Tautomeric Ratio in 4-Methylthiazol-2-ylguanidine, a Model Guanidinoheterocycle

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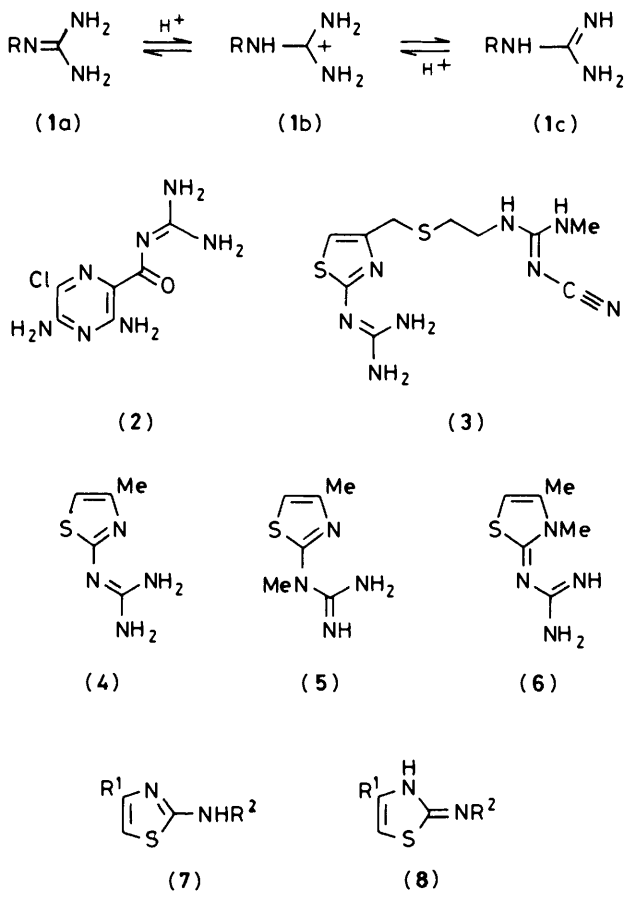
The pK_a values of fixed model tautomers have been used to assess tautomeric ratio in the title compound. Although pK_T values of 3.62 and 5.32 between the major and the two minor tautomers result, reasons are given for believing that the method exaggerates both ratios. Nevertheless the arylimino tautomer is very dominant and evidence is adduced that this conclusion may be general for guanidinoheterocycles. If so, only this tautomer may be considered as the form that interacts with the histamine H_2-receptor.

Except for a pioneering paper by Charton,[1] tautomeric preference among substituted guanidines has received scant attention. Recently however the guanidine unit has appeared in a number of pharmaceutical products and this has stimulated a desire to know more. For those histamine H_2-receptor antagonists that contain the guanidine unit this is particularly important, since there is suggestive evidence[2] to implicate antagonism as a property which may depend, wholly or in part, on the free-base form. This form (**1a** or **c**) is that for which the problem exists; tautomeric preference is extinguished in the common cation (**1b**).

Crystal structures have been determined for a number of compounds containing the cyanoguanidine unit;[3-7] all these show nitrile on imino-nitrogen [R in (**1a**)]. The position for nitro[8] and sulphonyl[9] guanidines is similar. In addition, n.m.r. evidence and CNDO/2 calculation for amiloride (**2**) demonstrate[10] this form for the free base. The latter result is consistent with our recent evidence[11] that acylguanidines in general possess pK_T values in the region of 2.5—3.1 in favour of tautomer (**1a**). Somewhat more pertinent in the present context is the crystal structure of tiotidine (**3**);[6] in addition to a cyanoguanidine unit this contains a guanidinothiazole, the tautomeric preference of which lies in the same direction. All these results are consistent with Charton's qualitative argument[1] that deprotonation of the cation is expected from that nitrogen atom least able to support a positive charge; when R in (**1**) is electronegative, this argues for the preponderance of tautomer (**1a**).

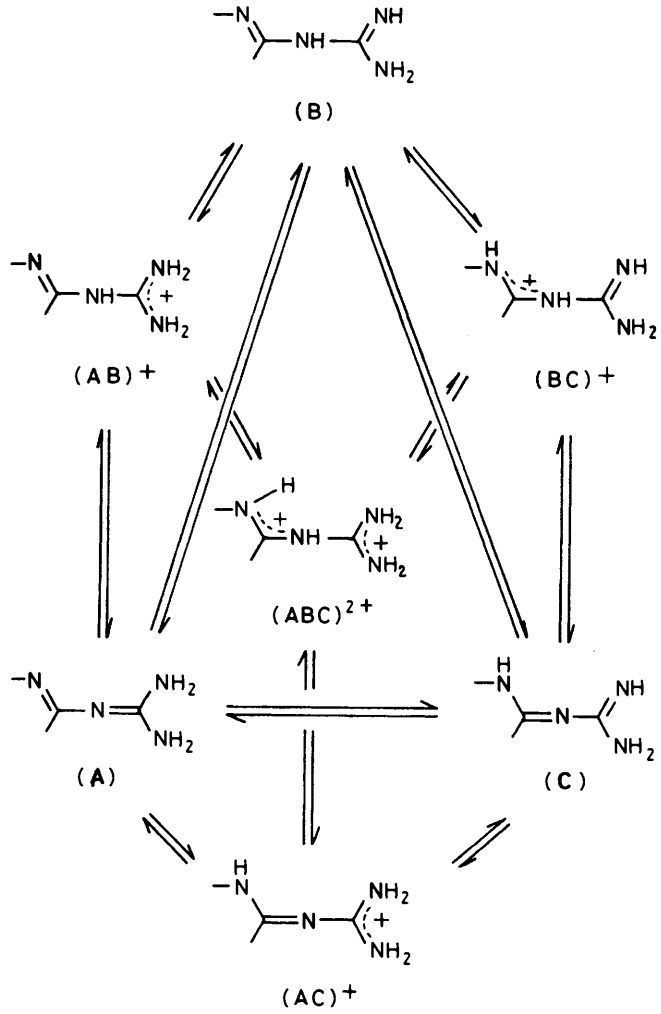
Nevertheless there is a dearth of information on tautomeric *ratio* as distinct from simple tautomeric preference. The present work is an attempt to help fill that gap. Since guanidinoheterocycles figure largely in our H_2-receptor antagonist programme[7,12] it seemed logical to pick an example close to the middle of the range in basicity covered, and a guanidinothiazole was accordingly chosen. Since tiotidine (**3**) was for this purpose a molecule of unnecessary complexity we concentrated our attention on its simpler analogue (**4**). Fixed forms (**5**) and (**6**) of the pertinent minor tautomers were prepared for comparison. Some of this work has been reported in outline in a review on this class of compound.[7]

Because of the possibilities for further tautomerisation involving the thiazole ring, the present study is one of unusual complexity. In such a case three free-base forms, three monocations, and one common dication are implicated:[13] seven potential species as compared with the three involved in (**1**). Although several studies of this type have been reported,[14] none possesses the scope for conformational ambiguity that complicates the issue here. Scheme 1 summarises the interrelationships between the species. These are sketched in terms of three formal tautomers of which (A) is coincident with the actual compound (**4**) while (B) and (C) are equivalent to (**5**) and (**6**) on the assumption, later to be discussed, that *N*-methylation in the latter pair has no appreciable effect on their basicities. The same convention is adopted in Scheme 2, which summarises the actual pK_a values obtained and the tautomeric ratios (pK_T in the direction indicated) in consequence deduced. Table 1 presents pertinent u.v. data for compounds (**4**)—(**6**). The lower pK_a values assume the H_0 scale; since however there is little difference between the scales in this region[15] and only comparative data for diprotonation are required for present purposes, it is considered unlikely that any appreciable error will have entered from this source.

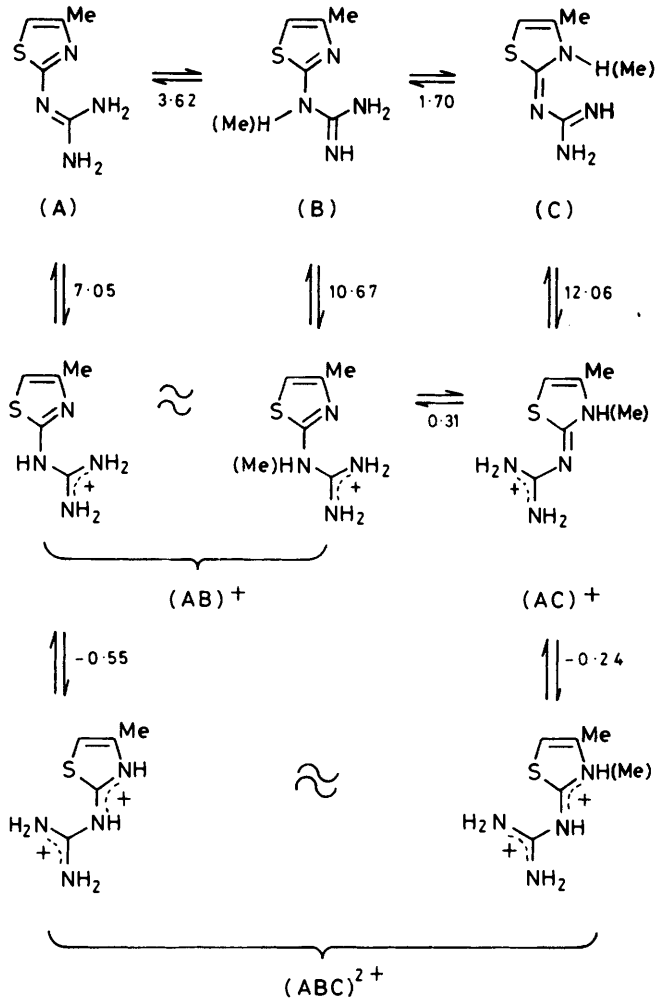


Results

The central problem in disentangling Scheme 1 lies in making sure that the monocationic species have been correctly



Scheme 1.



Scheme 2.

identified. Matters are much aided by the u.v. spectra, which for each species consists of a single strong band of unambiguous peak position. We may now conduct the analysis on established[13] lines. Any two free-base tautomers may share a common cation but the third cannot. Here the near-identity of the u.v. spectra for the cations of (**4**) and (**5**) identifies this common monocation as $(AB)^+$. This identification is supported by the close resemblance of this cation to free base (**5**), since (**4**) and (**5**) are respectively examples of what we have elsewhere[11] categorised as 'through-conjugated' and 'cross-conjugated' tautomers, and cation $(AB)^+$ comes into the latter category. The same argument distinguishes between the rival cations $(AC)^+$ and $(BC)^+$ that are possible for (**6**): the minimal u.v. difference between free base and cation identifies the latter as existing in the same 'through-conjugated' form so it has to be $(AC)^+$. Supporting evidence comes from a consideration of relative basicities if (**6**) is formally regarded as an amidine unit linked to an iminothiazole. For simple examples of these two units separately, pK_a values are expected to lie above 12 (ref. 1) and below 10 (ref. 16), respectively, and since any electron drift will go from iminothiazole to amidine, not *vice versa*, protonation on the amidine moiety is indicated. Hence $(BC)^+$ is redundant and the twelve equilibria of Scheme 1 collapse to the nine of Scheme 2. The two forms of the dication $(ABC)^{2+}$ derived from (**4**) and (**6**) show a u.v. spectral resemblance which is close enough to confirm their formal identity but the spectra are sufficiently different to indicate that ring methylation, at least, does result in some perturbation; see further discussion later.

Table 1. U.v. and pK_a data (±s.d.)

	Base	Cation	Dication
(**4**) pK_a	7.05 ± 0.05		−0.55 ± 0.04
$\lambda_{max.}$/nm	288	269	286
log ε	4.15	4.01	3.97
(**5**) pK_a	10.67 ± 0.05		
$\lambda_{max.}$/nm	272	266	
log ε	3.99	3.90	
(**6**) pK_a	12.06 ± 0.03		−0.24 ± 0.05
$\lambda_{max.}$/nm	295	301	277
log ε	4.10	4.14	3.88

Discussion

These raw data taken at face value identify (**4**) as the overwhelmingly predominant tautomer, by a factor of 4 000 over (**5**) which in turn is favoured by a factor of 50 over (**6**). We

Table 2. Tautomeric ratios for substituted aminothiazoles (7) ⇌ (8)[a]

		pK_a			
R^1	R^2	(7)	(8)	pK_T	Ref.
H	H	5.32	9.50	4.18	16
H	CH_2Ph	5.15	8.98	3.83	16
H	Ph	4.33	6.30	1.97	16
Me	$C(=NH)NH_2$	*b*	*b*	<1.70[c]	This work (B),(C)
Me	COMe			>0	20,21
Me	$C(NH_2)_2^+$	−0.55	−0.24	0.31[c]	This work $(AB)^+$,$(BC)^+$
H	$SO_2C_6H_4CH_3$-*p*	<0[c]	<−1[c]	<−1[c]	16

[a] pK_T in favour of the amino tautomer. [b] Related *via* the inaccessible common cation $(BC)^+$. [c] See text.

have next to consider what hidden factors may perturb this straightforward solution.

The chief of these must be steric and conformational. In Scheme 2 we show each species in the conformation we believe it is most likely to adopt. There can be little doubt concerning this in (A), (B), (C), and $(AB)^+$ where an intramolecular hydrogen bond is likely to exist even in water,* but the conformations of the cations $(AC)^+$ and $(ABC)^{2+}$ are more open to dispute. For these the *E*-conformation favoured by the others would involve severe steric and electrostatic repulsion between the partially charged NH groups, and we postulate a preference for the *Z*-conformation illustrated. This has no consequences provided that the *N*-methylation actually present in (**5**) and (**6**) does not radically affect the position. For (**5**) there is almost bound to be some twisting between the thiazole and amidine units, though if the degree of this differs little between cation and free base, as the comparative u.v. intensities tend to suggest, pK_a and hence tautomeric ratio could be little affected. The case of (**6**) is different. Here the effect of *N*-methylation on the cation $(AC)^+$ is likely to be minimal but the free base could be seriously affected: ring methylation must destroy any intramolecular hydrogen bond and may even force a switch in conformation. It is impossible to quantify this effect but it is likely to make pK_T for (B)/(C) rather less than the 1.70 that appears in Scheme 2, even allowing for the somewhat improved stability of (**B**) relative to (**5**). Balanced against this, however, is the probability that $(ABC)^{2+}$ as derived from (**6**) is likely to be twisted by *N*-methylation relative to its opposite number derived from (**4**), as indeed their u.v. spectra suggest. If so, the resulting destabilisation must favour $(AB)^+$ relative to $(AC)^+$ more than appears in Scheme 2 and, in consequence, cancel some of the gain in stability of (C) relative to (B) already noted.

A minor complication, not so far considered, is that each of (B) and (C) is in reality two tautomers not one since the imino double bond is mobile; as for the formally related acylguanidines[11] *five* free base tautomers are possible. As in that case, however, it is probable that little intrinsic difference within each pair exists, and since (B) and (C) are very minor tautomers, the position is not substantially affected. In any case this complication is present in the model compounds (**5**) and (**6**) and there is no reason to suppose that (B) and (C) would differ appreciably in this respect.

We tentatively conclude that, in reality, (A) is probably favoured over (B) by *ca.* 10^3, and that (C) is disfavoured by perhaps a power of ten more. Even this reduced margin, however, is sufficient to ensure that (A) is the only 2-guanidinothiazole tautomer that can seriously be considered as a candidate for interaction at the histamine H_2-receptor.

In attempting to generalise this result to other guanidinoheterocycles of higher or lower pK_a we have to guess at the relation, if any, between pK_a (for either tautomer) and pK_T. Some clues are available from the parallel case of the amino- and imino-thiazoles (7) ⇌ (8). In Table 2 we assemble some pertinent data from the literature alongside those provided by (**5**) and (**6**) as models for (B) and (C) respectively. Some of these examples are not straightforward: in particular, there are problems[16] concerning the interpretation of the pK_a values of the fixed tosyl forms and the (very rough) estimates of Table 2 are our own. There is however no doubt, from crystal structure[18] and solution n.m.r.[19] evidence, that the imino form is favoured. For acetyl the evidence is qualitative and rests on the observation that, while some acyl derivatives are firmly in the amino form,[20] others are so close to the borderline that both forms have been isolated.[21] The general import of Table 2 is that tautomeric ratio increasingly favours the imino form (or disfavours the amino form) as overall pK_a falls. Qualitatively of course this is consistent with Charton's argument[1] as already noted. Quantitatively it appears, very roughly, that pK_T changes by approaching one unit for each change by two units in the pK_a of the imino form. There is suggestive evidence that a very similar pattern may obtain for the substituted guanidines. By definition, pK_T is zero for guanidine itself. In acetylguanidine, with pK_a *ca.* 8, pK_T approaches 3;[11] *i.e.* $\Delta pK_T < 3$ for ΔpK_a *ca.* 6. In the present case both numbers are perhaps slightly larger. Unfortunately there are no data for cyano- or nitro-guanidine, either of which would make an excellent test case; here pK_T is expected to be high.

Since the heterocyclic guanidines of interest[12] as histamine H_2-antagonists possess[17] pK_a values in the range 4—10 it probably follows that pK_T lies in the range 2—4. Given the high energetic penalty attaching to any other course there seems no reasonable doubt that each of these compounds, if it interacts with the receptor in the free-base form, must do so as the dominant arylimino tautomer.

Experimental

pK_a Values were determined at 25 °C by u.v. spectroscopy using standard experimental and computational techniques.[22] Dication values involved absorbance measurements on individual solutions of known H_0 value.[15] The remaining pK_a values were obtained by the stepwise titration under pH-stat conditions of solutions initially at $I = 0.01$ but, for (**5**) and (**6**), inevitably at higher ionic strength by the end of the titration. Isosbestic points were coherent throughout and unaffected by this, and no

* For (**4**) there is clear evidence for this from the octanol–water partition coefficient.[17]

systematic deviations appeared in the pK_a calculations. Return of these solutions to pH 7 and u.v. re-examination confirmed that no decomposition had occurred. Water was distilled deionised; other reagents were of analytical reagent grade. Reagents employed in the syntheses were obtained commercially if not otherwise specified, and used as received. Mass spectra were obtained with a Kratos (A.E.I.) MS-902 spectrometer, n.m.r. spectra with a Varian EM-390 or Perkin-Elmer R12 spectrometer with tetramethylsilane as internal standard, and u.v. spectra with a Pye-Unicam SP8-100 spectrophotometer equipped with a thermostatted cell titration vessel of 5 cm path length.

Methylation of the Guanidine (**4**).—Compound (**4**) was prepared by the method of Beyer and Hantschel [23] and isolated as the hydrochloride, m.p. 193—194 °C (lit.,[23] 195 °C). From the hydrochloride (3 g) in water (5 ml) the free base was precipitated by addition of aqueous sodium hydroxide; the solid was filtered off, washed with water (25 ml), and dried *in vacuo* to yield the guanidine (1.78 g, 73%), m.p. 128—131 °C. A suspension of the guanidine (940 mg) and dimethyl sulphate (660 mg, 0.87 mol. equiv.) in dry nitromethane (18 ml) was stirred overnight at room temperature. The resulting solution was extracted with water (2 × 6 ml) and the combined aqueous extracts were extracted with dichloromethane (2 × 6 ml) before being evaporated to dryness *in vacuo*. The residue was dried by azeotroping with toluene before being twice recrystallised from ethanol–diethyl ether to yield 1-*methyl*-1-(4-*methylthiazol*-2-*yl*)*guanidine* (**5**) as its methyl sulphate (270 mg, 16%), m.p. 110—113 °C (Found: C, 29.6; H, 5.0; N, 19.6%; M^+, 170. $C_7H_{14}N_4O_4S_2$ requires C, 29.8; H, 5.0; N, 19.9%); δ_H [60 MHz; $(CD_3)_2SO$] 2.30 (3 H, s, Me), 3.36 (3 H, s, OMe), 3.44 (3 H, s, NMe), 7.16 (1 H, s, 5-H), 8.42 (4 H, br, 2 NH_2^+). The position of *N*-methylation follows from the great difference in pK_a from (**4**) and non-identity with the isomer (**6**), a small amount of which was formed in parallel as demonstrated by t.l.c. [dichloromethane–methanol (20%)—aqueous ammonia (2%)] but which, along with starting material, was removed by the recrystallisation process.

Preparation of the Guanidine (**6**).—3,4-Dimethylthiazole-2(3*H*)-imine was prepared by the method of Wilson and Woodger [24] and isolated as its hydroiodide, m.p. 165—168 °C (lit.,[24] 167—168 °C). This material (1.28 g, 5.0 mmol) was heated under reflux with dimethyl *N*-tosyldithiocarbonimidate [25] (1.43 g, 5.2 mmol) dissolved in aqueous N-sodium hydroxide (5 ml) and ethanol (20 ml) for 5 h to yield, after cooling and filtration, 1.56 g of crude material. On recrystallisation from dimethylformamide this gave 1-[3,4-*dimethylthiazol*-2(3H)-*ylidene*]-2-*methyl*-3-p-*tosylisothiourea* (1.39 g, 47%), m.p. 260 °C (Found: C, 47.3; H, 4.7; N, 11.7%; M^+, 355. $C_{14}H_{17}N_3O_2S_3$ requires C, 47.3; H, 4.8; N, 11.8%). This compound (600 mg) dissolved in alcoholic ammonia (100 ml) was heated in a Carius tube at 150 °C for 18 h, then cooled; the resulting suspension was evaporated to dryness *in vacuo* to yield, after recrystallisation from absolute ethanol, 1-[3,4-*dimethylthiazol*-2(3H)-*ylidene*]-2-p-*tosylguanidine* (360 mg, 66%), m.p. 222—223 °C (Found: C, 48.0; H, 5.0; N, 17.2%; M^+, 324. $C_{13}H_{16}N_4O_2S_2$ requires C, 48.1; H, 4.9; N, 17.3%). This guanidine (162 mg) dissolved in trifluoroacetic acid (1 ml) was stirred with boron tris(trifluoroacetate) (4 ml of a molar solution in trifluoroacetic acid; 8 molar excess) at 0 °C for 72 h. The solution was evaporated to dryness at room temperature *in vacuo* and the oily residue was dissolved in methanol; this solution was evaporated to dryness and the process was repeated several times. The resulting oil was dissolved in ethanol and treated with ethereal hydrogen chloride, and the resulting solid was recrystallised from absolute ethanol (2 ml) to yield 1-[3,4-*dimethylthiazol*-2(3H)-*ylidene*]*guanidine* (**6**) as its dihydrochloride (60 mg, 50%), m.p. 170—185 °C (decomp.) (Found: C, 29.9; H, 5.0; N, 22.7%; M^+, 170. $C_6H_{12}Cl_2N_4S$ requires C, 29.6; H, 4.9; N, 23.0%); δ_H [90 MHz; $(CD_3)_2SO$] 2.25 (3 H, s, Me), 3.42 (3 H, s, NMe), 6.70 (1 H, s, 5-H), 7.20 (1 H, br, NH^+), and 7.88 (4 H, br, 2 NH_2^+).

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