Notes

Studies on Amphiprotic Compounds.[1] 4. Application of the α^H_2 Hydrogen-Bonding Acidity Scale to Complexation between Pyridine *N*-Oxide and Monomeric Hydrogen-Bond Donors in Cyclohexane

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Introduction

Equilibrium constants (as log K_c values) for the 1:1 hydrogen-bond (HB) complexation, eq 1, in tetrachloromethane solvent at 25.0 °C have been analyzed to yield new scales of solute HB acidity and solute HB basicity.[2-5]

$$AH + B \underset{}{\overset{K_c}{\rightleftharpoons}} AH\cdots B \qquad (1)$$

In eq 1, AH is the HB donor and B is the HB acceptor, all species being present as the monomeric form in dilute solution. It was established that log K_c values for a series of acids against a given reference base in CCl_4 could be represented by eq 2, in which L_B and D_B characterize the

$$\log K_c \text{ (series of acids against reference base B)} = L_B \log K^H_A + D_B \qquad (2)$$

reference base and log K^H_A is a new parameter that characterizes the HB acidity of the series of acids.[2,3] Forty-five equations of type 2 yielded log K^H_A values for 186 HB acids. In this analysis, use was made of the observation that all the 45 equations intersected at a point where log $K^H_A = -1.1$, when equilibrium constants were expressed in $dm^3\ mol^{-1}$ at 298 K. This observation then enables a HB acidity parameter, α^H_2, to be defined with an origin of zero, via eq 3.[2,3]

$$\alpha^H_2 = (\log K_c + 1.1)/4.6363 \qquad (3)$$

The scaling factor of 4.6363 serves only to yield a suitable spread of α^H_2. A set of equations, similar to eq 2, could be constructed to give a general HB basicity parameter, log K^H_B, which in turn was used to define a HB basicity scale with an origin of zero, through eq 4.[4,5]

$$\beta^H_2 = (\log K^H_B + 1.1)/4.6363 \qquad (4)$$

Finally, the α^H_2 and β^H_2 scales could be combined to give a single expression for log K_c values in tetrachloromethane, eq 5.[6]

$$\log K_c = 7.354\alpha^H_2\beta^H_2 - 1.094 \qquad (5)$$

Equation 5 has been applied to a data matrix of 1312 experimental log K_c values with a correlation coefficient of 0.9956 and a standard deviation (sd) of 0.093 log units; 89 primary α^H_2 and 215 primary β^H_2 values are presently available.

Although tetrachloromethane is the most commonly used solvent in the measurement of K_c values for reaction 1, cyclohexane has also often been used and is probably the second most widely used solvent. It has been shown[7] that pyridine *N*-oxide (PyO) is a very convenient base for the determination of K_c values for reaction 1 in cyclohexane, particularly in cases where HA is either strongly self-associated or is a weak HB acid.

The present work is intended to link results obtained using PyO in cyclohexane[8] with the scales of HB acidity, α^H_2, and log K^H_A, set up with solvent tetrachloromethane.[2,3]

Results and Discussion

Here we report a series of equilibrium constants, K_{PyO} (in $dm^3\ mol^{-1}$) pertaining to equilibrium 6 in highly dilute

$$AH + OPy \rightleftharpoons AH\cdots OPy \qquad (6)$$

solution in cyclohexane at 23.3 °C. The experimental values given in Table I have been determined by UV–visible spectrometry, using a method already described.[7]

Important consequences and features of these results are as follows:

(1) A wide variety of HB acids, including the CH, NH, OH, and SH functionalities have been studied, and the results span a range of over 4 orders of magnitude in K_{PyO}.

(2) The parameters α^H_2 and K_{PyO} are related[9] through eq 7:

$$\alpha^H_2 = (0.069 \pm 0.028) + (0.185 \pm 0.010) \log K_{PyO} \qquad (7)$$

$$n = 22,\ r^2 = 0.986,\ \text{sd} = 0.03 \text{ in } \alpha^H_2 \text{ units}$$

This indicates that *the HB acidity ranking found in tetrachloromethane holds also for the system P_yO/cyclohexane.*

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(1) Part 3 in this series: Abboud, J.-L. M.; Roussel, C.; Gentric, E.; Sraidi, K.; Lauransan, J.; Guihéneuf, G.; Kamlet, M. J.; Taft, R. W. *J. Org. Chem.* **1988**, *53*, 1545.
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(9) Error limits for these correlations are *two* standard deviations.

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Table I. Experimental K_{PyO} and K_p Values for Reactions 1 and 9 and α^H_2 Acidity Parameters for Selected HB Proton Donors

proton donor	K_{PyO}[a]	K_p[b]	α^H_2[c]	α^H_2[d]	log K^H_A[c]
CH_3OH[e]	25.3 ± 1.3	2.2×10^4	0.37	0.33	0.603
C_2H_5OH[e]	18.9 ± 0.5	4.3×10^4	0.33	0.30	0.442
n-C_3H_7OH[e]	19.4 ± 0.6	–	0.33	0.30	0.363
i-C_3H_7OH[e]	18.7 ± 0.5	5.1×10^4	0.32	0.30	0.405
s-C_4H_9OH[e]	17.3 ± 0.4	–	0.32	0.29	–
t-C_4H_9OH[e]	18.0 ± 0.5	5.1×10^4	0.32	0.30	0.383
Cl_3CCH_2OH[f]	$(3.30 \pm 0.17) \times 10^2$	–	0.50	0.54	1.218
F_3CCH_2OH[e]	$(7.88 \pm 0.40) \times 10^2$	3.2×10^9	0.57	0.61	1.530
$(CF_3)_2CHOH$[e]	$(5.40 \pm 0.27) \times 10^3$	2.0×10^{12}	0.77	0.78	2.474
C_6H_5OH[f]	$(9.47 \pm 0.01) \times 10^2$	2.0×10^8	0.60	0.63	1.665
4-FC_6H_4OH[f]	$(1.87 \pm 0.03) \times 10^3$	6.3×10^9	0.63	0.69	1.818
4-ClC_6H_4OH[f]	$(2.23 \pm 0.01) \times 10^3$	4.0×10^{10}	0.67	0.70	2.007
3-$(CO_2CH_3)C_6H_4OH$[f]	$(2.25 \pm 0.04) \times 10^3$	–	–	0.69	–
C_6F_5OH[f]	$(4.85 \pm 0.02) \times 10^3$	–	0.76	0.76	2.441
C_2H_5SH[f]	0.584 ± 0.023	–	0.00	0.01	–1.182
n-C_3H_7SH[f]	0.667 ± 0.010	–	0.00	0.02	–1.182
i-C_3H_7SH[f]	0.652 ± 0.057	–	0.00	0.02	–1.182
t-C_4H_9SH[f]	0.735 ± 0.035	–	0.00	0.03	–1.182
C_6H_5CCH[f]	1.23 ± 0.03	–	0.12	0.07	–0.56
CH_2Cl_2[f]	2.41 ± 0.03	–	0.13	0.13	–0.50
Cl_3CH	4.73 ± 0.16	–	0.20	0.18	–0.185
$HCON(H)CH_3$[f]	50.5 ± 2.5	–	0.38[h]	0.38	0.676[h]
$CF_3CON(H)C_6H_5$[f]	$(8.78 \pm 0.44) \times 10^2$	–	–	0.62	–
pyrazole[g]	$(4.05 \pm 0.16) \times 10^2$	–	–	0.55	–
3(5)-methylpyrazole[g]	$(3.51 \pm 0.54) \times 10^2$	–	–	0.54	–
4-methylpyrazole[g]	$(3.29 \pm 0.16) \times 10^2$	–	–	0.53	–
3,5-dimethylpyrazole[g]	$(2.32 \pm 0.16) \times 10^2$	–	–	0.54	–
3,4,5-trimethylpyrazole[g]	$(2.00 \pm 0.16) \times 10^2$	–	–	0.49	–
4-bromopyrazole[g]	$(1.05 \pm 0.06) \times 10^2$	–	–	0.63	–
3,5-methyl-4-bromopyrazole[g]	$(1.03 \pm 0.10) \times 10^2$	–	–	0.63	–
pyrrole[f]	40.3 ± 1.4	–	0.41	0.36	0.7934

[a] In $dm^3\ mol^{-1}$ in *c*-C_6H_{12} at 23.3 °C. [b] In atm^{-1} at 300 K. [c] See refs 2 and 3. [d] Calculated through eq 7. [e] Values taken from ref 1. [f] This work and ref 8. [g] Values from ref 12. [h] Value for *N*-methylacetamide. [i] Estimated value.

(3) A direct comparison between log K_{PyO} and log K^H_A yields eq 8:

$$\log K^H_A = (-0.85 \pm 0.11) + (0.885 \pm 0.053) \log K_{PyO} \quad (8)$$

$$n = 21,\ r^2 = 0.986,\ \text{sd} = 0.15 \text{ log units}$$

The slope of this linear relationship (0.89) is a direct measure of the relative sensitivity of two model processes. The P_yO/*c*-C_6H_{12} system is seen to be more sensitive than the general acid/CCl_4 system by a factor of 1.00:0.89.

(4) Caldwell and Kebarle[10] have determined the equilibrium constants K_P for the formation of the 1:1 HB complex between iodide ion and several HB acids in the gas phase (reaction 9):

$$AH + I^- \rightleftarrows AH\cdots I^- \quad (9)$$

Values of K_P (in atm^{-1}) at 300 K are given in Table I. We find that α^H_2, K_{PyO}, and K_p are related through eqs 10 and 11:

$$\alpha^H_2 = (0.08 \pm 0.07) + (0.0564 \pm 0.0092) \log K_P \quad (10)$$

$$n = 9,\ r^2 = 0.965,\ \text{sd} = 0.04\ \alpha^H_2 \text{ units}$$

$$\log K_{PyO} = (-0.230 \pm 0.040) + (0.339 \pm 0.048) \log K_P \quad (11)$$

$$n = 9,\ r^2 = 0.968,\ \text{sd} = 0.19 \text{ log units}$$

Although the quality of these correlations is somewhat lower than that of eqs 7 and 8, it is clear that *the solution HB acidity ranking defined by* α^H_2 *or log* K_{PyO} *also holds in the gas phase* for the compounds listed in Table I,[11] at least in the case of the associations with large anions, for differential polarizability contributions from the hydrogen-bonding acids are then likely to be small.[10]

(5) Equation 4 provides a means of determining α^H_2 values from K_{PyO}. This method has been applied to several NH acids for which little or no information was so far available (see Table I). A comparison of the HB acidities of some NH and OH proton donors reveals that the HB acidities of pyrrole and *N*-methylformamide are comparable to, but larger than, that of methanol. Pyrazole is as acidic as 1,1,1-trifluoroethanol; 4-bromopyrazole and 1,1,1-trifluoroacetanilide are as strong as phenol. These comparisons highlight the *appreciable HB acidity of these NH acids as well as their large sensitivity to structural and substituent effects.*[12] Work is now under way to further extend the data base of K_{PyO} values for these families of compounds.

Experimental Section

The equilibrium constants have been determined by the same technique and with the same instruments used in previous studies.[7]

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(11) (a) A more extensive correlation, involving H_2O,[10a] several carboxylic acids,[10a] and phenols[10b] leads to eq 12:

$$\alpha^H_2 = (0.111 \pm 0.046) + (0.0534 \pm 0.053) \log K_P \quad (12)$$

$$n = 18,\ r^2 = 0.961,\ \text{sd} = 0.032\alpha^H_2 \text{ units}$$

The agreement between eqs 10 and 12 is, therefore, quite good. (b) At this point however, the existence of family-dependent relationships involving HB acids with other functionalities cannot be ruled out. An extension of the K_P data base should be carried out to ascertain this matter.

All the compounds were commercial, of the highest purity available, dried, and further purified by standard methods. Structures were confirmed by their IR and NMR spectra. Purities were checked by GLC and or TLC. The origin and treatment of c-C_6H_{12} and PyO have also been described.[7]

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Registry No. C_6H_5OH, 108-95-2; 4-FC_6H_4OH, 371-41-5; 4-ClC_6H_4OH, 106-48-9; 3-$(CO_2CH_3)C_6H_4OH$, 19438-10-9; C_6F_5OH, 771-61-9; C_2H_5SH, 75-08-1; n-C_3H_7SH, 107-03-9; i-C_3H_7SH, 75-33-2; t-C_4H_9SH, 75-66-1; C_6H_5CCH, 536-74-3; CH_2Cl_2, 75-09-2; Cl_3CH, 67-66-3; $HCONHCH_3$, 123-39-7; $CF_3CONHC_6H_5$, 404-24-0; Cl_3CCH_2OH, 115-20-8; PyO, 694-59-7; pyrrole, 109-97-7; pyrazole, 288-13-1; 3-methylpyrazole, 1453-58-3; 4-methylpyrazole, 7554-65-6; 3,5-dimethylpyrazole, 67-51-6; 3,4,5-trimethylpyrazole, 5519-42-6; 4-bromopyrazole, 2075-45-8; 3-methyl-4-bromopyrazole, 13808-64-5.

(12) This is in line with recent reports on the acidity and basicity of azoles, both in the gas phase and in solution (see, e.g.: Catalán, J.; Abboud, J.-L. M.; Elguero, J. In *Advances in Hetereocyclic Chemistry*; Katritzky, A. R., Ed.; Academic Press: New York, 1987; Vol. 41, pp 187–274).

An Improved One-Pot Method for the Stereoselective Synthesis of the (2*S*,3*R*)-3-Amino-2-hydroxy Acids: Key Intermediates for Bestatin and Amastatin

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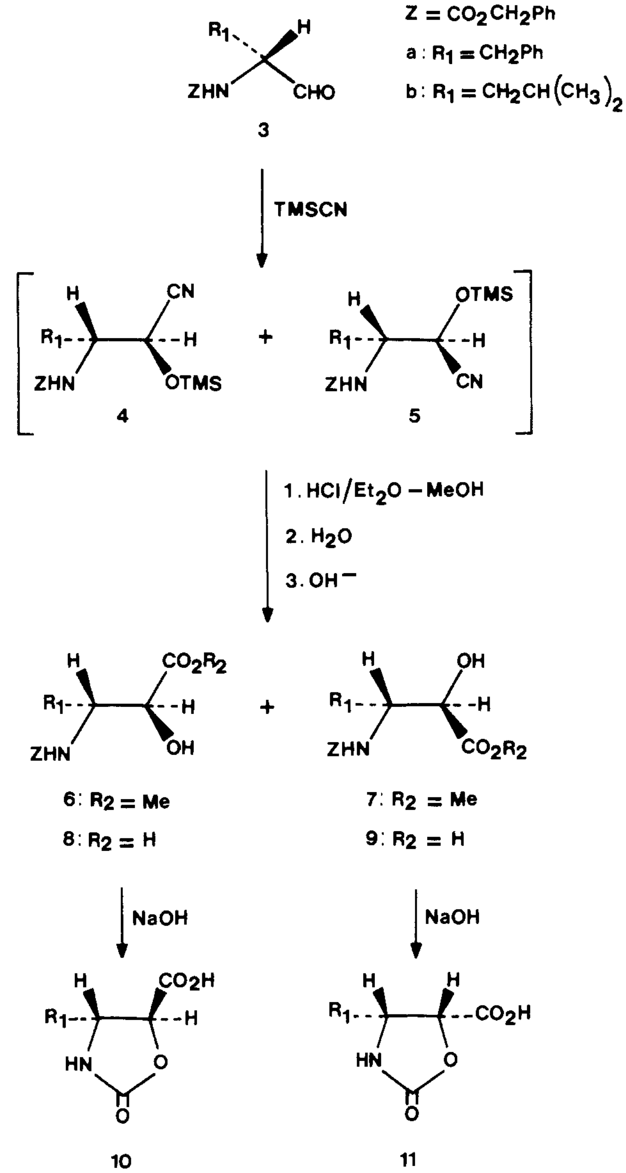
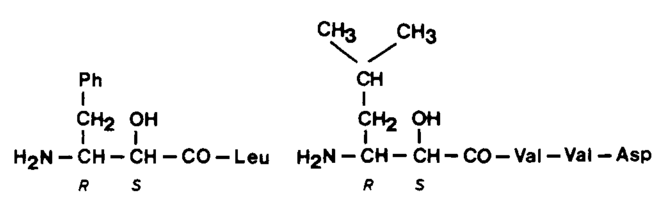
Bestatin (1), an aminopeptidase B and leucine-aminopeptidase inhibitor,[1] and amastatin (2), an aminopeptidase A inhibitor,[2] are two low molecular weight peptidic immunomodifiers,[3-6] with antitumor and antimicrobial activities.[7] The presence and absolute configurations of the (2*S*,3*R*)-3-amino-2-hydroxy-4-phenylbutanoic acid [(2*S*,3*R*)-AHPBA] and (2*S*,3*R*)-3-amino-2-hydroxy-5-methylhexanoic acid [(2*S*,3*R*)-AHMHA] residues in 1 and 2, respectively, are crucial for their bioactivities. Among the several methods reported for the preparation of AHPBA and AHMHA, key intermediates for the preparation of 1 and 2, that involving aqueous hydrolysis of the cyanohydrin, obtained from the corresponding N-protected α-amino aldehyde, has been the most extensively used.[8,9]

Scheme I



However, this method is not stereoselective, and, as deprotection occurs during hydrolysis, a protection step is required to separate the resulting diastereomers, and to form the peptidic bond. Therefore, the overall yield of N-protected AHPBA or AHMHA is low (<30%). Other methods give either (2*S*,3*R*)-*N*-Z-AHPBA (Z = benzyloxycarbonyl) stereoselectively, but in low overall yield (14%),[10] or as a racemic mixture of the threo[11,12] isomers of AHPBA in less than 30%.



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