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# On the Prediction of p$K_a$ Values of Amino Sugars

Shigeharu Inouye

*Central Research Laboratories, Meiji Seika Kaisha, Ltd.*[1]

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Acid dissociation constants (p$K_a$) are useful in structure determination of organic bases and acids.[2,3] Systematic investigation of the relationship between the p$K_a$ values and the structures of organic bases has led to the establishment of a method for predicting the p$K_a$ value,[4] which was successfully applied in structure determination of the Streptomyces antibiotics.[5] In the field of amino sugars, however, correlation of p$K_a$ with structure has been little studied.[6,7] Such a study is desirable not only for structure elucidation, but also for determination of the relative reactivities of the amino groups in amino sugars.

We have now measured the p$K_a$ values in aqueous solution of 25 amino sugars, together with 6 amino alcohols and alkylamine. The results were summarized in Table I, which indicated that the basic strength of an amino sugar is primarily dependent on the location of an amino group, and, to a less extent, on the steric requirement. Thus, the p$K_a$ values of the terminal amino groups in the six examples including a pentose (VIII), hexoses (X—XII) and disaccharides (XIII, XIV) fell in the narrow region of 8.8—8.9, while the p$K_a$ values of five 3-amino sugars (III—VII) were found in the region of 7.6—8.2. Most of 2-amino sugars (I, II, XII—IX) were much weaker bases than 3-amino sugars ($\Delta$p$K_a$, 0—1.0). 1-Amino sugars (XV, XVI) and 5-amino sugars (piperidinoses) (XX, XXI) were belonged to the weakest bases, whose p$K_a$ values lay in the range of 5—6. Since the p$K_a$ of the four classes of amino sugars mentioned above differed significantly from each other, it is possible to predict the position of an amino group by measuring p$K_a$ value of an amino sugar.

This fact was utilized for the assignment of the two p$K_a$ values of diamino sugars. Each of the titration curves of four diamino sugars (XXII—XXV) showed two inflection points, indicating the approximate separation of each successive step in the dissociation. Based on the observed p$K_a$ differences between 6-amino and 3-amino sugars and between 6-amino and 2-amino sugars, the higher p$K_a$ values (second dissociation constant) could be assigned to the terminal amino group and lower values (first dissociation constant) to the C-3 or C-2 amino group in the respective cases.

Of particular interest was the fact that the p$K_a$ values decreased regularly as the number of the electronegative groups such as hydroxyl, amino, acetamido, *etc.*, increased in the vicinity of basic center. For example, the p$K_a$ decrease in the order of 6-amino, 3-amino and 2-amino hexoses could be correlated with the number of polar groups attached to the adjacent $\beta$-carbon atoms (two carbon atoms away from the amino group), which increased one, two, three in that order. Unusually low p$K_a$ values of glycosylamines and piperidinoses

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Table I. p$K_a$ Values of Amino Sugars and Amino Alcohols in Aqueous Solution at 23±1°

| Compound | p$K_a$ Found | p$K_a$ Calcd. |
|---|---|---|
| Methyl 2–Amion–2–deoxy–*α*–D–glucopyranoside (I) | 7.54 | 7.4[x] |
| Methyl 2–Amino–2–deoxy–*β*–D–glucopyranoside (II) | 7.23[n] | 7.1 |
| Methyl 3–Amino–3–deoxy–*α*–D–glucopyranoside (III)[a] | 7.82 | 7.6 |
| Methyl 3–Amino–3–deoxy–*β*–L–glucopyranoside (IV)[a] | 7.58 | 7.6 |
| Methyl 3–Amino–3–deoxy–*α*–D–mannopyranoside (V)[a] | 8.08 | 7.9[x] |
| O–*α*–3–Amino–6–acetamido–3,6–dideoxy–D–glucopyranosyl–(1→4)–O–[*α*–3–acetamido–3–deoxy–D–glucopyranosyl–(1→6)]–2–deoxystreptamine (VI)[b] | 7.92 | 7.6 |
| O–*α*–3–Amino–6–acetamido–3,6–dideoxy–D–mannopyranosyl–(1→4)–O–[*α*–3–acetamido–3–deoxy–D–glucopyranosyl–(1→6)]–2–deoxystreptamine (VII)[b] | 8.17 | 7.9[x] |
| 1,2–O–Isopropylidene–5–amino–5–deoxy–*α*–D–xylofuranose (VIII)[c] | 8.84 | 8.9 |
| 1,2–O–Isopropylidene–5–amino–5–deoxy–*α*–D–glucofuranose (IX)[d] | 7.82 | 8.1 |
| Methyl 6–Amino–6–deoxy–*α*–D–glucopyranoside (X)[e] | 8.86 | 8.9 |
| Methyl 3–Acetamido–6–amino–3,6–dideoxy–*α*–D–glucopyranoside (XI)[a] | 8.84 | 8.8 |
| Methyl 3–Acetamido–6–amino–3,6–didoexy–*α*–D–mannopyranoside (XII)[a] | 8.80 | 8.8 |
| O–*α*–6–Acetamido–6–deoxy–D–glucopyranosyl–(1→4)–O–[*α*–3–acetamido–6–amino–3,6–dideoxy–D–glucopyranosyl–(1→6)]–2–deoxystreptamine (XIII)[f] | 8.90 | 8.8 |
| O–*α*–6–Acetamido–6–deoxy–D–glucopyranosyl–(1→4)–O–[*α*–3–acetamido–6–amino–3,6–dideoxy–D–mannopyranosyl–(1→6)]–2–deoxystreptamine (XIV)[g] | 8.91 | 8.8 |
| *β*–D–Glucopyranosylamine (XV) | 5.57[o] | 5.6 |
| *β*–D–Mannopyranosylamine (XVI))[h] | 5.35[o] | 5.6 |
| 2–Amino–2–deoxy–D–glucopyranose (XVII) | 7.67[p] | 7.5[x] |
| 2–Amino–2–deoxy–D–galactopyranose (XVIII) | 7.68[q] | 7.5[x] |
| 2–Amino–2–deoxy–D–mannopyranose (XIX) | 7.42[r] | 7.5[x] |
| 5–Amino–5–deoxy–D–xylopyranose (XX)[i] | 5.72[s] | 5.9[t] |
| 5–Amino–5–deoxy–D–glucopyranose (XXI)[j] | 5.32[u] | 5.0[t] |
| Methyl 3,6–Diamino–3,6–dideoxy–*α*–D–glucopyranoside (XXII)[a] | 7.28, 8.97 | 6.9, 8.9 |
| Methyl 3,6–Diamino–3,6–dideoxy–*α*–D–mannopyranoside (XXIII)[a] | 7.42, 8.95 | 7.2,[x] 8.9 |
| Methyl 3,6–Diamino–3,6–dideoxy–*α*–D–altropyranoside (XXIV)[k] | 7.35, 8.84 | 6.9, 8.9 |
| Methyl O–*α*–2,6–Diamino–2,6–dideoxy–L–idopyranosyl–(1→3)–*β*–D–ribopyranoside (XXV)[2] | 7.08, 8.96 | 6.7, 8.9 |
| 4,6–Diaminocyclohexane–1,2,3–triol (2–deoxystreptamine) (XXVI)[e] | 7.14, 8.95 | 6.9, 9.2 |
| 2–Amino–2–deoxy–D–glucitol (XXVII) | 8.81 | 8.7[x] |
| 2–Amino–2–(hydroxymethyl)–propane–1,3–diol (XXVIII) | 8.12[v] | 8.2[x] |
| 2–Amino–ethanol (XXIX) | 9.56 | 9.7 |
| 3–Amino–1–propanol (XXX) | 10.11 | 10.3 |
| Cyclohexylamine (XXXI) | 10.63[w] | 10.6 |
| *cis*–1,3–Diaminocyclohexane (XXXII)[9] | 8.29, 10.30[9] | 8.3, 10.6 |
| *trans*–1,3–Diaminocyclohexane (XXXIII)[9] | 8.54, 10.36[9] | 8.3, 10.6 |
| *trans*–2–Aminocyclohexanol (XXXIV)[m] | 9.63 | 9.7 |

*a*) S. Inouye, *Chem. Pharm. Bull.* (Tokyo), **14**, **902** (**1966**).
*b*) S. Inouye, *Chem. Pharm. Bull.* (Tokyo), **16**, **573** (**1968**).
*c*) S. Akiya and T. Osawa, *Yakugaku Zasshi*, **76**, 1276 (1956).
*d*) S. Inouye, T. Tsuruoka, T. Ito, and T. Niida, *Tetrahedron*, **24**, 2115 (1968).
*e*) H. Ogawa, T. Ito, S. Kondo, and S. Inoue, *Bull. Agr. Chem. Soc. Japan*, **23**, 289 (1959).
*f*) S. Inouye, *J. Antibiotics*, Ser A, **19**, 6 (1967).
*g*) S. Inouye, *Chem. Pharm. Bull.* (Tokyo), **15**, 1888 (1967).
*h*) H.S. Isbell and H.L. Frush, *J. Org. Chem.*, **23**, 1309 (1958).
*i*) H. Paulsen, F. Leupold, and K. Todt, *Ann.*, **692**, 200 (1966).
*j*) S. Inouye, T. Tsuruoka, and T. Niida, *J. Antibiotics*, Ser A, **18**, 288 (1966).
*k*) S. Inouye, *Chem. Pharm. Bull.* (Tokyo), **14**, 1058 (1966).
*l*) S. Inouye and H. Ogawa, *J. Chromatog.*, **13**, 536 (1964).
*m*) F.R. Hewgill and R.R. Jeffries, *J. Chem. Soc.*, 805 (1956).
*n*) literature value, 7.15 at 30°.[7]
*o*) approximate p$K_a$ value of *β*–anomer.
*p*) approximate p$K_a$ of a mixture of *α*–anomer (59%) and *β*–anomer (41%). literature values, 7.8 at 25—26°,[6] 7.47 at 30°.[7]
*q*) approximate p$K_a$ of a mixture of *α*–anomer (55%) and *β*–anomer (45%). literature value, 7.7 at 25—26°.[6]
*r*) approximate p$K_a$ of a mixture of *α*–anomer (38%) and *β*–anomer (62%). literature value, 7.3 at 25—26°.[6]
*s*) approximate p$K_a$ of a mixture of *α*–anomer (42%), *β*–anomer (35%) and a piperideine or vinylamine species (23%).
*t*) p$K_a$ value subtracted from the p$K_a$ of piperidine (11.2).
*u*) approximate p$K_a$ of a mixture of *α*–anomer (60%) and *β*–anomer (40%).
*v*) literature vlaue, 8.18.[14]
*w*) literature value, 10.64.[14]
*x*) p$K_a$ value corrected for the base–strengthening *cis*–effect.

were ascribable to much stronger base-weakening effect of the oxygen atom substituted at the same ($\alpha$-) carbon atom as the dissociating group.

Based on these observations, an attempt was made to predict the p$K_a$ values of amino sugars, using the modified procedure of Clark and Perrin's.[4] The starting p$K_a$ value for the calculation was 10.6 of cyclohexylamine (XXXI), from which was subtracted 2.7 units when a hydroxyl group was substituted at the same carbon atom as an amino group, 0.9 unit when substituted at the $\beta$-carbon atom, 0.3 unit when substituted at the $\gamma$-carbon atom (three carbon atoms away from the basic center) and 0.1 unit when substituted at the $\delta$-carbon atom (four carbon atoms away from the basic center). The decrease of the parameter per a single bond was 1/3, which was very close on that found for carboxylic acids (1/2.8).[8] To an alkoxy group attached to the $\beta$-carbon, was given a slightly larger parameter of 1.1, with the same transmission coefficient of 1/3. This was derived from the fact that the p$K_a$ value of 2-amino glucose (XVII) decreased associated with 1-O-methylation ($\Delta$p$K_a$, 0.3), 3-O-methylation ($\Delta$p$K_a$, 0.35)[7] and 3,4,6-tri-O-methylation ($\Delta$p$K_a$, 0.55).[7] From the comparison of the p$K_a$ values of diamino sugars, were estimated the parameters for an amino (0.8) and an acetamido groups (1.4) attached to the $\beta$-carbons with the transmission coefficient of 1/3, and an ammonium group (1.8) at the $\gamma$-carbon. The magnitudes of these base-weakening parameters were very close to those presented by Clark and Perrin,[4] except for that of a hydroxyl group. They suggested variable parameters in the range of 0.4 and 1.2 p$K_a$ units for the effect of the $\beta$-hydroxyl group in their calculation. Another large difference lay in the transmission coefficient. The coefficient of 1/3 used in this paper accounted better for the observed p$K_a$ values than the coefficient of 1/2 as they proposed.

The base-weakening effect of a pyranose ring was approximated to the combined effects of the two oxygen atoms of pentane-1,5-diol-dialkylether, just as morpholine.[4] In the case of the symmetric diacidic bases (XXVI, XXXII, XXXIII), the statistical parameter of 0.3, which is an entropy term, was further taken into account. Then, the p$K_a$ values of amino sugars and amino alcohols could be calculated assuming the additivity of these parameters, and the results were given in Table I, in parallel with the observed values. For instance, the p$K_a$ value of methyl 2-amino-2-deoxy-$\beta$-D-glucopyranoside (I) was calculated by successively subtracting 0.9 unit (effect of C-3 hydroxyl), 2.2 units (effect of C-1 methoxyl and ring oxygen), 0.3 unit (effect of C-4 hydroxyl) and 0.1 unit (effect of ring oxygen) from 10.6 (p$K_a$ of alkylamine). The predicted value 7.1 was very close to the observed value (7.23). The agreement was satisfactory in many cases including the data reported by other workers (XXXII—XXXIV), and therefore the validity of this calculation was demonstrated.

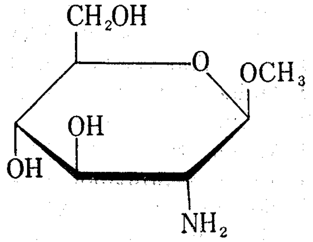

Chart 1

Though the relative p$K_a$ values could be correlated with the polar substituent effect, a slight discrepancy was observed for some compounds, which were indicated by an asterisk in Table I. In these cases, addition of 0.3 unit gave much closer values on the observed ones. The last parameter was derived from a consideration of the base-strengthening effect of the *cis*-substituent as described below.

Deviation arising from the steric requirement was seen in the p$K_a$ differences (0.25—0.3 unit) between $\alpha$- and $\beta$-anomers of 2-amino glucosides (I and II), and between the two C-2 epimers of 3-amino hexosides (III and V, VI and VII). In all the cases, the only difference in structure lay in the relative configuration of the hydroxyl group (or methoxyl group) against the equatorial basic center, which was *cis*-axial in I, V and VII, and *trans*-equatorial in I, III and VI. The increased basicity of the *cis*-compounds agreed with the previous

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8) M. Imoto, "Yuki Denshiron," I, Kyoritsu Shuppan, Tokyo, 1954, p. 152.

$pK_a$ studies on *cis*– and *trans*–2–aminocyclohexanols,[9] –cyclopentanols[10] and some derivatives of codeine.[11]

It is noteworthy that the $pK_a$ value of the reducing amino sugar does not describe the equilibrium of a single species, but, in general, composite value influenced by a number of equilibria including $\alpha,\beta$–anomerization and pyranose–furanose isomerization. However, because of the rapid equilibration of the conjugated acid and its base as compared with the other equilibria, the equilibrium positions of the others may remain almost unchanged during titration. If so, the measured $pK_a$ value is, as a first approximation, the weighted average of the various species present in the original solution. Thus, the $pK_a$ value of XVII initially equilibrated was approximated to the averaged $pK_a$ of a mixture of $\alpha$–anomer (59%) and $\beta$–anomer (41%), the proportion of which was determined by the (NMR) spectroscopy in deuterium oxide. The $pK_a$ values of the remaining reducing sugars (XV, XVI, XVIII—XXI) were assigned similarly to the mixtures of $\alpha$– and $\beta$–anomers, the ratios of which were shown at the footnote of Table I. In this connection, it was interesting to note that the $pK_a$ value of the solution of XVII initially equilibrated was 0.1 unit lower than that of the freshly prepared solution of $\alpha$–D–anomer hydrochloride, suggesting the stronger basicity of $\alpha$–anomer.

## Experimental

Most of the amino sugars and amino alcohols used were prepared in this laboratory according to the procedures reported in the literatures. The melting points and $[\alpha]_D$ values corresponded closely with literature values. Substances XVII, XVIII, XIX, XXVIII, XXIX and XXX in Table I were obtained commercially, and used without further purification.

**Determination of $pK_a$ Values**——A solution of the compound to be measured ($2—3\times10^{-3}$ mole) and equivalent HCl in freshly distilled $H_2O$, was titrated with 0.1 N NaOH in a Metrohm autotitrator with a EU 120X glass electrode coupled with a calomel electrode at 23±1°. The concentration of monoamino sugars was 0.01 M at a point of half–neutralization (ionic strength, 0.01). The concentration of diamino sugars was arranged to be 0.01 M at a point of 3/4 neutralization (ionic strength, 0.02). The $pK_a$ value was determined according to Parke and Davis,[12] from the pH of half–neutralization, and reproducible with ±0.05 $pK_a$ unit. The $pK_a$ values of diamino sugars containing two amino groups of close basicity ($\Delta\ pK_a<2.7$) were corrected for the overlap titration according to Neyes.[13]

The $pK_a$ values thus obtained were "mixed constants" ($pK_a{}^M$), which should be related to the thermodynamic constant ($pK_a{}^T$) by the equation, $pK_a{}^T \fallingdotseq pK_a{}^M - 0.05$ (for $pK_a{}^M$ of monoamino sugars and $pK_{aII}^M$ of diamino sugars), or $\fallingdotseq pK_a{}^M - 0.15$(for $pK_{aI}^M$ of diamino sugars). As a check of this, the $pK_a{}^T$ of V was determined at 25° according to Albert and Serjeant[14] using a HRL pH meter Model P, which was calibrated up to 0.01 pH unit. The $pK_a{}^T$ found for V was 8.04±0.03, indicating the validity of $pK_a{}^M$ obtained above.

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11) H. Rapoport and S. Masamune, *J. Am. Chem. Soc.*, **77**, 4330 (1955).

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13) A. Albert and E.P. Serjeant, "Ionization Constants of Acids and Bases. A Laboratory Manual," (Japanese Edition), Maruzen, Co., Tokyo, 1963, p. 45.

14) Reference 12), p. 28.