Prediction of Tautomeric Equilibria for *N,N′,N″*-Trisubstituted, *N,N′*-Disubstituted and *N*-Monosubstituted Guanidines

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The methods, based on Brønsted acid–base equilibria, for prediction of the tautomeric equilibria constants (as pK_T) and of the pK_a values of individual tautomers are proposed, and applied to *N,N′,N″*-triaryl-, *N,N′*-diaryl-, and *N*-aryl-guanidines. The tautomeric equilibria constants obey a linear relation with σ° constants: $pK_T = -\rho_T\Delta\sigma^\circ$.

Tautomerization in guanidines is a very fast reaction. The measurements of tautomeric equilibrium constants (pK_T) are difficult or even impossible. For this reason the possibility of predicting pK_T values is an important question in organic chemistry. In previous papers[1-3] it has been shown that the application of correlation analysis methods to the study of tautomeric and Brønsted acid–base equilibria in compounds containing the amidine moiety –NH–C(X)=N– is a way of predicting the pK_T values. These compounds exist as a mixture of two tautomers and only one tautomeric equilibrium can be observed.

Guanidines (**1**)–(**4**) contain at least one hydrogen atom at each of the two amino nitrogen atoms and thus they exist as a mixture of three tautomers B_1, B_2, and B_3. The protonation of the imino nitrogen atom yields only one guanidinium cation BH^+, which as the conjugate acid of the three tautomeric bases dissociates as shown in the Scheme. This Scheme is more complicated than those for the previously studied compounds.

Three tautomeric and three acid–base equilibria can be observed, but only the macroscopic dissociation constant, defined as $K_{a_m} = [(B_1) + (B_2) + (B_3)](H^+)/(BH^+)$ can be measured by direct methods. The measured dissociation constant K_{a_m} is the sum of the microscopic dissociation constants K_{a_1}, K_{a_2}, and K_{a_3} [equation (1)], where $K_{a_i} = (B_i)(H^+)/(BH^+)$.

$$K_{a_m} = K_{a_1} + K_{a_2} + K_{a_3} \qquad (1)$$

In the case of symmetrically trisubstituted guanidines (**1**), when $R^x = R^y = R^z$, and unsubstituted guanidine (**4**) the tautomers B_1, B_2, and B_3 are identical, and thus the microscopic constants are the same ($K_{a_1} = K_{a_2} = K_{a_3} = K_{a_s}$), and all of the pK_T values are equal to zero. Equation (1) for the measured pK_{a_m} values of tautomeric mixture gives equation (2).

$$pK_{a_m} = pK_{a_s} - \log 3 \qquad (2)$$

For symmetrically disubstituted guanidines (**1**) and (**2**), when $R^x = R^y$, both tautomers B_1 and B_2 are identical, but differ from tautomer B_3, and thus $K_{a_1} = K_{a_2} \neq K_{a_3}$, $pK_{T(12)} = 0$ and $pK_{T(13)} = pK_{T(23)}$. Similarly for guanidines (**3**) tautomers B_2 and B_3 are the same, and thus $K_{a_1} \neq K_{a_2} = K_{a_3}$, $pK_{T(12)} = pK_{T(13)}$, and $pK_{T(23)} = 0$. The measured dissociation constants for guanidines (**1**) and (**2**), when $R^x = R^y$, and guanidines (**3**) are expressed by equations (3) and (4), respectively.

$$K_{a_m} = 2K_{a_1} + K_{a_3} \qquad (3)$$

$$K_{a_m} = K_{a_1} + 2K_{a_2} \qquad (4)$$

The three tautomeric equilibria constants $K_{T(ij)}$ between tautomers B_i and B_j, defined as $K_{T(ij)} = (B_i)/(B_j)$, obey equation (5). It is easy to show that the ratio of the concentration of

$$K_{T(12)}K_{T(23)} = K_{T(13)} \qquad (5)$$

tautomers B_i and B_j is determined by their basicities. The $pK_{T(ij)}$ values are the difference of the pK_a values of the pair of corresponding tautomers B_i and B_j [equation (6)].

$$pK_{T(ij)} = pK_{a_i} - pK_{a_j} = \Delta pK_{a(ij)} \qquad (6)$$

The microscopic dissociation constants of single tautomers, and thus the pK_T values, are not experimentally accessible by the basicity method. However, the pK_T values can be estimated from some general equations between pK_T and parameters of structure obtained by application of correlation analysis methods to the study of the equilibria from the Scheme, or from the pK_a values of certain model compounds.

General Structure–Basicity Relations.—Studies on the influence of substitution on the basicity of non-tautomerizing guanidines have shown that the pK_a values of aryl derivatives obey the Hammett equation, and the pK_a values of alkyl, aralkyl, and aryl derivatives can be correlated with the pK_a values of corresponding amines.[4] The observed ρ and α values are close to the corresponding ρ and α values found for amidines. On this basis it can be assumed that structure–basicity relationships in guanidines are similar to those observed in amidines.[5,6]

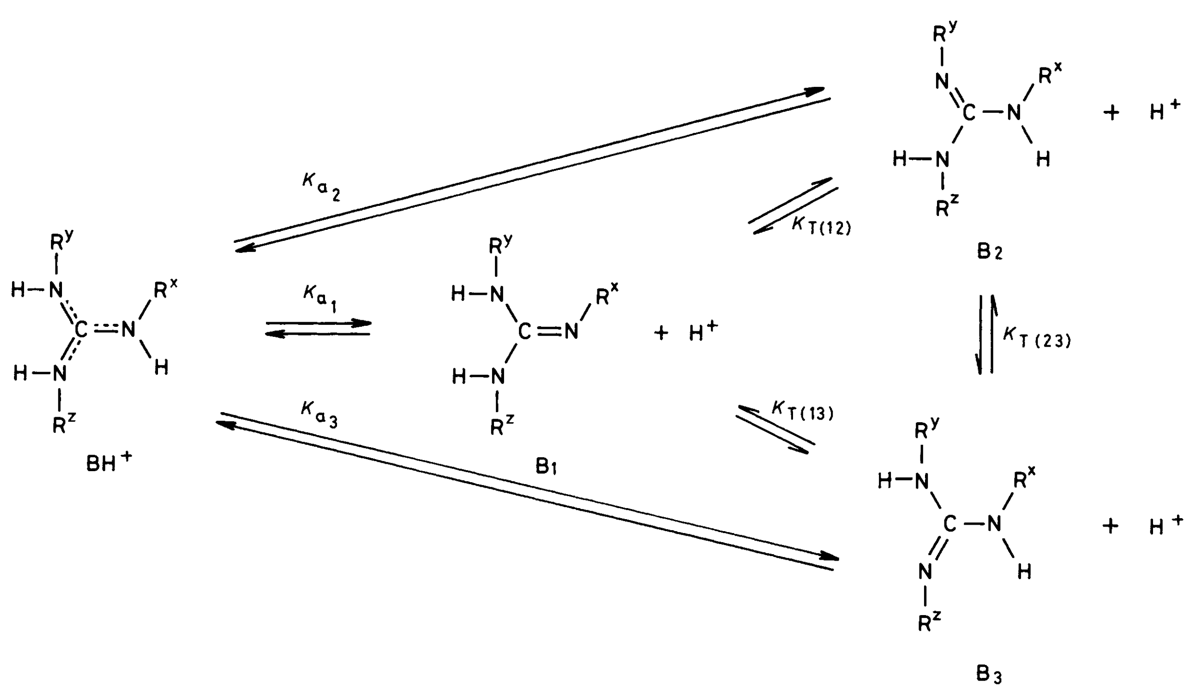
For aryl derivatives of guanidines (**1**), with $R^x = XC_6H_4$, $R^y = YC_6H_4$, and $R^z = ZC_6H_4$, the pK_a values of individual tautomers can be calculated from equations (7) or (8), where

$$pK_{a_i}(\mathbf{1}) = pK_a^\circ(\mathbf{1}) - \rho_{Im}\sigma_k^\circ - \rho_{Am}(\sigma_l^\circ + \sigma_n^\circ) \qquad (7)$$

$$pK_{a_i}(\mathbf{1}) = pK_{a_H} - \rho_{Im}(\sigma_k^\circ - \sigma_H^\circ) - \rho_{Am}(\sigma_l^\circ + \sigma_n^\circ - 2\sigma_H^\circ) \qquad (8)$$

$pK_a^\circ(\mathbf{1})$ is the microscopic pK_a value of guanidine (**1**) with unsubstituted phenyl rings at each of the nitrogen atom (R^x, R^y, R^z = Ph), pK_{a_H} is the microscopic pK_a value of unsubstituted guanidine (**4**), when R^x, R^y, R^z = H. ρ_{Im} and ρ_{Am} parameters denote the sensitivity of the guanidine group to substitution at the imino and amino nitrogen atoms, and $\sigma_{k.l.n}^\circ$ are the σ° constants of substituents at the imino and the amino nitrogen atoms, respectively. $pK_a^\circ(\mathbf{1})$ and pK_{a_H} can be calculated, according to equation (2), from the measured pK_{a_m} values of corresponding guanidine.

Equation (8) for tautomers B_1, B_2, and B_3 in guanidines (**2**), with $R^x = XC_6H_4$ and $R^y = YC_6H_4$, gives equations (9)–(11),



(1) *N,N′,N″*-Trisubstituted guanidines, $R^x, R^y, R^z \neq H$
(2) *N,N′*-Disubstituted guanidines, $R^x, R^y \neq H, R^z = H$
(3) *N*-Monosubstituted guanidines, $R^x \neq H, R^y, R^z = H$
(4) Unsubstituted guanidine, $R^x, R^y, R^z = H$

Scheme.

respectively, where σ°_X, σ°_Y, and σ°_H are the σ° constants of substituents X, Y, and hydrogen atom.

$$pK_{a_1}(\mathbf{2}) = pK_{a_H} - \rho_{Im}(\sigma^\circ_X - \sigma^\circ_H) - \rho_{Am}(\sigma^\circ_Y - \sigma^\circ_H) \quad (9)$$

$$pK_{a_2}(\mathbf{2}) = pK_{a_H} - \rho_{Im}(\sigma^\circ_Y - \sigma^\circ_H) - \rho_{Am}(\sigma^\circ_X - \sigma^\circ_H) \quad (10)$$

$$pK_{a_3}(\mathbf{2}) = pK_{a_H} - \rho_{Am}(\sigma^\circ_X + \sigma^\circ_Y - 2\sigma^\circ_H) \quad (11)$$

For aryl derivatives of guanidines (**3**), with $R^x = XC_6H_4$, the relations for pK_a values of tautomers B_1 and B_2 are reduced to equations (12) and (13). Tautomer B_3 is the same as B_2 and thus $pK_{a_3}(\mathbf{3}) = pK_{a_2}(\mathbf{3})$.

$$pK_{a_1}(\mathbf{3}) = pK_{a_H} - \rho_{Im}(\sigma^\circ_X - \sigma^\circ_H) \quad (12)$$

$$pK_{a_2}(\mathbf{3}) = pK_{a_H} - \rho_{Am}(\sigma^\circ_X - \sigma^\circ_H) \quad (13)$$

The relations between measured pK_{a_m} values of tautomeric mixture and σ° constants can be obtained from equations (1) and corresponding equations (7)–(13). For guanidines (**1**) a non-linear relationship [(14) or (15)] is found. Relation (15) for guanidines (**2**) and (**3**) reduces to equations (16) and (17), respectively.

$$pK_{a_m}(\mathbf{1}) = pK^\circ_a(\mathbf{1}) - \log[10^{\rho_{Im}\sigma^\circ_X + \rho_{Am}(\sigma^\circ_Y + \sigma^\circ_Z)} + 10^{\rho_{Im}\sigma^\circ_Y + \rho_{Am}(\sigma^\circ_X + \sigma^\circ_Z)} + 10^{\rho_{Im}\sigma^\circ_Z + \rho_{Am}(\sigma^\circ_X + \sigma^\circ_Y)} \quad (14)$$

$$pK_{a_m}(\mathbf{1}) = pK_{a_H} - \log[10^{\rho_{Im}(\sigma^\circ_X - \sigma^\circ_H) + \rho_{Am}(\sigma^\circ_Y + \sigma^\circ_Z - 2\sigma^\circ_H)} + 10^{\rho_{Im}(\sigma^\circ_Y - \sigma^\circ_H) + \rho_{Am}(\sigma^\circ_X + \sigma^\circ_Z - 2\sigma^\circ_H)} + 10^{\rho_{Im}(\sigma^\circ_Z - \sigma^\circ_H) + \rho_{Am}(\sigma^\circ_X + \sigma^\circ_Y - 2\sigma^\circ_H)}] \quad (15)$$

$$pK_{a_m}(\mathbf{2}) = pK_{a_H} - \log[10^{\rho_{Im}(\sigma^\circ_X - \sigma^\circ_H) + \rho_{Am}(\sigma^\circ_Y - \sigma^\circ_H)} + 10^{\rho_{Im}(\sigma^\circ_Y - \sigma^\circ_H) + \rho_{Am}(\sigma^\circ_X - \sigma^\circ_H)} + 10^{\rho_{Am}(\sigma^\circ_X + \sigma^\circ_Y - 2\sigma^\circ_H)}] \quad (16)$$

$$pK_{a_m}(\mathbf{3}) = pK_{a_H} - \log[10^{\rho_{Im}(\sigma^\circ_X - \sigma^\circ_H)} + 2 \times 10^{\rho_{Am}(\sigma^\circ_X - \sigma^\circ_H)}] \quad (17)$$

As the ρ_{Im} and ρ_{Am} values are not the same (ρ_{Im} is about twice higher than ρ_{Am} value) the relations between pK_{a_m} and substituent constant are by no means a straight line. The only exceptions are symmetrically *N,N′,N″*-trisubstituted guanidines (**1**), when $R^x = R^y = R^z$. For aryl derivatives equation (15) implies that in such a case pK_{a_m} values should obey the linear Hammett equation (18).

$$pK_{a_m} = pK_{a_H} - \log 3 - (\rho_{Im} + 2\rho_{Am})(\sigma^\circ_X - \sigma^\circ_H) \quad (18)$$

In the case of symmetrically disubstituted guanidines (**1**) and (**2**), when $R^x = R^y$, both tautomers B_1 and B_2 are identical but differ from tautomer B_3, and thus equations (14) or (15) and (16) are non-linear for aryl derivatives.

Summarizing, the measured dissociation constants (pK_{a_m}) in all cases of guanidines studied, except symmetrically *N,N′,N″*-trisubstituted guanidines (**1**), should obey a non-linear relation (15). The second hydrogen on the amino nitrogen atoms in guanidines (**2**) and (**3**) can be treated as a substituent with a σ°_H constant. The relation found for guanidines (**1**) can be used for guanidines (**2**) and (**3**). The pK_a values of individual tautomers B_1, B_2, and B_3 for all types of guanidines (**1**)–(**3**) can be predicted from the linear relation (8). Equations (9)–(13) result directly from relation (8).

General Structure–Tautomerism Relationships.—Relations between pK_T values and substituent constants can be obtained from equation (6) and corresponding equations (7)–(13). In guanidines (**1**) the three tautomeric equilibrium constants obey equations (19)–(21), where $\rho_T = \rho_{Im} - \rho_{Am}$. In guanidines (**2**)

$$pK_{T(12)}(\mathbf{1}) = -\rho_T(\sigma^\circ_X - \sigma^\circ_Y) \quad (19)$$

$$pK_{T(23)}(\mathbf{1}) = -\rho_T(\sigma^\circ_Y - \sigma^\circ_Z) \quad (20)$$

$$\mathrm{p}K_{\mathrm{T}(13)}(\mathbf{1}) = -\rho_{\mathrm{T}}(\sigma^{\circ}_{\mathrm{X}} - \sigma^{\circ}_{\mathrm{Z}}) \qquad (21)$$

the $\mathrm{p}K_{\mathrm{T}(12)}$, $\mathrm{p}K_{\mathrm{T}(23)}$, and $\mathrm{p}K_{\mathrm{T}(13)}$ values obey relations (19), (22), and (23), respectively. In guanidines (**3**) tautomers B_2 and B_3 are the same, and thus $\mathrm{p}K_{\mathrm{T}(23)} = 0$ and $\mathrm{p}K_{\mathrm{T}(12)} = \mathrm{p}K_{\mathrm{T}(13)}$. For $\mathrm{p}K_{\mathrm{T}(12)}$ relation (23) is obtained.

$$\mathrm{p}K_{\mathrm{T}(23)}(\mathbf{2}) = -\rho_{\mathrm{T}}(\sigma^{\circ}_{\mathrm{Y}} - \sigma^{\circ}_{\mathrm{H}}) \qquad (22)$$

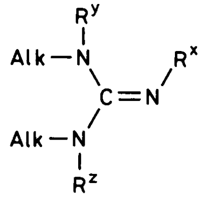
$$\mathrm{p}K_{\mathrm{T}(13)}(\mathbf{2}) = -\rho_{\mathrm{T}}(\sigma^{\circ}_{\mathrm{X}} - \sigma^{\circ}_{\mathrm{H}}) \qquad (23)$$

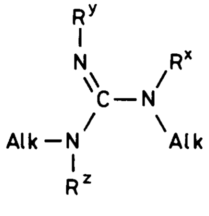
Generally the $\mathrm{p}K_{\mathrm{T}}$ values obey linear relationships. Equations (19)–(23) can be expressed by relation (24), where $\mathrm{p}K_{\mathrm{T}(ij)}$ is the tautomeric equilibrium constant between tautomers B_i and B_j, ρ_{T} denotes the sensitivity of the $-\mathrm{NH}-\overset{|}{\mathrm{C}}=\mathrm{N}-$ group to the different effects of the substituent on the imino and the amino nitrogen atoms, and $\Delta\sigma^{\circ}_i$ is the difference of the σ° constants of substituents on the imino and the amino nitrogen atoms in tautomer B_i ($\Delta\sigma^{\circ}_i = \sigma^{\circ}_{\mathrm{Im}} - \sigma^{\circ}_{\mathrm{Am}}$). The second hydrogen atom on the amino nitrogen atom in guanidines (**2**) and (**3**) is treated as a substituent with a $\sigma^{\circ}_{\mathrm{H}}$ constant.

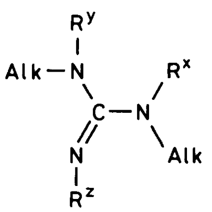
$$\mathrm{p}K_{\mathrm{T}(ij)} = -\rho_{\mathrm{T}}\Delta\sigma^{\circ}_i \qquad (24)$$

The values of tautomeric equilibrium constants depend on the effects of the substituents on the imino nitrogen atom, which is the site of protonation, and on the amino nitrogen atom, which is the proton donor in the prototropic tautomerism. For all types of tautomerizing guanidines, the proton is transferred from the amino to the imino nitrogen atom, as in the case of tautomerizing amidines ($-\mathrm{NH}-\mathrm{CR}=\mathrm{N}- \rightleftharpoons -\mathrm{N}=\mathrm{CR}-\mathrm{NH}-$). The relation [(24)] obtained for this is similar to that found previously.[1–3]

General Methods for pK_{T} *Prediction.*—For the prediction of the $\mathrm{p}K_{\mathrm{T}}$ values in guanidines (**1**)–(**3**) the general structure–tautomerism relation (24) can be applied, using the ρ_{Im} and ρ_{Am} values obtained for the corresponding non-tautomerizing guanidines, *e.g.* methyl derivatives, as was shown in the previously studied compounds.[1–3] It seems possible that using a uniform scale of substituent constants representing the polar effects of substituents on the nitrogen atoms, it will be possible to predict the $\mathrm{p}K_{\mathrm{T}}$ values for tautomerizing guanidines containing substituents of any kind, as in the case of formerly investigated amidines.[5,6]


(**1**) - B$'_1$


(**1**) - B$'_2$


(**1**) - B$'_3$

When investigation of the series of guanidines (**1**)–(**3**) is impossible, the $\mathrm{p}K_{\mathrm{T}}$ values can be predicted on the basis of the $\mathrm{p}K_{\mathrm{a}}$ measurements of corresponding alkyl derivatives of three tautomers B_1, B_2, and B_3.

For guanidines (**1**) the method used by Katritzky *et al.*[7] can be applied. According to this method, the $\mathrm{p}K_{\mathrm{T}}$ values can be estimated as the difference of the $\mathrm{p}K_{\mathrm{a}}$ values of corresponding pair of alkyl-derivatives [(**1**)-B$'_1$, (**1**)-B$'_2$, and (**1**)-B$'_3$]. Equation (25) is used, where *i* and *j* are the numbers of corresponding alkyl-derivatives.

$$\mathrm{p}K_{\mathrm{T}(ij)}(\mathbf{1}) = \mathrm{p}K'_{\mathrm{a}_i}(\mathbf{1}) - \mathrm{p}K'_{\mathrm{a}_j}(\mathbf{1}) \qquad (25)$$

In the case of symmetrically disubstituted guanidines (**1**), when $\mathrm{R}^x = \mathrm{R}^y$, $\mathrm{p}K_{\mathrm{T}(12)} = 0$ and $\mathrm{p}K_{\mathrm{T}(13)} = \mathrm{p}K_{\mathrm{T}(23)}$ (*vide infra*). The $\mathrm{p}K_{\mathrm{T}(13)}$ value can be calculated from equation (25) as the difference of the $\mathrm{p}K_{\mathrm{a}}$ values of derivatives (**1**)-B$'_1$ and (**1**)-B$'_3$, where $\mathrm{R}^x = \mathrm{R}^y$.

For guanidines (**2**), the method proposed for *N*-monosubstituted amidines[2] can be used. The $\mathrm{p}K_{\mathrm{T}}$ values can be determined on the basis of the $\mathrm{p}K_{\mathrm{a}}$ values of corresponding derivatives: (**2**)-B$'_1$, (**2**)-B$'_2$, (**2**)-B$'_3$, (**2**)-B$''_1$, (**2**)-B$''_2$, (**2**)-B$''_3$, and (**2**)-B$'''_3$. Equations (26)–(28) are used, where $\mathrm{p}K''_{\mathrm{a}_3}(\mathbf{2})$ and $\mathrm{p}K'''_{\mathrm{a}_3}(\mathbf{2})$ are the microscopic $\mathrm{p}K_{\mathrm{a}}$ values of symmetrically substituted *N*,*N′*-dialkylguanidines (**2**)-B$''_3$ and (**2**)-B$'''_3$, and thus they are *ca.* log 2 higher than the measured $\mathrm{p}K_{\mathrm{a}_\mathrm{m}}$ values.[3]

$$\mathrm{p}K_{\mathrm{T}(12)}(\mathbf{2}) = \mathrm{p}K'_{\mathrm{a}_1}(\mathbf{2}) - \mathrm{p}K'_{\mathrm{a}_2}(\mathbf{2}) \qquad (26)$$

$$\mathrm{p}K_{\mathrm{T}(13)}(\mathbf{2}) = \mathrm{p}K'_{\mathrm{a}_1}(\mathbf{2}) - \mathrm{p}K'_{\mathrm{a}_3}(\mathbf{2}) + \mathrm{p}K''_{\mathrm{a}_3}(\mathbf{2}) - \mathrm{p}K''_{\mathrm{a}_1}(\mathbf{2}) \qquad (27)$$

$$\mathrm{p}K_{\mathrm{T}(23)}(\mathbf{2}) = \mathrm{p}K'_{\mathrm{a}_2}(\mathbf{2}) - \mathrm{p}K'_{\mathrm{a}_3}(\mathbf{2}) + \mathrm{p}K'''_{\mathrm{a}_3}(\mathbf{2}) - \mathrm{p}K''_{\mathrm{a}_2}(\mathbf{2}) \qquad (28)$$

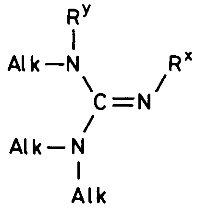
In symmetrically disubstituted guanidines (**2**), when $\mathrm{R}^x = \mathrm{R}^y$, $\mathrm{p}K_{\mathrm{T}(12)} = 0$ and $\mathrm{p}K_{\mathrm{T}(13)} = \mathrm{p}K_{\mathrm{T}(23)}$ (*vide infra*). The $\mathrm{p}K_{\mathrm{T}(13)}$ value can be calculated on the basis of the $\mathrm{p}K_{\mathrm{a}}$ values of derivatives (**2**)-B$'_1$, (**2**)-B$'_3$, (**2**)-B$''_1$, and (**2**)-B$''_3$, where $\mathrm{R}^x = \mathrm{R}^y$, using equation (27).

For guanidines (**3**) $\mathrm{p}K_{\mathrm{T}(12)} = \mathrm{p}K_{\mathrm{T}(13)}$ and $\mathrm{p}K_{\mathrm{T}(23)} = 0$. For $\mathrm{p}K_{\mathrm{T}}$ prediction the method proposed for *N*-monosubstituted amidines[2] can be applied. The $\mathrm{p}K_{\mathrm{T}(12)}$ value can be estimated from the $\mathrm{p}K_{\mathrm{a}}$ values of two pairs of alkyl derivatives of tautomers B_1 and B_2 [(**3**)-B$'_1$, (**3**)-B$'_2$, (**3**)-B$''_1$, and (**3**)-B$''_2$] using equation (29), where $\mathrm{p}K''_{\mathrm{a}_2}(\mathbf{3})$ is the microscopic $\mathrm{p}K_{\mathrm{a}}$ value of symmetrically substituted *N*,*N*,*N′*,*N″*-tetra-alkylguanidine (**3**)-B$''_2$, and thus it is about log 2 higher than the measured $\mathrm{p}K_{\mathrm{a}_\mathrm{m}}$ value.[3]

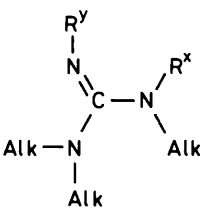
$$\mathrm{p}K_{\mathrm{T}(12)}(\mathbf{3}) = \mathrm{p}K'_{\mathrm{a}_1}(\mathbf{3}) - \mathrm{p}K'_{\mathrm{a}_2}(\mathbf{3}) + \mathrm{p}K''_{\mathrm{a}_2}(\mathbf{3}) - \mathrm{p}K''_{\mathrm{a}_1}(\mathbf{1}) \qquad (29)$$

pK_{T} *Prediction for* N-*Aryl-*, N,N′-*Diaryl- and* N,N′,N″-*Triarylguanidines.*—The methods presented above, based on correlation analysis, have been applied to prediction of $\mathrm{p}K_{\mathrm{T}}$ values for several aryl derivatives of tautomerizing guanidines (**1**)–(**3**).

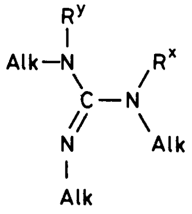
According to literature reports it has been found, by u.v., i.r., and n.m.r. methods, that aryl groups are attached to the imino nitrogen atom rather than the amino nitrogen,[8–10] and that *N*-arylguanidines exist predominantly as the arylimino tautomer, On this basis it can be assumed that for *N*-arylguanidines (**3**; $\mathrm{R}^x = \mathrm{XC_6H_4}$ and R^y, $\mathrm{R}^z = \mathrm{H}$) their measured $\mathrm{p}K_{\mathrm{a}_\mathrm{m}}$ values are approximately equivalent to the $\mathrm{p}K_{\mathrm{a}}$ values of the predominant tautomer B_1 ($\mathrm{p}K_{\mathrm{a}_1} = \mathrm{p}K_{\mathrm{a}_\mathrm{m}}$), and thus they should obey equation (12). The $\mathrm{p}K_{\mathrm{a}}$ values measured in water[11] correlate very well



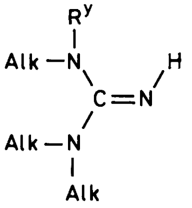
(**2**)-B_1'



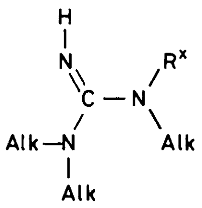
(**2**)-B_2'



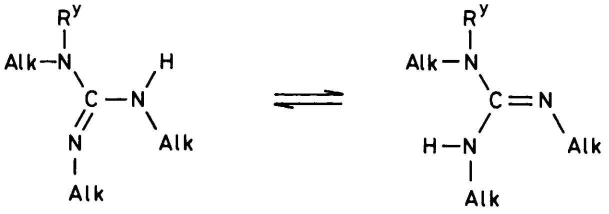
(**2**)-B_3'



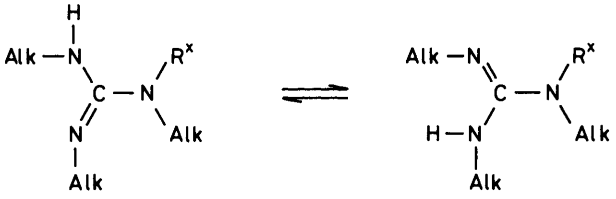
(**2**)-B_1''



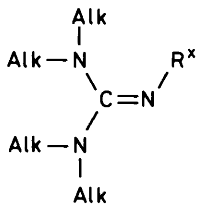
(**2**)-B_2''



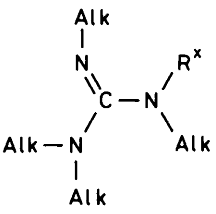
(**2**)-B_3''



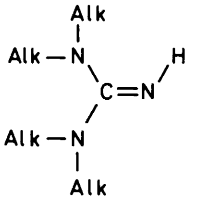
(**2**)-B_3'''



(**3**)-B_1'



(**3**)-B_2'



(**3**)-B_1''

(**3**)-B_2''

(r = 0.999) with σ° substituent constants.[12] The value obtained for the slope of regression line (ρ = 2.18) is a measure of the transmission of the substituent effects through a phenyl ring to the imino nitrogen atom, *e.g.* it is the value of ρ_{Im} parameter. Moreover, in the literature[4] it has been found that in ethanol the slopes of regression lines for non-tautomerizing guanidines are close to those obtained for formamidines. In the case of N^1-methyl-N^1,N^2-diarylformamidines the ratio $\rho_{\mathrm{Im}}/\rho_{\mathrm{Am}}$ is equal to 1.90.[13] Assumption that the ratio is similar in water gives ρ_{Am} = 1.15. This value can be used for guanidines.

For *N*-arylguanidines (**3a–e**) the p$K_{\mathrm{T(12)}}$ values have been estimated from equation (27), using $\rho_{\mathrm{T}} = \rho_{\mathrm{Im}} - \rho_{\mathrm{Am}} = 1.03$ and $\sigma_{\mathrm{H}}^{\circ} = -1.49$.[2] Calculated p$K_{\mathrm{T(12)}}$ values and the amounts of tautomers B_1 and B_2 are summarized in Table 1. The p$K_{\mathrm{T(13)}}$ values are equal to the p$K_{\mathrm{T(12)}}$ values, and p$K_{\mathrm{T(23)}}$ = 0. The results obtained confirm the literature conclusion that the arylimino tautomer B_1 prevails in *N*-arylguanidines (**3**). In some cases the concentration of the arylamino tautomer B_2 or B_3 can be undetectable. The pK_{a} values of single tautomers can be predicted from equations (12) and (13), and the p$K_{\mathrm{a_m}}$ values of

Table 1. pK_a and pK_T values for *N*-arylguanidines (**3**; $R^x = XC_6H_4$, R^y, R^z = H) in water at 25 °C.

	Substituent	pK_{a_m}				
Compound	X	Calculated	Measured	$pK_{T(12)}$	$B_1{}^a$/mol%	$B_2 = B_3{}^a$/mol%
(3a)	4-NO_2	9.14	9.28 [b]	−2.4	99.2	0.4
(3b)	4-Cl	10.37	10.5 [b]	−1.8	96.8	1.6
(3c)	H	10.89	11.0 [b] 10.77 [c]	−1.5	94.0	3.0
(3d)	4-Me	11.17	11.4 [b]	−1.4	92.6	3.7
(3e)	4-OMe	11.36	11.5 [b]	−1.3	90.8	4.6

[a] Calculated from equations $K_{T(12)} = x/y$ and $x + 2y = 1$, where x and y are the mole fractions of B_1 and B_2, respectively. [b] As in ref. 11. [c] As in ref. 14.

Table 2. pK_T values in water predicted for *N,N′,N″*-triarylguanidines (**1**; $R^x = XC_6H_4$, $R^y = YC_6H_4$, $R^z = ZC_6H_4$) and *N,N′*-diarylguanidines (**2**; $R^x = XC_6H_4$, $R^y = YC_6H_4$, R^z = H).

	Substituents								
Compound	X	Y	Z	$pK_{T(12)}$	$pK_{T(23)}$	$pK_{T(13)}$	$B_1{}^a$/mol%	$B_2{}^a$/mol%	B_3/mol%
(1a)	4-Me	H	H	0.14	0	0.14	26.6	36.7	36.7
(1b)	H	H	H	0	0	0	33.3	33.3	33.3
(1c)	4-Cl	H	H	−0.25	0	−0.25	47.0	26.5	26.5
(1d)	4-NO_2	H	H	−0.84	0	−0.84	77.6	11.2	11.2
(1e)	4-Me	4-Cl	H	0.39	−0.25	0.14	20.7	50.8	28.5
(1f)	4-Me	4-NO_2	H	0.98	−0.84	0.14	8.4	80.0	11.6
(1g)	4-Cl	4-NO_2	H	0.60	−0.84	−0.25	18.0	71.6	10.4
(1h)	4-Me	4-Cl	4-NO_2	0.39	0.60	0.98	7.6	18.6	73.8
(2a)	4-Me	H		0.14	−1.53	−1.40	40.9	56.5	2.6
(2b)	H	H		0	−1.53	−1.53	49.3	49.3	1.4
(2c)	4-Cl	H		−0.25	−1.53	−1.78	63.3	35.6	1.1
(2d)	4-NO_2	H		−0.84	−1.53	−2.38	87.0	12.6	0.4
(2e)	4-Me	4-Cl		0.39	−1.78	−1.40	28.4	69.8	1.8
(2f)	4-Me	4-NO_2		0.98	−2.38	−1.40	9.4	90.2	0.4
(2g)	4-Cl	4-NO_2		0.60	−2.38	−1.78	20.0	79.7	0.3
(2h)	4-NO_2	4-NO_2		0	−2.38	−2.38	49.9	49.9	0.2

[a] Calculated from equations $K_{T(12)} = x/y$, $K_{T(23)} = y/(1 - x - y)$, where x and y are the mole fractions of B_1 and B_2, respectively.

tautomeric mixture from equation (17), using $\rho_{Im} = 2.18$, $\rho_{Am} = 1.15$, and $pK_{a_H} = 14.16$. The microscopic pK_{a_H} value is obtained, according to equation (2), by addition of log 3 to its pK_{a_m} value measured in water.[15] Calculated pK_{a_m} values are compared with those measured in water (Table 1). As seen, the pK_{a_m} values can be predicted with satisfactory accuracy (error < 0.3 pK_a units) on the basis of the non-linear equation (17).

For *N,N′,N″*-triarylguanidines (**1a**–**h**) and *N,N′*-diarylguanidines (**2a**–**h**) the pK_T values have been also estimated (Table 2) on the basis of equation (27). The error in the pK_T prediction does not exceed 0.5 pK_T units. The results obtained show that the tautomer containing the stronger electron-withdrawing substituents at the imino nitrogen atom predominates in tautomeric mixture. However in the case of symmetrically disubstituted guanidines (**1**) two tautomers are the same, and thus, in some cases, the concentration of third tautomer, when it contains the stronger electron-withdrawing substituent at the imino nitrogen atom, is smaller than the sum of the concentrations of these two identical tautomers, *e.g.* in compound (**1c**). For *N,N′*-diarylguanidines (**2a**–**h**) the concentration of tautomer B_3, with the hydrogen atom at the imino nitrogen atom, is very small and in some cases is undetectable.

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