Acid–Base Properties of Biological Phenylalkylamines Characterised by CD-pH Titrations

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The acid–base chemistry of eleven selected chiral biological and drug molecules is characterised in terms of log *K* values by CD-pH titrations.

Characterization of acid–base properties of the biological and xenobiotic phenylalkylamines has been the subject of several studies, using various methods, as surveyed below.

The experimental techniques that can monitor protonation–deprotonation processes in solution include pH-potentiometry, which is certainly the most used method.[3–5] Of the spectroscopic techniques, UV–VIS photometry is suitable if the basic site is a strong chromophore, such as phenolate or thiolate. However, protonations of less intense chromophores (*e.g.* carboxylate or even more so amines) can only be observed with very limited sensitivity, particularly, when strong chromophores predominate the spectrum. NMR-pH titrations can be quite generally applied when the molecule contains a non-labile proton, or other NMR active nucleus adjacent to the basic site.[9]

When chirally perturbed, protonation-sensitive chromophores exist in a molecule, CD-pH titration may be also an appropriate method to characterise basicities. Provided that molar ellipticity is high, the CD-pH technique can be orders of magnitude more sensitive than pH-potentiometry, throughout the pH scale. Nevertheless, CD-pH titrations have only been sporadically used to determine log *K* values to characterise basicities[17] and resulted in controversial data.[18]

In this study the pH-dependent chiroptical properties of eleven biologically active phenylalkylamines were investigated.

Basicities of the investigated primary, secondary and tertiary phenylalkylamines reflect several or intramolecular effects, such as *N*-methylation, *C*-ethinylation or *β*-hydroxylation. Basicity differences between ephedrine and *ψ*-ephedrine could be interpreted in terms of different rotamer populations. Table 2 contains log *K* values determined in this work, and collected from the literature. Literature data of the same compounds show in some cases discrepancies ≥ 0.3, that precluded meaningful comparisons, and necessitated a comprehensive study.

Table 2 Protonation constants of chiral phenylalkylamines (25 °C, $I = 0.1$)

		Literature	
Compound	pK_a [a]	pK_a	Reference
(−)-(*R*)-Selegiline	7.59 ± 0.02	7.48 ± 0.01[b]	19
(+)-(*S*)-Selegiline	7.58 ± 0.02	7.48 ± 0.01[b]	19
(−)-(*R*)-Desmethylselegiline	7.83 ± 0.06	—	—
(−)-(*R*)-Amphetamine	10.08 ± 0.02	10.16 ± 0.06[b,c]	20
		10.13[b,d]	21
		10.03	22
		9.77 ± 0.05[b]	22
		9.93 ± 0.01[b,d]	23
(−)-(*R*)-Metamphetamine	10.34 ± 0.05	9.87[b]	22
(−)-(1*R*,2*S*)-Ephedrine	9.65 ± 0.07	9.58 ± 0.02[b]	24
		9.56	26
		9.72[d]	25
		9.84 ± 0.02[b,c]	27
(+)-(1*S*,2*R*)-Ephedrine	9.70 ± 0.08	9 58 ± 0.02[b]	24
		9.84 ± 0.0[b,c]	27
		9.75 ± 0.06[b,c]	20
(−)-(1*R*,2*S*)-Norephedrine	9.09 ± 0.06	9.75 ± 0.06[b,c]	20
		9.75[b,c]	30
		9.44 ± 0.04[d]	23
(+)-(1*S*,2*R*)-Norephedrine	9.07 ± 0.04	9.75 ± 0.06[b,c]	20
		9.75[b,c]	30
(−)-(1*R*,2*R*)-*ψ*-Ephedrine	9.90 ± 0.09	—	—
(+)-(1*S*,2*S*)-*ψ*-Ephedrine	9.95 ± 0.05	9.88[d]	25
		9.72[e]	25

[a] CD-pH, this work. [b] Racemic. [c] $I = 1.0$ KNO_3. [d] 20 °C [e] 22 °C.

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