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Separation of atropisomeric 1,4,5,6-tetrahydropyrimidinium salts by chiral HPLC and determination of their enantiomerization barriers

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Abstract

Chiral HPLC separation of a series of novel atropisomeric quaternary (**1**) and ternary (**2**) 1,2-disubstituted 1,4,5,6-tetrahydropyrimidinium salts bearing disymmetric aryl groups in positions 1 and/or 2 is described. A screening of different polysaccharide stationary phases (OD-R, OJ-R and AD-RH) and chromatographic conditions allowed for partial or baseline resolution of 16 over 26 compounds. When a semi-preparative separation was achieved, the corresponding enantiomerization barriers were determined employing the off-column method. The experimental data were compared inter se in order to establish the factors influencing the magnitude of the barriers and with those corresponding to the parent amidines.

Keywords: Chiral HPLC; Non-biaryl atropisomers; Enantiomerization barriers; Cyclic amidinium salts

1. Introduction

Atropisomerism is a property of some molecules that exist as enantiomeric forms due to restricted rotation around certain single bonds, which behave as chiral axes. Literature about atropisomers is generally restricted to biphenyl and binaphthyl derivatives, some of which are widely employed as chiral ligands in stereoselective reactions [1]. In the last years, there is a growing interest for the development of stable non-biaryl atropisomers. The stereochemistry of such compounds is interesting due to their potential employment in stereo and enantioselective synthesis [2–12]. Besides, some compounds have been reported in which the pharmacological activity is conditioned by the configuration of their stereogenic axes [13,14]. In particular, there are some reports concerning heterocyclic non-biaryl atropisomers [15–24]. In this context we synthesized in a previous work some novel atropisomeric six membered cyclic amidines (1,4,5,6-tetrahydropyrimidines) bearing disymmetrical aryl substituents, and studied their enantiomerization barriers employing variable temperature NMR and total lineshape analysis [25,26]. Typically, the enantiomerization barriers showed values below 70 kJ mol^{-1} and consequently the chiral separation of the enantiomers was not attempted. In connection to this, we also reported the existence of atropisomers in the corresponding tetrahydropyrimidinium salts **1** (R_1 = 2-nitrophenyl, R_2 = phenyl, 4-nitrophenyl, R_3 = methyl) [27]. The enantiomerization of such compounds could not be studied by dynamic NMR, and the existence of the atropisomers was evidenced only indirectly through the characteristics of their ^{1}H NMR spectra.

Chiral HPLC is both an analytical, as well as a preparative method for the separation of enantiomers, which allows for the isolation of pure antipodes in relatively large quantities. Besides, kinetic methods that employ analytical chiral HPLC can be used to study the interconversion of enantiomers with barriers above the working range of dynamic NMR (>80 kJ mol^{-1}) [28].

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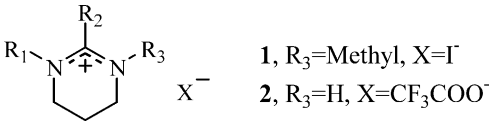
Table 1
1,4,5,6-Tetrahydropyrimidinium salts evaluated in this work



Compound	R_1	R_2
1a, **2a**	1-Naphthyl	Phenyl
1b, **2b**	1-Naphthyl	*tert*-Butyl
1c, **2c**	2,3-Dimethylphenyl	*tert*-Butyl
1d, **2d**	2-Chlorophenyl	Phenyl
1e, **2e**	2-Tolyl	Phenyl
1f, **2f**	2-Nitrophenyl	Phenyl
1g, **2g**	2-Nitrophenyl	*tert*-Butyl
1h	2-Nitrophenyl	Isopropyl
1i	2-Nitrophenyl	Ethyl
1j, **2j**	2,4,6-Trimethylphenyl	2-Chlorophenyl
1k, **2k**	2,4,6-Trimethylphenyl	2-Bromophenyl
1l, **2l**	2,4,6-Trimethylphenyl	2-Iodophenyl
1m, **2m**	2,3-Dimethylphenyl	2-Tolyl
1n, **2n**	2,3-Dimethylphenyl	2-Iodophenyl

The initial objective of this work was the separation of atropisomeric quaternary (**1**) and ternary (**2**) tetrahydropyrimidinium salts containing disymmetric aryl substituents in positions 1 and/or 2 of the heterocyclic ring (Table 1, compounds **1**,**2a-i**, **1**,**2j-l** and **1**,**2m**,**n**, respectively). In the cases where an analytical as well as a semi-preparative separation was achieved, we also determined the corresponding enantiomerization barriers employing the off-column method. The main advantage of this methodology is that the values obtained are not influenced by differential interactions with the chiral stationary phase, which can lead to differences in the activation energies determined for each enantiomer [29,30].

2. Experimental

2.1. Chemicals

EtOH, H_2O and CH_3CN are HPLC grade from SDS (Peypin, France). The solvents for chromatography experiments were degassed by a 10 min sonication before use. TFA, $NaClO_4$ and KPF_6 are from Aldrich. Cellulose tris(3,5-dimethylphenylcarbamate) chiral stationary phase, CHIRALCEL OD-R (particle size 10 μm, 250 mm × 4.6 mm) DAICEL column; cellulose tris(4-methylbenzoate) chiral stationary phase, CHIRALCEL OJ-R (particle size 5 μm, 150 mm × 2.1 mm) DAICEL column and amylose tris(3,5-dimethylphenylcarbamate) chiral stationary phase, CHIRALPAK AD-RH (particle size 5 μm, 150 mm × 4.6 mm) DAICEL column are available from Merck-Eurolab.

2.2. Methods

2.2.1. Synthesis

1,2-Disubstituted 1,4,5,6-tetrahydropyrimidines were synthesized and described elsewhere [25,26]. Ternary salts **2** were obtained in situ by treatment of the corresponding tetrahydropyrimidines with TFA. Quaternary salts **1** were obtained by refluxing the corresponding tetrahydropyrimidines with methyl iodide in dichloromethane solution for 24 h [27]. All new compounds gave satisfactory elemental analysis and NMR data.

2.2.2. Chromatographic screening

The chiral HPLC analysis and separation under reverse phase conditions were performed with Merck-Hitachi LiChrograph L-6000 pump, Merck-Hitachi L-4000 UV detector and Merck D-7000 system manager. The on-line chiroptical detectors were Jasco OR-1590 polarimeter and Jasco CD-1595 circular dichroism detectors. They were placed after the UV detector, so that the retention times given by the chiroptical detectors are shifted in comparison with those given by the UV detector. An aliquot of the assayed compound dissolved in acetonitrile was injected and run isocratically on the chiral RP-HPLC column. $NaNO_3$ was injected in order to measure the void volume of each chiral column.

2.2.3. Enantiomer enrichment and isolation

A semipreparative separation in the optimized chromatographic system was performed in order to collect fractions enriched in one of the enantiomers. Each compound was injected several times in succession and the first eluting enantiomer was collected for each separation. Fractions enriched in one enantiomer were pooled and the organic solvent (acetonitrile or methanol) was removed at room temperature. The aqueous residue was then extracted three-fold with an equal volume of dichloromethane in the case of compounds **1**; for compounds **2**, the extraction was performed with dichloromethane modified with 0.01 M TFA. The resulting organic phases were collected, filtered, dessicated and the solvent removed in vacuo at room temperature. The residue was dissolved in the solvent system chosen for the kinetic study.

2.2.4. Kinetic experiments

For compounds **1** and **2** that were separated in mobile phases containing acetonitrile, the solvent of choice for the kinetic experiment was acetonitrile (modified with 0.01 M TFA in the case of compounds **2**), since the salts were highly soluble in this solvent and no perturbation of the system was observed due to injection. For compounds **1** and **2** that were separated in mobile phases containing methanol, the solvent of choice was the mobile phase since it was observed that the use of a pure solvent (acetonitrile, water and methanol were assayed) resulted in a loss of resolution, and even a loss of retention. The isolated enantiomer (which typically presented more than 90% enantiomeric excess of the first eluting enantiomer) was dissolved in the chosen solvent and put into a flask immersed in a homogenized water bath at constant temperature, where it was left to enantiomerize. A given time was allowed for system equilibration (not less than 10% of the duration of the kinetic experiment), after which samples

were taken at equal intervals of time and were injected into the HPLC system. The racemization temperature was optimised in order to obtain ca. eight data points in 2 h, so that for each compound two or three temperatures were assayed before choosing the optimum one. The chromatographic profile obtained by chiral detection was then analyzed and peaks corresponding to each enantiomer were integrated, yielding their percent concentration. Plots of $\ln((A-50)/(A_0-50))$ against time were then obtained, where A is the percentual concentration of the enriched enantiomer at a given time t and A_0 is the percentual concentration of the enriched enantiomer at time zero. Data were then fitted into a regression model with the help of the software Infostat and a value for the slope was statistically obtained with a 95% degree of confidence. The slope corresponds to $2k_{rot}$, where k_{rot} is the enantiomerization rate constant [16,19,31], and the free energy difference ($\Delta G^{\neq}$) for the rotation was calculated from this value by the Eyring equation [32]. Experiments for the determination of enantiomerization barriers were carried out in duplicate.

3. Discussion

3.1. Chromatographic separation

Reverse phase HPLC was the technique of choice due to the ionic character of the compounds under study. Each compound was assayed in several chromatographic conditions, varying the sample preparation, the mobile phase composition, the flow rate, the running temperature, the type of chiral detection and the wavelength of detection. Several different conditions for the 26 compounds under analysis were assayed, until a system was found which completely or partially resolved the enantiomers. The chromatographic optimization procedure consisted of a trial-error screening on the three chiral columns (CHIRALCEL OD-R, OJ-R and CHIRALPAK AD-RH) using alcohol–water or acetonitrile–water mixtures and changing water ratio in the mobile phase in order to obtain retention factors between 1 and 5. The optimized conditions for the separation of compounds **1** and **2** are reported in Table 2. Some compounds were not resolved at all (Table 2).

In our work we assayed the polysaccharide stationary phases due to their loading capacity, since they allow for semi-preparative separations. Stationary phases OD-R and OJ-R could resolve most of the compounds. It is to be noted that compounds resolved in OJ-R were also resolved in OD-R, but with poorer results (data not shown).

In general, for compounds **1**, in which the stereogenic axis is the R_1–N1 bond, chiral recognition depends mainly on the structure of R_1. OD-R showed good results for R_1 = 1-naphthyl, 2,3-dimethylphenyl and 2-chlorophenyl, whereas OJ-R gave better separation results for R_1 = 2-tolyl and 2-nitrophenyl. The nature of R_2 does not modify chiral discrimination, except in the case of compound **1g** which is also resolved with OD-R, like 2-*tert*-butyl derivatives **1b,c**. Com-

Table 2
Optimum chromatographic conditions for compounds **1** and **2**

Compound	Stationary phase	Mobile phase	Additives	CD detection wavelength (nm)	Flow (ml/min)	Temperature (°K)	k_1	k_2	α
1a	OD-R	CH_3CN/H_2O (50:50)	KPF_6 0.1 M	254	1.0	295	4.73 (−)	4.95	1.05
1b	OD-R	CH_3CN/H_2O (55:45)	KPF_6 0.1 M	254	1.0	295	3.36 (−)	3.68	1.10
1c	OD-R	CH_3CN/H_2O (50:50)	KPF_6 0.1 M	254	1.0	295	2.36 (+)		1.00
1d	OD-R	CH_3CN/H_2O (55:45)	KPF_6 0.1 M	270	1.0	295	2.96 (+)		1.00
1e	OJ-R	CH_3OH/H_2O (55:45)	KPF_6 0.1 M	270	0.1	295	3.02 (−)		1.00
1f	OJ-R	CH_3OH/H_2O (55:45)	KPF_6 0.1 M	270	0.1	295	4.56 (−)		1.00
1g	OD-R	CH_3CN/H_2O (50:50)	KPF_6 0.1 M	270	0.7	278	6.08 (+)		1.00
1h	OJ-R	CH_3OH/H_2O (55:45)	KPF_6 0.1 M	270	0.1	295	2.36 (+)		1.00
1i	OJ-R	CH_3OH/H_2O (55:45)	KPF_6 0.1 M	270	0.1	295	1.74 (−)	2.02	1.16
1j, **1k**, **1l**				Unresolved					
1m				Unresolved					
1n				Unresolved					
2a	OD-R	CH_3CN/H_2O (50:50)	KPF_6 0.1 M, TFA 0.01 M	254	1.0	295	3.36 (−)	4.36	1.30
2b	OD-R	CH_3CN/H_2O (50:50)	KPF_6 0.1 M, TFA 0.01 M	254	0.7	278	2.64 (−)	3.62	1.37
2c	OD-R	CH_3CN/H_2O (50:50)	KPF_6 0.1 M, TFA 0.01 M	254	0.7	278	2.15 (+)		1.00
2d	OD-R	CH_3CN/H_2O (50:50)	KPF_6 0.1 M, TFA 0.01 M	270	1.0	295	1.84 (+)		1.00
2e	OD-R	CH_3CN/H_2O (50:50)	KPF_6 0.1 M, TFA 0.01 M	270	1.0	295	1.76 (−)		1.00
2f	OD-R	CH_3CN/H_2O (50:50)	KPF_6 0.1 M, TFA 0.01 M	270	0.7	275	1.33 (−)		1.00
2g, **2j**, **2k**				Unresolved					
2l				Unresolved					
2m	OD-R	CH_3CN/H_2O (50:50)	KPF_6 0.1 M, TFA 0.01 M	254	1.0	295	2.08 (+)	2.52	1.21
2n				Unresolved					

Polysaccharide stationary phases used were: OD-R (cellulose tris-((3,5-di-methylphenyl)carbamate) coated on silica), OJ-R (cellulose tris((4-methylphenyl)benzoate) coated on silica) and AD-RH (amylose tris((3,5-di-methylphenyl)carbamate) coated on silica). Retention factors are calculated from the UV chromatogram. When two values are informed, two peaks could be observed in the UV chromatogram. The sign (+) or (−) indicates the signal sign in the CD chiral detection for the first enantiomer at the reported wavelength. The column temperature indicates the temperature at which the chromatographic run was performed.

Table 3
Chromatographic conditions assayed for compounds **1a** and **2a**

Compound	Stationary phase	Mobile Phase	Additives	CD Detection Wavelength (nm)	Flow (ml/min)	Temperature (°K)	k_1	k_2	α
1a	OD-R	CH_3CN/H_2O (60:40)	KPF_6 0.1 M	254	1.0	295	0.46		1.00
	OD-R	CH_3CN/H_2O (50:50)	KPF_6 0.1 M	254	1.0	295	4.73	4.95	1.05
	OD-R	CH_3CN/H_2O (40:60)	KPF_6 0.1 M	254	1.0	295	20.1	21.3	1.06
	OD-R	CH_3OH/H_2O (90:10)	KPF_6 0.1 M	254	0.5	295	0		–
	OD-R	CH_3OH/H_2O (60:40)	KPF_6 0.1 M	254	0.5	295	0		–
	OD-R	CH_3OH/H_2O (50:50)	KPF_6 0.1 M	254	0.5	295	0		–
	OJ-R	CH_3CN/H_2O (50:50)	$NaClO_4$ 1.0 M	254	0.1	295	0		–
	OJ-R	CH_3CN/H_2O (50:50)	KPF_6 0.1 M	254	0.1	295	0.28		1.00
	OJ-R	CH_3OH/H_2O (50:50)	KPF_6 0.1 M	254	0.1	295	0		–
	OJ-R	CH_3CH_2OH/H_2O (50:50)	KPF_6 0.1 M	254	0.1	295	0		–
	OJ-R	$CH_3CH_2CH_2OH/H_2O$ (50:50)	KPF_6 0.1 M	254	0.1	295	0		–
	AD-RH	CH_3CN/H_2O (50:50)	$NaClO_4$ 1.0 M	254	0.5	295	0		–
	AD-RH	CH_3CN/H_2O (50:50)	KPF_6 0.1 M	254	0.5	295	1.11		1.00
	AD-RH	CH_3CN/H_2O (40:60)	KPF_6 0.1 M	254	0.5	295	3.65		1.00
2a	OD-R	CH_3CN/H_2O (50:50)	KPF_6 0.1 M, TFA 0.01 M	254	1.0	295	3.36	4.36	1.30
	OJ-R	CH_3CN/H_2O (50:50)	KPF_6 0.1 M	254	0.1	295	0		–
	OJ-R	CH_3OH/H_2O (50:50)	KPF_6 0.1 M	254	0.1	295	0	–	
	AD-RH	CH_3CN/H_2O (50:50)	KPF_6 0.1 M	254	0.5	295	0	–	
	AD-RH	CH_3CN/H_2O (40:60)	KPF_6 0.1 M	254	0.5	295	0	–	

pounds **1j-n**, bearing *ortho* substituted phenyl moieties on C2 were not resolved at all. Most compounds were retained by AD-RH, but could not be resolved (data not shown).

The mobile phase composition showed a strong dependence with the type of chiral stationary phase. Acetonitrile–water mixtures allowed the resolution of compounds on OD-R, whereas methanol–water mixtures allowed resolution on OJ-R. It is to be noted that no conditions were found to achieve resolution using acetonitrile mixtures on OJ-R and methanol mixtures on OD-R (Table 3). Additives such as poorly solvated counterions also proved to be a necessary condition for resolution. PF_6^- gave better results than ClO_4^-, and was therefore used in most chromatographic conditions assayed (Tables 2 and 3). In the case of compounds **2**, TFA was added at all stages of experimentation to ensure complete protonation of the tetrahydropyrimidines.

Sample preparation depended on the type of chiral stationary phase. In the case of compounds separated on OD-R, acetonitrile (modified with TFA for compounds **2**) was the solvent of choice. In the case of compounds separated on OJ-R, the mobile phase was the only system in which chiral discrimination was achieved, as compared to pure solvents like water, acetonitrile or methanol.

Chiral detection was performed either with a polarimeter or with a circular dichroism detector. Given the greater sensitivity of CD detection, this was the method of choice. Wavelength of chiral detection in CD was also a variable that improved resolution. Some compounds gave a stronger chiral signal at 254 nm, whereas others showed greater sensitivity of chiral detection at 270 nm.

Changes in solvent flow and running temperature also resulted in better resolution, especially in the case of compounds **2**. For example, by changing the flow from 1.0 to 0.7 ml/min for compound **2b**, the selectivity factor α changed from 1.32 to 1.37.

The values of the retention factor k were calculated following Eq. (1), where k is the retention factor, t_R the retention time for the compound and t_0 is the void volume time:

$$k = \frac{t_R - t_0}{t_0} \quad (1)$$

For compounds **1** and **2** ($1.0 \leq k \leq 6.0$), k values indicate that they interact with the stationary phase, but this interaction does not always result in chiral discrimination. In fact, although compounds **1** ($2.0 \leq k \leq 6.0$) were more retained in general than the corresponding compounds **2** ($1.0 \leq k \leq 3.5$), the chiral separation was better for the latter.

On the other hand, it is also important to determine the order of elution of the enantiomers, as characterized by the sign in chiral detection. Interestingly, compounds **1** share with their counterpart compounds **2** the same sign for the first eluting enantiomer, which may suggest a similar chiral recognition mechanism in the stationary phase.

The selectivity factor α was calculated from the UV signal. Baseline resolution was observed in the case of compounds **2a**,**b,m.** It is remarkable that the corresponding quaternary salts **1a,b**, although more retained, do not achieve baseline separation. Unresolved compounds **1j-l**,**n** and **2j-l**,**n** seem to indicate that R_2 = 2-halophenyl is unfavorable for chiral recognition, however, these compounds are highly retained in OD-R, OJ-R and AD-RH.

For compound **2m**, bearing two stereogenic axes, four stereoisomers can be expected. In fact, two pairs of enantiomers were resolved to the baseline in the chromatographic condition informed in Table 2. The relative proportion of both

Table 4
Experimental enantiomerization barriers for compounds **1** and **2**

Entry	Compound	Barrier (kJ mol^{-1})	Temperature (°K)	Solvent System	Counterion
1	**1a**	114.5–115.0	343	CH_3CN	PF_6^-
2	**1b**	109.6–110.8	333	CH_3CN	PF_6^-
3	**1c**	113.7–115.0	343	CH_3CN	PF_6^-
4	**1d**	98.4–98.8	293	CH_3CN	PF_6^-
5	**1e**	[a]			
6	**1f**	[a]			
7	**1g**	97.9–99.2	312	CH_3CN	
8	**1h**	105.8–106.7	333	CH_3OH/H_2O (55:45), KPF_6 0.1 M	PF_6^-
9	**1i**	103.3–103.8	308	CH_3OH/H_2O (55:45), KPF_6 0.1 M	PF_6^-
10	**2a**	107.1–107.9	318	CH_3CN, TFA 0.01 M	CF_3COO^-
11	**2b**	106.7–107.5	327	CH_3CN, TFA 0.01 M	CF_3COO^-
12	**2c**	[a]			
13	**2d**	94.2–94.6	293	CH_3CN, TFA 0.01 M	CF_3COO^-
14	**2e**	[a]	293	CH_3CN, TFA 0.01 M	CF_3COO^-
15	**2f**	87.6–88.0	275	CH_3CN, TFA 0.01 M	CF_3COO^-
16	**2m**	100.4–101.7	316	CH_3CN, TFA 0.01 M	CF_3COO^-

Reported values are informed as an interval of 95% degree of confidence. All barriers were confirmed by duplicate experiments.
[a] The enantiomerization barriers could not be determined due to partial hydrolysis of the compounds during racemization experiments.

diastereoisomers was 9:1, the major enantiomeric pair being less retained.

3.2. Barrier determination

Raw data for the calculation of the enantiomerization barriers were obtained by integration of the chiral signal. When the pure enantiomers are available, then a relationship between the absorbance in the UV and in the CD can be determined and a deconvolution performed on the chiral detection chromatogram, so as to obtain the absolute concentration of each enantiomer [33,34]. This was not our case, for we only achieved in general partial purification of the enantiomers. Thus, the integration was performed on the positive and negative peaks of the compound in chiral detection. Assuming that peaks are completely Gaussian in shape, each peak represents the enantiomeric excess of each enantiomer. Since the area superposed is equal for both enantiomers, then the non-superposed area is proportional to the concentration of each enantiomer. The experimental $\Delta G^{\neq}$ values obtained for compounds **1** and **2** are listed in Table 4.

For compound **2m**, the first eluting enantiomer of the major pair was isolated, and an enantiomerization barrier of 100.4–101.7 kJ mol^{-1} was determined. However, this experimental value is only approximate as fast equilibration towards the minor diastereoisomeric pair was observed during the experiment. Such interconversion also prevented the attempted isolation of the first eluting enantiomer of the minor pair, whose enantiomerization barrier could not be measured.

A comparative analysis of the enantiomerization barriers evidences the following general trends for the compounds under study. The interconversion rates for the atropisomers of ternary tetrahydropyrimidinium salts **2** are influenced by the size of the *ortho* substituents on R_1 (compare entries 10, 13 and 15). The same trend is observed for 2-phenyl substituted quaternary salts **1a,d** (entries 1,4). Rotational barriers also increase with increasing steric hindrance of R_2 (compare entries 8,9). However, the presence of a very bulky substituent like *tert*-butyl on C2 has in all cases the opposite effect (compare entries 1, 2 and 7–9). Evidently, the steric effect of the *tert*-butyl group would enhance the ground state energy of the molecules more than that of the transition state, thus lowering the interconversion barriers. A similar effect was previously observed in atropisomeric imides [35], and is opposite to the one observed in the parent amidines [25]. A comparison with the corresponding amidines [25] shows that protonation and quaternization significatively increase the enantiomerization barriers. For instance, 1-(2-chlorophenyl)-2-phenyltetrahydropyrimidine shows an interconversion barrier of 62.7 kJ mol^{-1}, while the values for the corresponding ternary and quaternary salts are 94.4 (**2d**) and 98.6 (**1d**), respectively. This effect would be the consequence of electron delocalization in the tetrahydropyrimidinium cations, which would result in shortening of the N1–C2 bond and also in a less staggered conformation of the substituents on N1 and C2. Both changes would intensify steric interactions between the substituents and would thus increase the energy barrier for the rotation of the R_1–N1 bond. Besides, a comparison between ternary salts **2** and the corresponding *N*-methyl derivatives **1** (compare entries 1 and 10, 2 and 11, 4 and 13) evidences that alkylation has a stronger effect on the magnitude of the barriers than protonation due to a buttressing effect of the methyl [17]. Apart from a buttressing effect of the methyl group, this could be explained bearing in mind that quaternisation is essentially non reversible, while the protonated species **2** are in fast equilibrium with small concentrations of the corresponding free bases in the experimental conditions, which would probably result in averaged values for the interconversion barriers.

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