Short Communication

Marine Alkaloids. 14. Prototropy of Chartellines from *Chartella papyracea*

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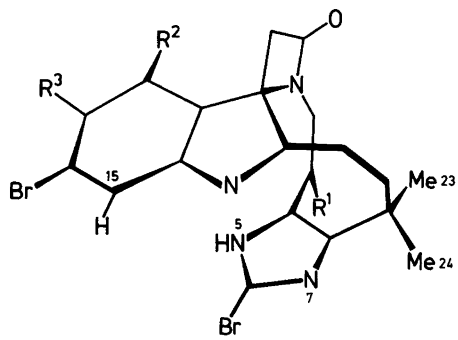
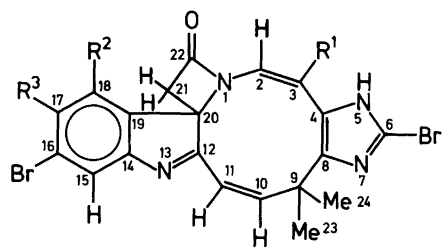
In a preceding paper of this series[1] we reported on the isolation and structure of four bromoalkaloids, viz. chartelline A (**3**), B (**2**), C (**1**) and the artifact methoxy-dechlorochartelline A (**4**), from the marine bryozoan *Chartella papyracea* (Ellis and Solander). The presence of the 2-bromoimidazole ring as part of the basic skeleton offers a potential source for tautomerism arising from the prototropic exchange between N5 and N7. In the solid state, chartelline A (**3**) was obtained as a 1:1 adduct with ethyl acetate. An X-ray determination established the structure as the N7-H isomer stabilized by a strong hydrogen bond to the carbonyl group of ethyl acetate, i.e. the tautomeric form of the structure shown for **3**. As discussed below, the ^{1}H NMR spectra (Table 1) of **1**–**4** indicate that in all cases the N5-H isomer (**a** form shown in the structures) is predominant in solution, while the N7-H isomer (**b** form) constitutes only a small amount or is undetected.

The drastic simplification of the ^{1}H NMR spectrum on addition of D_2O/CF_3COOD implies the existence of two slowly interconverting compounds with identical protonated forms arising from the imidazole ring. It is well known[3] that the rate of intermolecular proton transfer in imidazoles is usually much too fast to permit a differentiation on the NMR time scale. However, provided intermolecular association is sterically hindered or low-temperature spectra of dilute solutions in polar aprotic solvents are recorded, separate signals may be observed in the ^{1}H and ^{13}C NMR spectra of azoles.[3,4] Since we have been





1. $R^2 = R^3 = H$, $R^1 = Cl$, Chartelline C
2. $R^3 = H$, $R^1 = Cl$, $R^2 = Br$, Chartelline B
3. $R^1 = Cl$, $R^2 = R^3 = Br$, Chartelline A
4. $R^1 = OMe$, $R^2 = R^3 = Br$, Methoxy-dechlorochartelline A

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Table 1. ^{1}H NMR assignments (ppm) of the major (**a**) isomers of **1–4** in solution.[a]

	1 $CDCl_3$	**2** $CDCl_3$	**3**			**4**	
			$CDCl_3$	$(CD_3)_2CO$	DMSO-d_6	$CDCl_3$	$(CD_3)_2CO$
H-2	7.09	7.07	7.06	6.99	7.01	6.29	6.27
H-3	–	–	–	–	–	–	–
H-5	9.02	9.01	9.10	11.4	11.2	9.28	11.4
H-10	6.07	6.05*	6.02*	6.18*	6.10*	5.98*	6.15*
H-11	6.10	6.10*	6.08*	6.30*	6.31*	6.09*	6.19*
H-15	7.61	7.56*	7.71	7.71	7.70	7.72	7.71
H-17	7.42	7.52*	–	–	–	–	–
H-18	7.17	–	–	–	–	–	–
2 H-21	3.18 3.33	3.22 3.42	3.21 3.43	3.48 3.55	3.45 3.62	3.13 3.41	3.34 3.37
3 H-23	1.51*	1.49*	1.49*	1.54*	1.41*	1.46*	1.50*
3 H-24	1.54*	1.55*	1.55*	1.56*	1.44*	1.54*	1.53*
OMe	–	–	–	–	–	3.62	3.53
OH[b]	–	–	–	–	–	1.90br	2.85
% **a**	100	88	78	89	100	80	65

[a]Close-lying values marked with an asterisk may be interchanged. [b]Strongly dependent on small amounts of water in the solvent.

able to obtain complete ^{1}H and ^{13}C NMR data for both tautomers of **2–4** even in $CDCl_3$ at room temperature we conclude that intermolecular association is effectively prevented by the bulky substituents on the imidazole ring favouring association with the solvent instead. The formation of

Table 2. ^{1}H NMR assignments (ppm) of the minor (**b**) isomers of **2–4** in solution.[a]

	2 $CDCl_3$	**3**		**4**	
		$CDCl_3$	$(CD_3)_2CO$	$CDCl_3$	$(CD_3)_2CO$
H-2	7.11	7.12	7.10	6.39	6.38
H-3	–	–	–	–	–
H-7	8.90br	8.90	11.1	8.30	10.8
H-10	6.07	5.97*	6.14*	5.94*	6.10
H-11	6.13*	6.11*	6.24*	6.10*	6.10
H-15	7.68	7.85	7.74	7.83	7.73
H-17	7.54	–	–	–	–
H-18	–	–	–	–	–
2 H-21	3.29 3.41	3.28 3.41	3.53 3.60	3.19 3.37	3.40 3.40
3 H-23	1.45*	1.45*	1.44*	1.43*	1.42*
3 H-24	1.50*	1.57*	1.51*	1.55*	1.48*
OMe	–	–	–	3.58	3.57
OH	–	–	–	1.90br	2.85

[a]Close-lying values marked with an asterisk may be interchanged.

strong $-NH\cdots O$ hydrogen bonds is evidenced by the downfield shifts by ca. 2 ppm of the NH proton signal of either tautomer in DMSO-d_6 or acetone-d_6 relative to $CDCl_3$.

Previous assignments of NMR spectra of tautomeric mixtures of imidazole derivatives are few in number. In a study of topsentins, i.e. naturally occurring alkaloid imidazoles substituted only at C2 and C4 (imidazole numbering), observation of the C5-H/NH coupling constant served to verify the identity of the preferred tautomeric form.[5] This method cannot be used in the present case where both C4 and C5 in the imidazole ring bear substituents. In histidine derivatives,[6] comparison with the chemical shifts of authentic N1- and N3-alkylated derivatives allows a positive identification of the signals arising from the two tautomeric forms. However, the spatial variations of the imidazole ring relative to the indolenine residue following introduction of e.g. an alkyl group on the N5-H in the highly strained chartellines result in unpredictable chemical shifts, thus making this method useless here.

Examination of the ^{13}C data (not given) for the chartellines in $CDCl_3$, acetone-d_6 and DMSO-d_6 revealed that the differences in chemical shifts between the **a** and **b** forms even for the carbon resonances of the imidazole ring are never more than ca. 4 ppm and moreover are found at positions scattered all over the molecule (C-2, 9, 10, 15, 22, 23 and 24). It was expected[7] that the carbon attached to a pyridine-like nitrogen should be more deshielded than that bound to a pyrrole-like nitrogen, amounting to a chemical shift difference of 8–12 ppm. This is probably due to the unusual linking of the imidazole ring to the indolenine residue through different chains; alternatively, the rings may be involved in π–π interaction as suggested by their coplanarity.

Some of the solvent shifts (Table 1 and 2) were found for both tautomers. The H-10 and H-11 protons in **3a** and **3b** are strongly deshielded in acetone-d_6 and DMSO-d_6 compared to $CDCl_3$. This points to a solute-solvent association between the strong dipoles of the CO/SO groups of the solvent and the β-lactam group, affecting the H-10 and H-11 atoms placed directly in the deshielding region of the solvent CO/SO group. Since the two H-21 protons can only be marginally affected by this direct shielding, the observed net deshielding is attributed to the inductive withdrawal of electrons arising from the enhancement of the C^+-O^- dipole of the β-lactam relative to the $N^+=C-O^-$ dipole of the same group following solvation. The reduced amide resonance in β-lactam systems is a long-established feature of these compounds.[8]

Inspection of a space-filling model clearly shows that while solvation through N7-H (**b** form) may place one of the methyl groups (C-23/24) and C15-H within the shielding range of the CO/SO group, these hydrogen atoms are effectively removed from any shielding/deshielding regions of molecules solvated through N5-H (**a** form). Accordingly, the signals for the minor isomer exhibiting high-field solvent shifts ($CDCl_3$ to acetone) of H-15 and H-24 have been assigned to the **b** form. Both solvent shifts are absent or in the opposite direction in the other isomer. The anomalous shifts observed for H-23/24 in DMSO-d_6 may be indicative of the larger solvating ability of the strongly polar SO group.

In general, great care should be exercised in using the methods of solvent shifts in structural assignments of tautomeric mixtures of compounds as flexible as the chartellines. Nevertheless, from the results presented here it seems reasonable to conclude that solvation of the chartellines in solution takes place preferentially or exclusively through N5-H, in contrast to chartelline A in the solid phase, which is associated through N7-H to ethyl acetate.

References

1. Anthoni, U., Chevolot, L., Larsen, C., Nielsen, P. H. and Christophersen, C. *J. Org. Chem. 52* (1987) 4709.
2. Chevolot, L., Chevolot, A.-M., Gajhede, M., Larsen, C., Anthoni, U. and Christophersen, C. *J. Am. Chem. Soc. 107* (1985) 4542.
3. Papadopoulos, E. P. and Hollstein, U. *Org. Magn. Reson. 19* (1982) 188.
4. Toppet, S., Wouters, G. and Smets, G. *Org. Magn. Reson. 11* (1978) 578.
5. Bartik, K., Braekman, J.-C., Daloze, D., Stoller, C., Huysecom, J., Vandevyver, G. and Ottinger, R. *Can. J. Chem. 65* (1987) 2118.
6. Tanokura, M. *Biochim. Biophys. Acta. 742* (1983) 576.
7. Dvortsak, P., Reiter, J., Somorai, T. and Sohar, P. *Magn. Reson. Chem. 23* (1985) 194.
8. Proctor, P., Gensmantel, N. P. and Page, M. I. *J. Chem. Soc., Perkin Trans. 2* (1982) 1185.

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