and its monohydrate, were obtained at room temperature using a Nicolet P3 diffractometer. A crystal of the hydrated form was kept in the mother liquor and measured in a glass capillary as it has tendency to decompose in air.

The data were corrected for Lorentz and polarization effects. The absorption was checked for both compounds using the empirical ψ-scan method but it was so insignificant that correction was excluded. The structures were solved by direct and Fourier methods using MULTANBO and XRAY76 program systems and refined by full-matrix least squares, minimizing the function $\Sigma w(|F_o| - |F_c|)^2$ with $w = 1/\sigma^2(F_o)$. After refinement of all non-hydrogen atoms with anisotropic temperature factors, H atoms were located on difference maps. In the final refinements, fixed isotropic temperature factors for H atoms and varying anisotropic temperature factors for the all other atoms were used. The H-atom positions of the anhydrous form were not refined. The largest peaks on final difference maps had densities of 0.24 and 0.28 e Å^{-3} for the anhydrous and hydrated compounds, respectively. An anomalous dispersion correction was applied to the Cl atoms. An isotropic extinction correction was also included. The scattering factors for neutral non-hydrogen atoms were from Cromer and Mann,[5] and the H scattering factors were those of Stewart, Davidson and Simpson.[6]

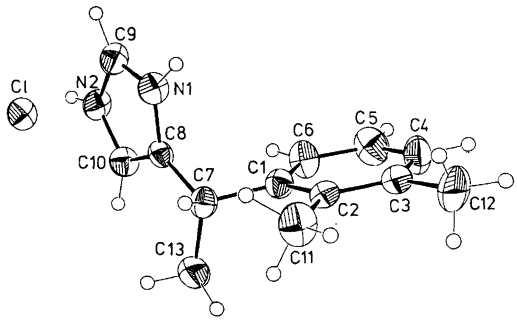


Fig. 1. ORTEP drawing of the anhydrous form $C_{13}H_{17}ClN_2$, together with the numbering system used.

Table 2. Fractional atomic coordinates ($\times 10^4$) with their e.s.d.'s in parentheses. Equivalent isotropic thermal parameters are calculated by $U_{eq} = \frac{1}{3} \Sigma_i \Sigma_j U_{ij} a_i^* a_j^* \boldsymbol{a}_i \cdot \boldsymbol{a}_j$.

Atom	*x*	*y*	*z*	U_{eq}
$C_{13}H_{17}ClN_2$				
Cl	1632(1)	1368(2)	−3764(1)	0.057
N1	4983(2)	2060(6)	−711(2)	0.047
N2	3612(2)	1645(6)	−1979(2)	0.048
C1	6304(3)	−353(7)	−301(3)	0.043
C2	7207(3)	−554(6)	529(3)	0.044
C3	7765(3)	−166(7)	507(4)	0.053
C4	7436(4)	404(8)	−299(5)	0.066
C5	6544(4)	601(8)	−1128(4)	0.067
C6	5979(3)	240(8)	−1120(3)	0.056
C7	5664(3)	−857(7)	−329(3)	0.045
C8	4889(3)	343(7)	−941(3)	0.036
C9	4197(3)	2868(8)	−1354(4)	0.052
C10	4021(3)	98(8)	−1739(3)	0.047
C11	7577(3)	−1199(9)	1430(3)	0.069
C12	8747(3)	−317(11)	1389(5)	0.088
C13	5354(3)	−2715(8)	−686(4)	0.065
$C_{13}H_{19}ClN_2O$				
Cl	8002(1)	6240(1)	−4812(1)	0.051
O1	9821(5)	4074(5)	−3432(3)	0.080
N1	6745(5)	763(5)	−3496(3)	0.060
N2	4884(7)	−2102(6)	−4056(3)	0.075
C1	5764(6)	2729(6)	−1706(4)	0.058
C2	6405(7)	4569(6)	−1316(4)	0.063
C3	7437(7)	5330(7)	−226(5)	0.073
C4	7802(8)	4269(10)	470(5)	0.084
C5	7236(9)	2493(10)	97(5)	0.084
C6	6181(7)	1694(7)	−992(5)	0.069
C7	4523(6)	1841(6)	−2892(4)	0.059
C8	4907(6)	375(5)	−3336(3)	0.056
C9	6663(9)	−758(7)	−3928(4)	0.071
C10	3734(8)	−1448(6)	−3695(4)	0.071
C11	5937(10)	5726(8)	−2065(5)	0.087
C12	8171(10)	7323(10)	218(6)	0.104
C13	2278(8)	1017(9)	−2987(5)	0.085

Mass spectrometry. The electron-ionization (EI) mass spectra were run on a Kratos MS80RFA mass spectrometer equipped with a DS-55 data system. For measuring low- and high-resolution mass spectra the medetomidine hydrochloride monohydrate samples were heated in a glass capillary in an ion source to the evaporation temperature (ca. 210 °C). Low-resolution experiments were performed at resolution 1000, and high-resolution experiments at resolution 7500. The temperature of the ionization chamber was 250 °C and the energy of the ionizing electrons was 70 eV. Perfluorokerosene was used as the reference compound. Metastable ions were measured by the linked scan and metastable mapping programs of Kratos.

The positive-ion chemical-ionization (CI) mass spectra of medetomidine hydrochloride monohydrate were measured with methane, isobutane or ammonia as reagent gases. The energy of the ionization electrons was 150 eV.

Thermal analysis. TG and DTG curves were recorded on a Mettler TA-3000 thermoanalyser. The

Table 3. Fractional hydrogen atom coordinates ($\times 10^3$).

Atom	*x*	*y*	*z*	*x*	*y*	*z*
$C_{13}H_{17}ClN_2$				$C_{13}H_{19}ClN_2O$		
H1	784	70	−32	849(8)	491(7)	121(4)
H2	628	103	−175	748(8)	177(7)	51(5)
H3	531	45	−171	561(7)	26(7)	−129(4)
H4	555	266	−14	791(7)	205(7)	−336(4)
H5	414	406	−119	774(8)	−79(7)	−412(4)
H6	296	185	−256	459(7)	−338(7)	−429(4)
H7	372	−108	−209	217(8)	−222(6)	−371(4)
H8	603	−81	42	492(7)	296(6)	−342(4)
H9	734	−49	167	655(7)	594(6)	−274(4)
H10	730	−240	129	452(8)	493(7)	−271(4)
H11	821	−137	204	599(7)	682(7)	−173(4)
H12	893	48	189	911(8)	815(6)	−21(4)
H13	889	−152	164	689(8)	745(6)	25(4)
H14	916	−10	144	884(8)	753(7)	100(4)
H15	492	−286	−140	190(8)	5(7)	−252(4)
H16	589	−354	−16	200(7)	209(6)	−273(4)
H17	495	−300	−69	152(7)	41(6)	−387(4)
H18				942(7)	497(7)	−672(4)
H19				1062(7)	386(6)	−389(4)

Table 4. Bond distances (Å) and angles (°) with e.s.d.'s in parentheses.

Bond	Length		Bond	Angle	
	$C_{13}H_{17}ClN_2$	$C_{13}H_{19}ClN_2O$		$C_{13}H_{17}ClN_2$	$C_{13}H_{19}ClN_2O$
C1–C2	1.399(6)	1.403(7)	C1–C2–C3	118.8(8)	120.0(5)
C2–C3	1.401(15)	1.382(7)	C2–C3–C4	120.5(6)	119.5(6)
C3–C4	1.350(14)	1.378(11)	C3–C4–C5	121.5(11)	120.9(6)
C4–C5	1.384(7)	1.357(12)	C4–C5–C6	119.0(9)	120.7(8)
C5–C6	1.390(15)	1.388(8)	C5–C6–C1	120.4(5)	119.5(6)
C6–C1	1.385(12)	1.382(9)	C6–C1–C2	119.9(9)	119.4(4)
C2–C11	1.509(12)	1.506(10)	C1–C2–C11	120.9(8)	120.8(4)
C3–C12	1.511(8)	1.519(10)	C3–C2–C11	120.3(4)	119.2(5)
C1–C7	1.531(13)	1.527(6)	C2–C3–C12	121.0(8)	121.2(6)
C7–C8	1.505(8)	1.497(9)	C4–C3–C12	118.5(10)	119.3(6)
C7–C13	1.526(8)	1.545(8)	C2–C1–C7	120.8(7)	120.6(5)
C8–N1	1.375(8)	1.393(8)	C6–C1–C7	119.3(4)	119.9(4)
N1–C9	1.353(8)	1.324(9)	C1–C7–C8	112.4(5)	112.4(5)
C9–N2	1.335(7)	1.303(7)	C1–C7–C13	109.5(7)	110.4(5)
N2–C10	1.366(8)	1.387(10)	C8–C7–C13	110.0(4)	108.8(4)
C10–C8	1.350(6)	1.358(6)	C7–C8–C10	132.9(6)	132.8(5)
			C7–C8–N1	121.5(4)	121.7(4)
			C8–N1–N9	110.9(4)	109.4(4)
			N1–C9–N2	105.3(5)	108.7(7)
			C9–N2–C10	110.4(4)	109.4(5)
			N2–C10–C8	107.9(5)	107.0(5)
			C10–C8–N1	105.5(5)	105.5(5)

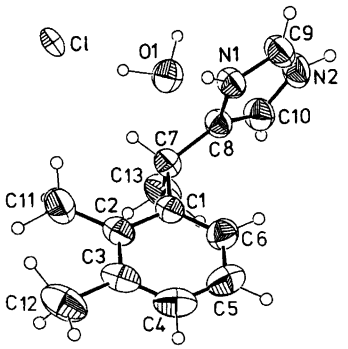


Fig. 2. ORTEP drawing of the hydrated form $C_{13}H_{19}ClN_2O$, together with the numbering system used.

sample weights and heating rates were from 5 to 10 mg and 5 K min^{-1}, respectively. Volatile decomposition products were analysed by a Kratos MS80RF Autoconsole mass spectrometer, using a direct insertion probe and temperature program from 50 to 380 °C at the rate of 50 K min^{-1}. The low-resolution mass spectra were measured during the heating at a scan rate of 12 s $decade^{-1}$.

Potentiometric titrations. A Radiometer PHM 64 digital potentiometer equipped with a glass electrode and an Ag,AgCl reference electrode was used for the e.m.f. measurements. The electrolyte in the reference electrode was 0.01 and 0.09 M with respect to NaCl and $NaClO_4$, respectively. The protonation constant of the title compound was determined in aqueous 0.1 M $NaClO_4$ with 0 and 50 wt%, with respect to ethanol. The method used has been described in detail earlier.[1] The total concentration of medetomidine varied between 0.002 and 0.015 M. Five titrations with different total concentrations were performed for both media studied. The protonation constants were calculated with the program SCOGS[7] on a Univac 1100/20 computer.

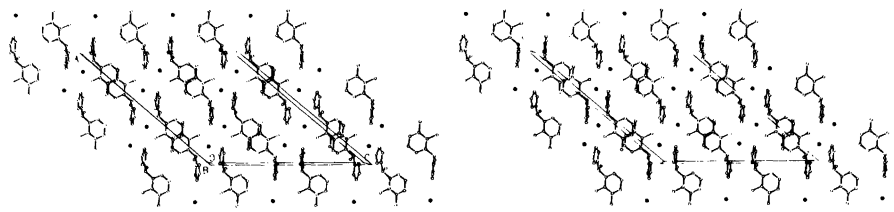


Fig. 3. A stereoscopic view of the unit-cell packing of $C_{13}H_{17}ClN_2$.

Table 5. Least-squares planes and deviations (Å) of atoms from the planes.

$C_{13}H_{17}ClN_2$

(*a*) Plane defined by C1, C2, C3, C4, C5, C6
$-4.8161x + 7.2952y + 7.0556z = -3.5021$

C1	−0.004(6)	N1	2.10(1)	C11	−0.01(1)
C2	0.001(6)	N2	1.57(1)	C12	0.04(1)
C3	−0.001(6)	C7	−0.08(1)	C13	−1.54(1)
C4	0.005(7)	C8	0.73(1)		
C5	−0.007(7)	C9	2.61(1)		
C6	0.007(7)	C10	0.41(1)		

(*b*) Plane defined by C8, N1, C9, N2, C10
$19.1879x + 1.7728y - 21.3490z = 11.4475$

C8	0.004(8)	C1	1.23(1)	C6	2.46(1)
N1	−0.004(7)	C2	1.15(1)	C7	−0.03(1)
C9	0.003(9)	C3	2.34(1)	C11	−0.17(1)
N2	−0.001(5)	C4	3.53(1)	C12	2.31(1)
C10	−0.002(9)	C5	3.62(1)	C13	−0.19(1)

Angle between planes (*a*) and (*b*) is 85.0(3)°

$C_{13}H_{19}ClN_2O$

(*c*) Plane defined by C1, C2, C3, C4, C5, C6
$6.2631x - 1.2248y - 6.049z = 4.8855$

C1	−0.001(6)	N1	2.03(1)	C11	−0.03(1)
C2	0.003(3)	N2	1.37(1)	C12	0.02(1)
C3	0.000(7)	C7	−0.08(1)	C13	−1.55(1)
C4	−0.004(8)	C8	0.65(1)		
C5	0.006(8)	C9	2.24(1)		
C6	−0.004(7)	C10	0.24(1)		

(*d*) Plane defined by C8, N1, C9, N2, C10
$1.6866x - 3.3197y + 11.3642z = -3.0881$

C8	0.001(5)	C1	1.22(1)	C6	2.44(1)
N1	0.000(4)	C2	1.16(1)	C7	−0.05(1)
C9	−0.001(6)	C3	2.32(1)	C11	−0.16(1)
N2	0.001(5)	C4	3.53(1)	C12	2.28(1)
C10	−0.001(5)	C5	3.59(1)	C13	−0.26(1)

Angle betweenb planes (*c*) and (*d*) is 83.9(2)°

Table 6. Hydrogen bonding.

Symmetry code: None *x, y, z*
(i) $x+\frac{1}{2}, -y+\frac{1}{2}, z+\frac{1}{2}$
(ii) $x-1, y, z+1$
(iii) $-x+1, -y, -z-1$

Bond A–H···B	Distance /Å			Angle /° A–H···B
	A–H	H···B	A···B	
$C_{13}H_{17}ClN_2$				
N2–H6···Cl	1.0	2.08	3.047(4)	160
N1–H4···Cl(i)	1.02	2.09	3.070(4)	160
$C_{13}H_{19}ClN_2O$				
N1–H4···O1	1.02(4)	1.71(5)	2.713(5)	167(5)
O1–H18···Cl	0.99(6)	2.22(6)	3.170(5)	162(4)
O1–H19···Cl(ii)	1.01(6)	2.18(5)	3.166(5)	164(4)
N2–H6···Cl(iii)	1.00(6)	2.32(4)	3.169(4)	142(5)

Results and discussion

Structure. Crystal data and experimental parameters are given in Table 1, and the final positional parameters of the non-hydrogen and hydrogen atoms in Tables 2 and 3, respectively. Views of the anhydrous and hydrated compounds are presented in Figs. 1 and 2. The bond lengths and angles are given in Table 4.

There are no significant differences between the corresponding structural parameters (bond lengths and angles) of the hydrated and anhydrous forms of medetomidine. The bond lengths and angles of the imidazole rings vary from 1.303 to 1.393 Å, and 105.5 to 110.9°, respectively. These values are in agreement with those reported for other imidazole derivatives.[1] The imidazole and benzene rings are coplanar within the limits of the experimental error (Table 5). The orientation of the imidazole ring with respect to the benzene ring is similar in the present two structures. The planes of these rings are inclined to another at 85.0 and 83.9° in the anhydrous and hydrated form, respectively. The corresponding angle in detomidine [4-(2,3-dimethylbenzyl)-1*H*-imidazole hydrochloride monohydrate] was found to be 80.5°.[1] However, the orientation of the benzene ring in detomidine is different to that in the present compounds lying on the other side of the imidazole plane.

Figs. 3 and 4 show views of the crystal packings. The hydrogen bonds as given in Table 6 occur between the imidazole nitrogen atoms and chloride ions in the anhydrous compound and

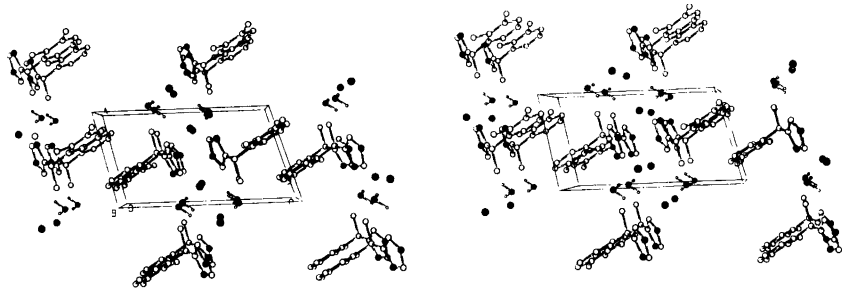


Fig. 4. A stereoscopic view of the unit-cell packing of $C_{13}H_{19}ClN_2O$.

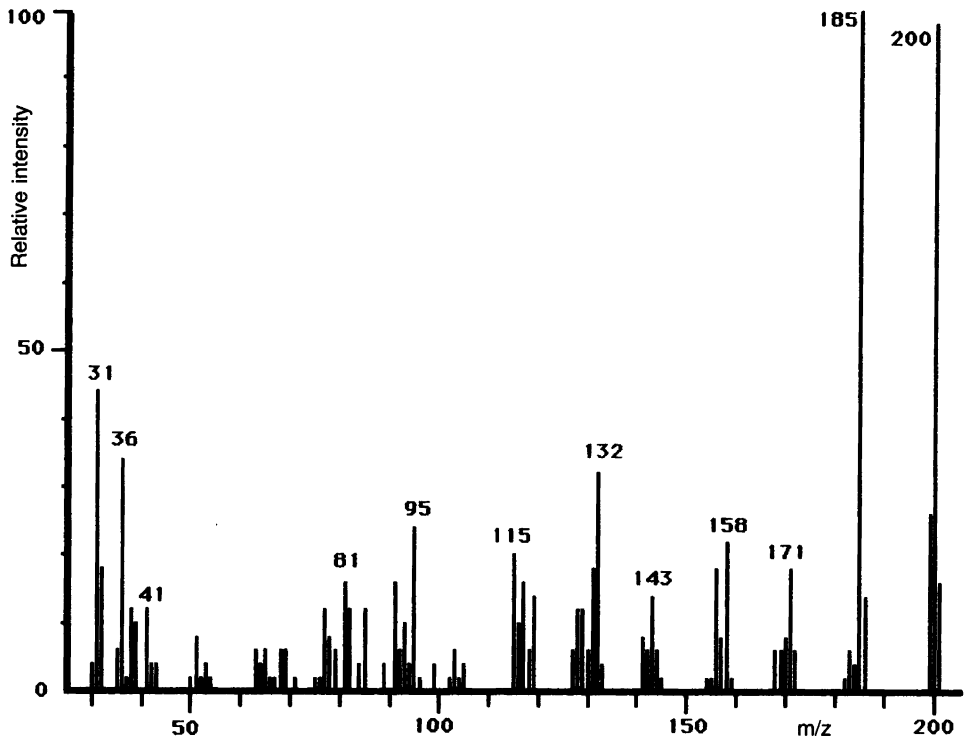
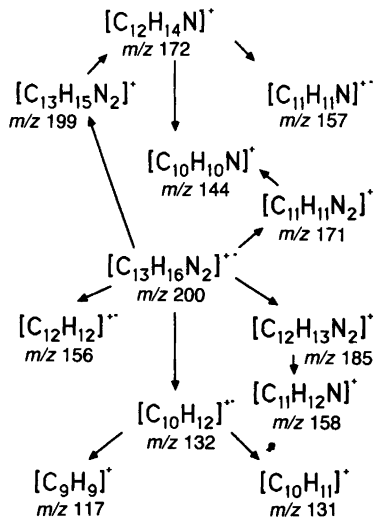


Fig. 5. The EI mass spectrum of medetomidine hydrochloride.



Scheme 1. The fragmentations of medetomidine confirmed by the metastable ions and accurate mass measurements.

between the imidazole nitrogen atoms and chloride ions in the anhydrous compound and between the imidazole nitrogen atoms and chloride ions and water molecules in the hydrated compound. Other intermolecular contacts correspond to normal van der Waals separations.

Mass spectrometry. Fig. 5 shows the 70 eV EI mass spectrum of medetomidine. The fragmentation of medetomidine (as a free base) is presented in Scheme 1. The fragmentation scheme has been confirmed by accurate mass measurements and metastable transitions using metastable maps produced from medetomidine. Table 7 lists accurate masses and calculated possible elemental compositions of ions.

In methane, isobutane and ammonia CI spectra of medetomidine the most abundant ion is the protonated molecule (m/z = 201). The intensities of all fragment ions were very low. The amount of protonation of the molecule was highest when ammonia was used as the reagent gas.

Table 7. Accurate masses of the fragments of medetomidine measured at a resolution of 7500.

Accurate mass		Formula
Found	Calc.	
200.1309	200.1314	$C_{13}H_{16}N_2$
199.1239	199.1235	$C_{13}H_{15}N_2$
185.1080	185.1079	$C_{12}H_{13}N_2$
172.1082	172.1126	$C_{12}H_{14}N$
171.0923	171.0922	$C_{11}H_{11}N_2$
158.0978	158.0970	$C_{11}H_{12}N$
157.0912	157.0892	$C_{11}H_{11}N$
156.0903	156.0939	$C_{12}H_{12}$
144.0804	144.0813	$C_{10}H_{10}N$
132.0929	132.0939	$C_{10}H_{12}$
131.0854	131.0861	$C_{10}H_{11}$
117.0697	117.0704	C_9H_9
105.0705	105.0704	C_8H_9
103.0549	103.0547	C_8H_7
95.0862	95.0861	C_7H_{11}
95.0608	95.0609	$C_5H_7N_2$
91.0520	91.0547	C_7H_7
91.0373	91.0421	C_6H_5N
79.0549	79.9548	C_6H_7
79.0430	79.0422	C_5H_5N
77.0392	77.0392	C_6H_5
69.0712	69.0704	C_5H_9
69.0451	69.0452	$C_3H_5N_2$
68.0506	68.0501	C_4H_6N
65.0398	65.0391	C_5H_5
65.0217	65.0265	C_4H_3N
51.0238	51.0234	C_4H_3

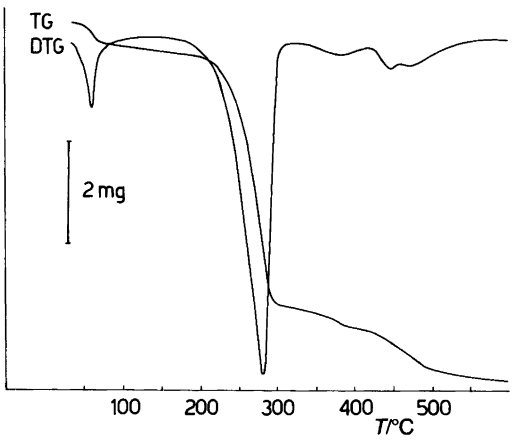


Fig. 6. TG and DTG curves from the thermal decomposition of medetomidine hydrochloride monohydrate in air. The sample weight was 6.76 mg and the heating rate 5 K min^{-1}.

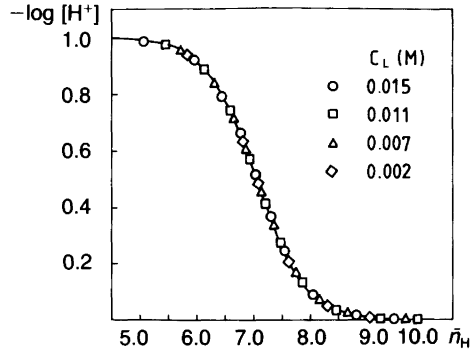


Fig. 7. Part of the potentiometric data obtained for aqueous solutions at I = 0.1 ($NaClO_4$) and 25 °C presented as an $\bar{n}_H(-\log [H^+])$ plot. Symbols are experimental values and the solid curve was calculated with the constant log K_1 = 7.04. $\bar{n}_H$(exptl) = $(C_H - [H^+] + [OH^-])/C_L$ and $\bar{n}_H$(calc.) = $K_1[H^+]/(1 + K_1[H^+])$.

Thermal behaviour. The TG and DTG curves in air and under normal pressure for the hydrated medetomidine are presented in Fig. 6. The first stage at 45–100 °C is dehydration. The observed change of weight in this step was −6.8 %. The calculated weight loss for the dehydration of one water molecule from $C_{13}H_{17}ClN_2 \cdot H_2O$ is 7.07 %. Except for this first step, which is absent in the TG and DTG curves of the anhydrous medetomidine, the thermal curves of the both forms are identical, as might be expected. The most dramatic weight loss takes place at ca. 200–320 °C (−74 %) followed by two small weight loss steps (−6 and −13 %) at 340–570 °C. To detect the reactions, volatile decomposition products were identified by mass spectrometry. The mass-spectrometric analysis confirmed the release of water at 45–100 °C in the case of medetomidine monohydrate. In addition, the MS analysis showed the simultaneous evaporation of HCl and medetomidine base at 200–320 °C. The two small steps in the TG curves are decomposition of the rest of the compound in the crucible. The results obtained are very similar to those reported earlier for detomidine.[1]

Protonation. Part of the potentiometric data in aqueous solution at I = 0.1 ($NaClO_4$) and 25 °C is presented as an $\bar{n}_H(-\log[H^+])$ plot in Fig. 7. The $\bar{n}_h$ analysis indicates that polymerization is negligible and the compound is a monoprotic acid in the

Table 8. Protonation constants of medetomidine, detomidine, imidazole, and 2(3)-hydroxyimidazole at I = 0.1 ($NaClO_4$) and 25.0 ± 0.1 °C in aqueous solution and water–ethanol (50 wt% ethanol) solvent mixture.

Compound	log K_1 (aq)	log K_1 (H_2O–EtOH)	Ref.
Medetomidine	7.04–0.02	6.29–0.01	This work
Detomidine	7.09–0.03	6.28–0.01	1
Imidazole	7.09[a]	–	8
	6.92[b]	5.63[b]	9
2(3)-Hydroxyimidazole	6.46	5.95	10

[a]0.1 M KCl. [b]0.1 M KBr.

pH range studied ($5 \leq pH \leq 10$). Identical results were obtained for the water–ethanol mixture. The protonation constants of medetomidine are given in Table 8 together with those of imidazole, detomidine and 2(3)-hydroxyimidazole. Within the limits of error, the log K_1 values are about the same for medetomidine, detomidine and imidazole. Thus, the substituents in medetomidine and detomidine have practically no effect on the proton attached to the imidazole ring. In each case the log K_1 values in the water–ethanol medium are lower than those in aqueous solution. This is due to the change of the reciprocal value of the permittivity as described earlier.[1,10]

References

1. Lajunen, L. H. J., Ruotsalainen, H., Turpeinen, U., Parhi, S., Kurkela, K. and Karjalainen, A. *Acta Pharm. Suec. 21* (1984) 163.
2. Karjalainen, A. J. and Kurkela, K. *U.S. Pat.* 4544664 (1985).
3. Savola, J.-M., Ruskoaho, H., Puurunen, J., Salonen, J. S. and Kärki, N. T. *J. Auton. Pharmac. 5* (1986) 275.
4. Virtanen, R. E., Karjalainen, A. J., Kurkela, K. O. A., Vähä-Vahe, A. T. and Vainio-Kivinen, O. M. *U.S. Pat.* 4670455 (1987).
5. Cromer, D. T. and Mann, J. B. *Acta Crystallogr., Sect. A 24* (1968) 321.
6. Stewart, R. F., Davidson, E. and Simpson, W. *J. Chem. Phys. 53* (1970) 1891.
7. Sayce, I. G. *Talanta 15* (1968) 1397; *18* (1971) 653; Sayce, I. G. and Sharma, V. S. *Talanta* 19 (1972) 831.
8. Bauman, J. E., Jr. and Wang, J. C. *Inorg. Chem. 3* (1964) 368.
9. Oszczapowicz, J. and Czurylowska, M. *Talanta 31* (1984) 559.
10. Lajunen, L. H. J., Nieminen, A. O. K., Holster, T. and Parhi, S. *Finn. Chem. Lett.* (1983) 155.

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