Imidazole Cyclotrimers (Trimidazoles), a Novel Heteroannular Series

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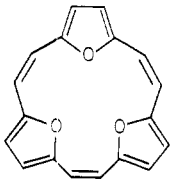
Fusion of 2-fluoroimidazoles results in the formation of cyclic trimers (trimidazoles) in 50–90% yield, via an addition–elimination pathway. If the monomer carries an additional substituent at C-4 (or C-5), three of the four possible isomeric trimers can be isolated. NMR signals for the ring protons are assigned on the basis of kinetics of solvent deuterium isotope exchange in alkaline and acid media, and consideration of the adjacent lone pair (ALP) effect. Cyclic trimers of histamine (tristamine) and L-histidine (L-tristidine) were synthesized from the corresponding 2-fluoro monomers. The trimidazoles have very low pK values (1.0–2.6), the result of electron withdrawal at N-1 and C-2. These compounds are potentially 18 π electron heteroaromatic systems, six of the π electrons being supplied by nitrogen atoms. On the basis of UV and NMR spectra, it is concluded that the trimidazoles have modest heteroannular ring currents.

In the course of studies on the synthesis and properties of 2-fluoroimidazoles **1**,[2] we found these compounds to undergo self-condensation to cyclic trimers **2** either in solution or upon fusion (Scheme I). The resulting heteroannular ring system, for which we propose the trivial name trimidazole,[3] is not entirely new. Analogous cyclotrimers have been obtained from derivatives of benzimidazole (**2j**)[4] and of 4,5-diphenylimidazole (**2i**),[5] in which C-2 bears a suitably activating substituent. Since the substituents used (Cl, SCH_3) are poorer leaving groups than fluorine in addition–elimination pathways, higher temperatures were found necessary to effect condensation than for 2-fluoroimidazoles, and the reaction pathways are not necessarily identical. A hexahydro derivative of **2a** has been obtained by ring expansion of tris(*C*-aziridinyl)triazine[5] and by self-condensation of 2-(methylthio)-2-imidazoline,[6] but efforts to dehydrogenate this product to **2a** have not been reported. The same ring expansion was achieved with the triazine adduct of 2,3-diphenylaziridine;[5] in this case, selenium dehydrogenation of the product to **2i** was demonstrated.

These cyclotrimers are of particular interest since they are undoubtedly planar and contain an 18 π electron system, in which six of the π electrons are supplied by imidazole nitrogen atoms. The possibility of an annular ring current was not considered in the reports on synthesis of **2i** or **2j**, nor is it likely that a ring current would be detected in these cases since it would have to compete with, or would be masked by, benzene or diphenylethylene resonance. In addition to the porphyrins and their oxygen or sulfur analogues,[7] macrocyclic aromaticity has been proposed for **3**;[8] in each of these cyclic polyolefins, however, the heteroatom is not a requisite component of the 18 π electron system, as it is in **2**. In this report, we describe the synthesis and properties of several members of series **2** and consider possible evidence for heteroannular aromaticity.



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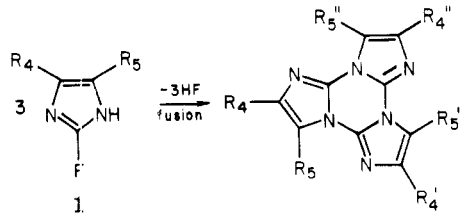
Results and Discussion

Synthesis. All 2-fluoroimidazoles examined, thus far, show the capability of forming cyclic trimers (Scheme I). The most reactive compound is 2-fluoroimidazole itself (**1a**), which trimerizes slowly even when the solid base or its hydrochloride is stored at −10 °C.[9] Since fluorine displacement may require ring protonation,[2] we assume that a slow release of hydrogen fluoride initiates the reaction, and it then becomes autocatalytic. In dilute acid solution at 50 °C, **1a** also undergoes trimerization, in addition to solvolysis at the monomer and dimer stages. Monomer **1b** is somewhat more stable than **1a**; solid samples of **1c–1h**, however, have remained unchanged after 1 year or more at 25 °C.[10] For preparative purposes, the solid 2-fluoroimidazole is heated to its fusion point (80–130 °C); the trimer is then separated by vacuum sublimation or preparative TLC, with overall yields of 50–90%. Mass spectral examination of the crude melts provided no evidence for dimeric intermediates or for cyclotetramers. Although **1g** and **1h** undergo facile loss of fluorine by solvolysis in aqueous media, reaction temperatures of 180–200 °C were found necessary to effect trimerization from the melt.[11]

Trimerization of 2-fluoro-4-X-imidazoles can produce four position isomers (numbered as in Scheme I): A, $R_4 = R_4' = R_4'' = X$; B, $R_5 = R_4' = R_4'' = X$; C, $R_5 = R_5' = R_4'' = X$; D, $R_5 = R_5' = R_5'' = X$. In the three condensations examined (**2b**, **2c**, and **2e**), the isomers were separable

(1) Visiting Associate, National Institutes of Health, 1973–1977.
(2) K. L. Kirk, W. Nagai, and L. A. Cohen, *J. Am. Chem. Soc.*, **95**, 8389 (1973).
(3) Compound **2a** is properly named triimidazo[1,2-a:1′,2′-c:1″,2″-e][1,3,5]triazine. For the sake of consistency in comparisons with monomeric imidazoles, we have retained the standard numbering system, as shown in Scheme I.
(4) E. R. Lavagnino and D. C. Thompson, *J. Heterocycl. Chem.*, **9**, 149 (1972).
(5) K. Zauer, I. Zauer-Csüllög, and K. Lempert, *Chem. Ber.*, **106**, 1628 (1973).
(6) G. R. Hauser and F. D. Blake, *J. Heterocycl. Chem.*, **7**, 997 (1970); F. C. Schaefer, *J. Am. Chem. Soc.*, **77**, 5922 (1955).
(7) M. J. Broadhurst, R. Grigg, and A. W. Johnson, *Chem. Commun.*, 23, 1480 (1969).
(8) G. M. Badger, J. A. Elix, and G. E. Lewis, *Aust. J. Chem.*, **19**, 1221 (1966); G. M. Badger, J. A. Elix, and U. P. Singh, *ibid.*, **19**, 257, 1461 (1966). For reviews of heteroannular systems, see P. Skrabal, *MTP Int. Rev. Sci.: Org. Chem., Ser. One*, **3**, 252 (1973); *MTP Int. Rev. Sci.: Org. Chem., Ser. Two*, 244 (1976).
(9) Samples stored at −80 °C appear to be stable indefinitely.
(10) The stabilizing effect of both electron-releasing and electron-withdrawing substituents is a logical consequence of the condensation mechanism. Electron-releasing groups facilitate ring protonation (high pK) but deactivate C-2 for nucleophilic addition–elimination pathways; electron-withdrawing groups facilitate addition at C-2 but retard ring protonation. Undoubtedly, bulkier substituents also contribute to stability through steric effects.
(11) The leaving ability of fluorine is very strongly dependent on solvation: H. Kimoto and L. A. Cohen, *J. Org. Chem.*, **44**, 2902 (1979).

Scheme I



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a, $R_4 = R_5 = H$; b, $R_4 = CH_3$; $R_5 = H$; c, $R_4 = CH_2CH_2NHCOCF_3$; $R_5 = H$; d, $R_4 = CH_2CH_2NH_2$; $R_5 = H$; e, $R_4 = CH_2CH(NHCOCF_3)COOCH_3$; $R_5 = H$; f, $R_4 = CH_2CH(NH_2)COOH$; $R_5 = H$; g, $R_4 = COOC_2H_5$; $R_5 = H$; h, $R_4 = R_5 = COOC_2H_5$; i, $R_4 = R_5 = C_6H_5$; j, $R_4 + R_5 =$ benzo

Table I. Ultraviolet Spectral Data (in C_2H_5OH)

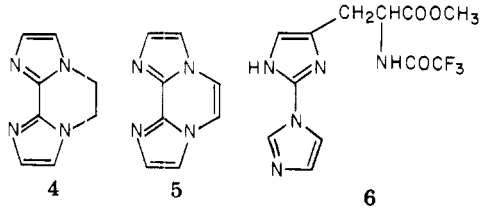
compd	λ_{max}, nm (log ϵ)
2a	228 (4.52), 235 (4.50), 255 (3.77)
2b-A[a]	234 (4.64), 241 (4.62), 260 (3.94)
6	248 (3.88)
4	283 (4.18), 290 (4.19)
triphenylene[b]	248 (4.9), 257 (5.2), 273 (4.3), 284 (4.3)
imidazole	206 (3.54)
s-triazine	272 (2.95)

[a] The spectra of 2b-B and 2b-C were essentially identical with that of 2b-A. [b] C. C. Barker, R. G. Emmerson, and J. D. Periam, *J. Chem. Soc.*, 1077 (1958).

by preparative TLC; the order of R_f values ran parallel to that of distribution, the most abundant isomer being the slowest moving. Structural assignments are based on the ratios of ring-proton (and ring-methyl) NMR signal areas and on the kinetics of proton exchange (see below). The following distributions were obtained: **2b**, 50% A, 37% B, and 13% C; **2c**, 45% A, 42% B, and 12% C; **2e**, 58% A, 40% B, and a trace of C. Slow fusion of **1b** gave a product which was composed almost entirely of **2b-A**. Isomer D was not detected in any case, although it may have been formed in trace amounts. Clearly, these isomer ratios do not follow a statistical distribution and may be determined by subtle steric and/or electronic effects.

The trifluoroacetyl blocking group is readily removed from **2c** in mild base to produce tristamine (**2d**), the cyclotrimer of histamine. Similar deblocking of **2e** produces L-tristidine (**2f**), the cyclotrimer of L-histidine.

Ultraviolet Spectra. The UV spectra of trimidazoles differ markedly from those of simpler imidazoles (Table I). The high ϵ values approach those of condensed polycyclic hydrocarbons and suggest the presence of an extensive π-electron system. Significant spectral absorption has been found for **4**,[12] but this compound is essentially a



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heterocyclic analogue of biphenyl. Compound **6**, which may be a more appropriate element of **2**, shows enough intensity at 248 nm to indicate that the trivalent nitrogen atom can participate in π-electron coupling between two

(12) P. Melloni, D. Fusar-Bassini, E. Dradi, and C. Confalonieri, *J. Heterocycl. Chem.*, 11, 731 (1974).

Table II. ^1H NMR Spectral Data[a]

compd	solvent[b]	δ H-4	δ H-5	J_{45}, Hz	δ 4-CH_3	δ 5-CH_3
2a		7.37	7.97	1.8 (d)		
	D_2O	7.24	7.71	2.0 (d)		
	0.4 N DCl	7.44	7.99	2.0 (d)		
2b-A			7.50	1.0 (q)[c]	2.39	
2b-B		6.92	7.49	1.0 (q)[c]	2.38	2.79
2b-C		6.95	7.51	1.0 (q)[c]	2.39	2.80
2c-A			7.72			
2c-B		7.03	7.69			
2c-C		6.94	7.69			
2e-A			7.63			
2e-B		6.98	7.65			
4[d]	Me_2SO-d_6	6.96	7.18			
5[d]	Me_2SO-d_6	7.43	7.72			
6[e]	$CDCl_3$	6.73				
8[f]		7.10	7.42			
9[f]		7.12	7.58			
10[f]	1 N DCl		7.27		2.35	
11[f]	1 N DCl	7.32				2.36

[a] Relative to internal or external tetramethylsilane. [b] In CD_3OD, unless otherwise given. [c] Coupling of the ring proton to the adjacent methyl protons. [d] Taken from ref 12. [e] Imidazole protons: H-2, δ 8.11; H-4, δ 7.09; H-5, δ 7.52. [f] This investigation: **8**, 1-methyl-2-nitroimidazole; **9**, 1-(*p*-toluenesulfonyl)imidazole; **10**, 1,4-dimethylimidazole; **11**, 1,5-dimethylimidazole.

Table III. Specific Rate Constants for Proton Exchange in Cyclotrimers[a]

compd	$k_{C(5)}$	$k_{C(4)}$	$k_{E'(5)}$	$k_{E'(4)}$
2a	9.4×10^{-3}	2.0×10^{-4}	2.0×10^{-4}	*b*
2b-A	2.1×10^{-3}		0.17	
2b-B	2.0×10^{-3}		0.16	*c*

[a] M^{-1} min^{-1} at 50 °C in CD_3OD–D_2O (3:2). [b] No exchange observed in 48 h.

imidazole rings; simple 2-aminoimidazoles, on the other hand, show only end absorption. Furthermore, the spectrum of **6** lacks the band multiplicity and fine structure seen in the spectra of the cyclotrimers. Thus, the spectra of **2** may, indeed, be associated with a modest heteroannular ring current.

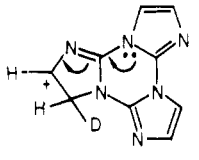
Basicity. Trimer **2a** forms a fairly stable monohydrochloride, with $pK_{app} = 1.5$ and $pK = 1.0$. Since **2a** has three equivalent sites for protonation, pK includes a statistical factor of −log 3.[13] The UV spectrum of the salt is very similar to that of the free base, indicating that proton binding occurs at a nitrogen sp^2 lone pair and that the low basicity of **2a** is not directly related to a loss of resonance energy. Substituent constants for the imidazolyl group are not yet available; on the basis of $pK_{app} = 4.53$ for 2-(2-imidazolyl)imidazole and 3.6 for 1-acetylimidazole,[14] a value of 1.5 for **2a** seems quite reasonably the result of substituent effects alone. Alkylation increases trimer basicity, **2b-A** showing $pK_{app} = 2.13$ and $pK = 1.70$ (pK_{app} − log 3).[13] The effect of the methyl group in increasing pK (0.65 unit) is close to that observed for 4-methylimidazole (0.56 unit).[15b] Isomer **2b-B** is more basic than **2b-A**, with pK_{app} and $pK = 2.63$. The increase of 0.5 unit in basicity corresponds to that found for 1,5-dimethylimidazole relative to the 1,4-isomer.[15b] Since the

(13) J. T. Edsall and J. Wyman, "Biophysical Chemistry", Academic Press, New York, 1958, p 487.
(14) W. P. Jencks and J. Regenstein in "Handbook of Biochemistry", H. A. Sober, Ed., Chemical Rubber Co., Cleveland, OH, 1968, p J-175.
(15) (a) Y. Takeuchi, H. J. C. Yeh, K. L. Kirk, and L. A. Cohen, *J. Org. Chem.*, **43**, 3565 (1978); (b) Y. Takeuchi, K. L. Kirk, and L. A. Cohen, *ibid.*, **43**, 3570 (1978).

one imidazole ring in **2b-B** carrying the C-5 methyl group is undoubtedly the preferred site of protonation, no statistical adjustment was applied to pK_{app} for this isomer.

^{1}H NMR Spectra and Isotope Exchange. The NMR proton signals for **2a** show a sizeable separation of 0.6 ppm (Table II). Assignments were made on the basis of rates of exchange with NaOD (Table III) and consideration of the ALP effect.[15] In 0.4 N NaOD in CD_3OD–D_2O (60:40) at 50 °C, the lower field signal exchanges with $t_{1/2}$ = 3 h and the higher field signal with $t_{1/2}$ = 144 h. Since k_{obsd} for loss of either signal varies directly with base concentration and since neither proton signal is diminished in neutral media, both protons apparently exchange by a vinyl carbanion mechanism.[15] The specific rate constant for H-5 exchange (Table III, $k_{C(5)}$) approaches the value obtained for exchange of H-5 in 1-methyl-2-nitroimidazole (pK = −0.44) in D_2O.[15b] Since OD^- will be a somewhat stronger base in the mixed solvent system, the result can be considered reasonably consistent with that expected for a monomeric imidazole of comparable pK. Accordingly, the lower field signal is assigned to H-5, the proton more distant from the sp^2 lone pair at N-3. The observation of carbanion exchange at C-4 is surprising, however, since the ALP effect at N-3 should preclude exchange entirely under the experimental conditions.[15b] Except for the possibility that imidazole ring geometries in the monomer and trimer may differ somewhat, we have no immediate explanation for this result.

Very slow electrophilic exchange (path E′)[16] is also observed at C-5 ($t_{1/2}$ = 720 h in 0.4 N DCl at 50 °C) but not at C-4. The E′ pathway is significant for imidazoles which have a low pK and a substituent capable of providing resonance stabilization for the intermediate carbonium ion. In our studies with monomeric imidazoles, fluorine was the only substituent found capable of meeting both requirements.[16] The cyclotrimers extend the scope of this mechanism, since they offer very low pK values and, apparently, are capable of stabilizing a C-4 carbonium ion through nitrogen participation (**7**). Analogous resonance stabili-



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zation cannot be written for a carbonium ion at C-5. Thus, the assignment of NMR signals is consistent for both the acid and the base exchange results. The rate constant for acid-catalyzed exchange ($k_{E'(5)}$) is considerably smaller than those found for fluoroimidazoles, but resonance stabilization (as in **7**) should also be significantly weaker than that due to a fluorine atom.

If **2a** is capable of supporting an annular ring current, the δ values for H-4 and H-5 should appear at lower field than those for monomeric models.[17] The δ value for H-4 is, indeed, at lower field than H-4 values for various model imidazoles (Table II), but not strikingly so; a somewhat larger downfield shift is seen for H-5 in **2a**. We see no obvious reason for a ring current effecting greater displacement at H-5 than at H-4, and part of the displacement at H-5 may be due to an anisotropic deshielding effect of the N-3 lone pair[18] of a neighboring imidazole ring (or of the neighboring ring, itself). On the other hand, an analogous trend is seen for **5**, which is potentially a 14 π electron heteroaromatic system devoid of the same possibilities for lone-pair anisotropy. Furthermore, the proton signals of **2a** are not deshielded by partial ring protonation, a process which should reduce the anisotropy effect.

For various conjugated systems, ortho coupling constants have been found to decrease with decreasing bond order.[19] An annular ring current should reduce the double bond character of the 4,5-bond in **2a** and, hence, the value of J_{45}. Many 1-methyl-2-X-imidazoles give J_{45} values of 0.5–1.0 Hz, while **2a** shows values of 1.8–2.0 Hz. Clearly, J has changed in the wrong direction, but the significance of this criterion may depend on whether the J bond order relationship is truly applicable to such systems.[19]

The single ring-proton signal in **2b-A** disappears readily in base ($t_{1/2}$ = 14 h in 0.4 N NaOD in 60% CD_3OD at 50 °C); the signal is assigned to H-5 on the basis of the facile exchange. This exchange occurs 4.5-fold more slowly than that of **2a**, the result of electronic retardation by the methyl group. Similarly, carbanion exchange of H-5 in 1,4-dimethylimidazole occurs 4.4-fold more slowly than that in 1-methylimidazole.[15] Structural assignments for **2b-B** and **2b-C** are based on the ratios of H and CH_3 NMR signal areas and the fact that the H-4 signals are not reduced by base in 20 days at 50 °C. This result, in contrast with that observed for **2a**, is wholly consistent with the expectation resulting from the ALP effect. Acid-catalyzed exchange of H-5 in **2b-A** occurs very readily ($t_{1/2}$ = 3.7 h in 0.4 N DCl at 50 °C) because the carbonium ion intermediate is so well stabilized by hyperconjugation with the methyl group. The effectiveness of the methyl group is revealed by the 200-fold difference in $t_{1/2}$ values for **2a** and **2b-A**; the difference is even more striking in a comparison of $k_{E'}$ values (830-fold), which take into account the difference in pK between the two cyclotrimers. Under the same acid conditions, H-4 in **2a-B** shows no evidence of exchange in 48 h. This difference in reactivity between H-5 and H-4 follows the pattern observed with 4-fluoro-1-methylimidazole and 5-fluoro-1-methylimidazole.[16]

Cyclotrimers **2b-B** and **2b-C** show the same separation in H-4 and H-5 δ values (ca. 0.6 ppm) as that found for **2a**; in the methylated trimers, however, both proton signals are displaced upfield because of the electron-releasing tendency of the methyl groups. Almost identical upfield shifts are found for 1,4- and 1,5-dimethylimidazole relative to 1-methylimidazole.[15a] As in the case of **2a**, comparison of δ values with those of model compounds suggests the possibility of a weak ring current. The methyl signals of **2b** should also be shifted downfield by ring-current effects; the data of Table II show that such displacements do occur, primarily at C-5. Ring-proton NMR signals for the isomers of **2c–f** are very close to those for the corresponding isomers of **2b**; accordingly, structural assignments in the former cases were made by analogy.

Chemical Reactivity. Preliminary studies on ring substitution were performed with **2a** and **2b-A**; the results are based on mass spectral analysis, no attempt having been made, to date, to isolate products. Cyclotrimer **2a** reacted readily with bromine in dioxane to give a mixture of mono-, di-, and tribrominated derivatives. In methanol or tetrahydrofuran as solvent, bromination was accompanied by incorporation of one or more solvent molecules to give complex mixtures involving both substitution and addition. Nitration of **2a** at 100 °C provided trace quantities of a dinitro derivative, together with extensive destruction of

(16) Y. Takeuchi, K. L. Kirk, and L. A. Cohen, *J. Org. Chem.*, preceding paper in this issue.
(17) L. M. Jackman and S. Sternhall, "Applications of Nuclear Magnetic Resonance Spectroscopy in Organic Chemistry", Pergamon Press, Oxford, 1969, p 94.
(18) Reference 17, p 82.
(19) Reference 17, p 303.

the ring system. Nitration of **2b-A** occurred with less ring degradation; a complex mixture of nitrated products was obtained in which the methyl groups had also been oxidized to various stages. On the basis of UV analysis, there was no evidence for a charge-transfer complex between **2a** and tetracyanoethylene, nor have we found any indications for complexing of trimidazoles with transition metals.

Conclusions

The UV spectra of the cyclotrimers provide reasonable evidence for an extensive π-electron system. NMR evidence for a heteroannular ring current is somewhat better than borderline; we have no precedent, however, to predict how much downfield displacement a ring current might produce in such a system. Additional studies on physical and chemical properties of the cyclotrimers are in progress; hopefully, other evidence for macrocyclic aromaticity will become available. Tristamine (**2d**) and tristidine (**2f**) combine the features of their metabolically essential monomers with those of polycyclic, aromatic hydrocarbons. Such compounds may have interesting biological properties, and exploratory studies have been undertaken.

Experimental Section[20]

Trimidazole Hydrochloride (2a·HCl). The parent cyclotrimer was prepared as previously described; mp 196–197 °C.[2] A methanolic solution of **2a** was saturated with hydrogen chloride, and the solution was evaporated to dryness under reduced pressure (with bath at ambient temperature). The residual solid was recrystallized from ethanol (mp 237–239.5 °C); the UV spectrum of the salt (in C_2H_5OH) was almost identical with that of the free base.[2] Titration of the monohydrochloride in water provided an apparent pK of 1.48.

Anal. Calcd for $C_9H_6N_6$·HCl: C, 46.06; H, 3.01; N, 35.82. Found: C, 45.84; H, 3.22; N, 35.53.

Trimethyltrimidazole (2b). A 100-mg sample of 2-fluoro-4-methylimidazole (**1b**)[15b] was heated slowly in a sublimation apparatus to 130 °C (bath temperature), at which point fusion was complete. The melt was allowed to solidify and was then sublimed[21] at 130 °C under reduced pressure to give 68 mg (85%) of colorless prisms, mp 178–179 °C. According to its NMR spectrum, this sublimate was composed almost entirely of a symmetrical isomer, subsequently shown to be **2b-A**. Further purification was effected by TLC (see below), without change in melting point. Titration in water provided pK_{app} = 2.13. Although the free base is somewhat soluble in water, the hydrochloride salt began to precipitate toward the end of the titration.

Anal. Calcd for $C_{12}H_{12}N_6$: C, 59.98; H, 5.04; N, 34.98. Found: C, 59.80; H, 5.06; N, 35.30.

In a second 100-mg run, the monomer was brought to 130 °C more rapidly, resulting in a less homogeneous product. The crude product was fractionated on two preparative TLC plates (silica gel GF, 1 mm thickness) with ethyl acetate as developing solvent. Three isomer fractions were obtained; the residue weights, in order of decreasing R_f, were as follows: **2b-C**, 7 mg; **2b-B**, 20 mg; **2b-A**, 27 mg, with an overall yield of 68%. For further purification, these fractions were sublimed under reduced pressure.

***N,N′,N″*-Tris(trifluoroacetyl)tristamine (2c).** A sample of **1c** (50 mg, 0.23 mmol)[2] was kept in an oil bath at 115–120 °C for 30 min. The melt was cooled and dissolved in a 1:1 mixture of methanol and ethyl acetate. This solution was applied to a preparative TLC plate (silica gel GF, 1.5 mm thickness), and the plate was developed with 10% cyclohexane in ethyl acetate; the plate was dried and was redeveloped a total of six times to achieve satisfactory resolution. Three fluorescent bands were obtained which, after elution with ethyl acetate and evaporation, provided residues with essentially identical mass spectra. The residue weights, in order of decreasing R_f, were as follows: **2c-C**, 4 mg; **2c-B**, 14 mg; **2c-A**, 15 mg. An overall yield of 73% was obtained. Structural assignments for the isomers were based on their NMR spectra (Table II) and the ratios of peak areas.

Tristamine (2d). A small sample of **2c** (mixed isomers) in 0.5 N sodium hydroxide was stored overnight at ambient temperature. The solution was neutralized and was applied to a Dowex 50 (H^+ form) column.[2] The column was eluted with 5% ammonium hydroxide, and the eluate was evaporated to dryness, leaving an almost colorless, crystalline residue. The mass spectrum confirmed that total removal of the trifluoroacetyl blocking group had occurred, to produce tristamine (**2d** isomers).

***N,N′,N″*-Tris(trifluoroacetyl)-L-tristidine Trimethyl Ester (2e).** A 50-mg sample of **1e**[2,22] was fused (130 °C) and cooled. The product was fractionated by preparative TLC (as for **2c**), using ether–cyclohexane (1:1) for development. The plate was developed a total of 15 times, with air-drying after each run. Three bands were obtained which, after ethyl acetate extraction and evaporation, gave residues with identical mass spectral parent peaks. The residue weights, in order of decreasing R_f, were as follows: **2e-C**, ca. 1 mg; **2e-B**, 17 mg; **2e-A**, 25 mg. An overall yield of 91% was obtained.

L-Tristidine (2f). A 10-mg sample of **2e** (mixed isomers) was suspended in 0.5 mL of 0.5 N sodium hydroxide, and the mixture was stirred at ambient temperature for 15 h. The resulting solution was neutralized and applied to a Dowex 50 (H^+ form) column.[2] The column was eluted with 5% ammonium hydroxide, and the eluate was evaporated to dryness, leaving an almost colorless, crystalline residue. This material was homogeneous, according to its mass spectrum and TLC on silica gel with BEAW (1-butanol–ethyl acetate–acetic acid–water, 1:1:1:1); resolution of the isomer mixture could not be effected at the zwitterion stage. Since the alkaline deblocking of **1e** occurred without apparent racemization,[2] we assume that the chiral centers in **2e** survive a similar treatment.

Other Cyclotrimers. Compounds **1g** and **1h**[23] failed to undergo condensation at 130 °C but did form the corresponding cyclotrimers **2g** and **2h** at a bath temperature of 180–200 °C. Mass spectra of the crude products suggested contamination by dimers and linear trimers containing one fluorine atom, as well as their hydrolysis products (with hydroxyl in place of fluorine).

***N*-Trifluoroacetyl-2-(1-imidazolyl)-L-histidine Methyl Ester (6).** A 10-mg sample of **1e** was mixed with 10 equiv of imidazole, and the mixture was fused at 130 °C. The condensation product was isolated by preparative TLC (ether–cyclohexane, 1:1), and its structure was confirmed by NMR and mass spectra.

Isotope Exchange of Ring Protons. A 20-mg sample of trimer was dissolved in 0.3 mL of CD_3OD, to which was added 0.2 mL of D_2O, DCl, or NaOD of appropriate concentration. Kinetics of exchange were followed, at 50 °C, as previously described for monomeric imidazoles.[15] According to the NMR spectra, the ring systems of trimers **2a** and **2b** are stable to both acid and base treatment, this conclusion being confirmed by mass spectral analysis at the termination of each exchange experiment. Some values of k_{obsd} (as $t_{1/2}$) are given in the text, and specific rate constants are summarized in Table III. The latter values were calculated as for monomeric imidazoles[15b] by using (for $k_{B'}$) the statistically corrected pK values given in the text.

Registry No. **1b**, 57212-35-8; **1c**, 50444-84-3; **1e**, 71518-43-9; **1g**, 71518-44-0; **1h**, 71518-45-1; **2a**, 228-48-8; **2a**·HCl, 71518-46-2; **2b-A**, 71518-47-3; **2b-A**·HCl, 71518-48-4; **2b-B**, 71518-49-5; **2b-C**, 71518-50-8; **2c-A**, 71518-51-9; **2c-B**, 71518-52-0; **2c-C**, 71518-53-1; **2d-A**, 71549-32-1; **2d-B**, 71518-54-2; **2d-C**, 71518-55-3; **2e-A**, 71549-33-2; **2e-B**, 71518-56-4; **2e-C**, 71518-57-5; **2f-A**, 71518-58-6; **2f-B**, 71518-59-7; **2f-C**, 71549-40-1; **2g-A**, 71518-60-0; **2g-B**, 71518-61-1; **2g-C**, 71518-62-2; **2h**, 71518-63-3; **4**, 54475-93-3; **5**, 54475-96-6; **6**, 71518-64-4; **8**, 1671-82-5; **9**, 2232-08-8; **10**, 6338-45-0; **11**, 10447-93-5; triphenylene, 217-59-4; imidazole, 288-32-4; *s*-triazine, 290-87-9.

(20) All compounds were checked for homogeneity by TLC and NMR and for identity by NMR and mass spectroscopy.

(21) If sublimation is attempted without prior fusion, the trimer is contaminated with a significant amount of starting material.

(22) E. De Clercq, A. Billiau, V. G. Edy, K. L. Kirk, and L. A. Cohen, *Biochem. Biophys. Res. Commun.*, **82**, 840 (1978).

(23) The syntheses of these compounds will be described elsewhere.