Novel Artificial Receptors for Alkylammonium Ions with Remarkable Selectivity and Affinity

Sung-Gon Kim and Kyo Han Ahn*[a]

Abstract: The benzene-based tripodal tris(oxazolines) have been developed as the most selective and strong receptors toward linear alkylammonium ions reported to date. Among six tris(oxazolines) based on 2,4,6-trimethylbenzene framework, the phenylglycinol-derived receptor **4** exhibits the largest association constant toward nBuNH$_3^+$ ($\log K_{ass} = 6.65 \pm 0.02$), while a similar value toward tBuNH$_3^+$ ($\log K_{ass} = 3.80 \pm 0.01$) compared with others, which corresponds to the selectivity ratio of nBuNH$_3^+$/tBuNH$_3^+$ as high as $\approx$700. The tris(oxazoline) **6** that has bare oxazoline ring exhibits still a large association constant toward sterically hindered tBuNH$_3^+$ ($\log K_{ass} = 5.26 \pm 0.02$). Both receptors **4** and **6** extract β-phenethylammonium ion from water into chloroform almost completely. When the benzene frame is changed from 2,4,6-trimethylbenzene to 2,4,6-triethylbenzene, dramatic changes in the affinity as well as in the selectivity are observed. The association constant observed by tris(oxazoline) **8** toward nBuNH$_3^+$ approaches 10^8 M^{-1} and the selectivity ratio of nBuNH$_3^+$/tBuNH$_3^+$ is increased to 2700. This selectivity is even more enhanced to 4000 with tris(oxazoline) **9**. The enhanced binding affinity and high selectivity observed with receptors **4** and related derivatives **7**–**9** compared with others can be explained by an optimized steric and electronic environment provided by the phenyl substituents, which has been unambiguously demonstrated by X-ray crystallographic and ^{1}H NMR spectroscopic studies on the host–guest complexes. The new receptor system has several unique features such as ready availability, structural simplicity, and in particular, versatility in derivatization. By virtue of these advantages, it can be readily tailored as selective receptors toward biologically important amines.

Keywords: alkylamines · tripodal oxazolines · hydrogen bonds · host–guest chemistry · molecular recognition

Introduction

Recently, we have developed a benzene-based tripodal oxazoline receptor system for selective recognition of NH_4^+ over K^+,[1] which has potential applicability in clinical and environmental chemistry. One of the receptors exhibited a large binding affinity toward NH_4^+ and a remarkable NH_4^+-selectivity over K^+.[2] The NH_4^+-binding affinity was dependent on the oxazoline substituents, which suggested that the selective recognition of a certain type of alkylammonium ions over others could be achieved by optimizing the steric and electronic influence of the substituents. In designing synthetic receptors for organic guests, the challenging problem is how to rationally incorporate interesting guest structures into receptor structures.[3] Herein, we wish to report a successful result involving novel tripodal oxazoline receptors.

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An efficient recognition system for alkylammonium ions such as n-butylammonium and β-phenethylammonium ions is valuable in clinical application,[4] because they are the structural motifs in biologically important amines such as GABA and dopamine.[5] The selective recognition of isomeric butylammonium ions has been reported recently by Chang[6] and Pappalardo[7] using calixarene-based receptors. A dramatic increase in selectivity was observed in going from calix[6]arene- to calix[5]arene-based receptors, demonstrating a crucial complementary interaction between a host and a guest for a successful molecular recognition. In this regard, our oxazoline receptors provide a great opportunity to examine the steric and electronic interactions between the receptor and guest molecules.

Results and Discussion

We synthesized various tris(oxazolines) **1**–**6** with different substituents and studied the host–guest interactions (Scheme 1).

Since all receptors are insoluble in water and the ammonium salts are also insoluble in the organic layer in the absence of receptors, we determined the association constant

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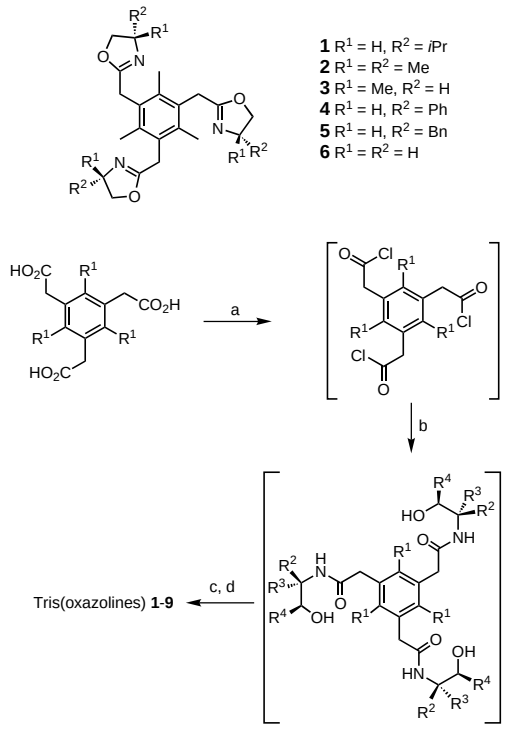
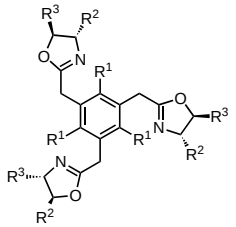


Scheme 1. Synthesis of tris(oxazolines). a) $(COCl)_2$, cat. DMF, CH_2Cl_2, 25 °C; b) amino alcohol, Et_3N, CH_2Cl_2, 25 °C; c) $SOCl_2$, benzene, 25 °C; d) NaOH, MeOH, reflux.

by the picrate extraction method.[8] Table 1 summarizes the association constants determined with tris(oxazolines) **1–6** having 2,4,6-trimethylbenzene framework.

For a given butylammonium ion, a dramatic change in the binding affinity was observed. Within the series, the largest association constant for nBuNH$_3^+$ is marked by receptor **4** that has phenyl substituents on oxazoline rings ($\log K_{ass} = 6.65 \pm 0.02\,\text{M}^{-1}$). The receptor **6** that has no substituent on oxazoline rings also exhibits a similar level of affinity toward nBuNH$_3^+$, whereas those with isopropyl or dimethyl substituents, oxazolines **1** and **2**, show much lower affinities. The oxazoline **3** that has methyl substituent is a borderline case. These results apparently indicate that the steric interactions involving the oxazoline substituents significantly affect the binding affinity. In addition, hydrophobic interactions play a role in the case of receptor **4**, in which phenyl substituents of oxazoline rings encompass the guest, thereby providing a "hydrophobic wall".[9] Notably, the oxazoline receptor **5** having benzyl substituents exhibits much lower affinities than the phenyl-substituted oxazoline **4**. The benzyl substituents may not provide the hydrophobic wall but exert steric strain toward the guests. Likewise, sterically more demanding alkylammonium ions will disfavor complexation than sterically less demanding nBuNH$_3^+$. In the case of tBuNH$_3^+$, a much lower affinity is observed with receptor **4**. The nBuNH$_3^+$/tBuNH$_3^+$ selectivity of as high as $\approx$700 is obtained. The binding affinity toward nBuNH$_3^+$ and the selectivity ratio obtained with receptor **4** are comparable to those obtained with the calix[5]arene-based receptor[7] that has been the most efficient one reported to date. It is noteworthy that oxazoline **6** exhibits a high affinity ($K_{ass} \approx 10^5\,\text{M}^{-1}$) toward sterically demanding tBuNH$_3^+$. Oxazoline **4** also shows a significant affinity toward sBuNH$_3^+$ ($K_{ass} \approx 10^5\,\text{M}^{-1}$), which is a prerequisite for high chiral recognition.[10] Besides, we studied the binding affinity toward β-phenethylammonium ion that is structurally related to biogenic amines such as dopamine and serotonin. Interestingly, with oxazoline receptors **4** and **6**, we could not correctly determine the association constants due to large fluctuations in the observed data. For the β-phenethylammonium ion, even receptor **3** exhibits an association constant as high as $10^6\,\text{M}^{-1}$. It is likely that two receptors have very strong affinities toward the ammonium ion ($K_{ass} \approx 10^8\,\text{M}^{-1}$) that makes the direct measurement unreliable. Both receptors **4** and **6** extracted β-phenethylammonium ion almost completely, which is very promising for the possible application to the detection of dopamine and its analogues.

The benzene-based tripodal oxazolines are in fast equilibrium between the two conformers, *syn*,*syn*- and *syn*,*anti* isomers, in which the relative positioning of three oxazoline ligands are different.[11] Receptors that are capable of favorable preorganization are expected to enhance the binding affinity.[12] Tripodal oxazolines based on 2,4,6-triethylbenzene frame are synthesized to see this point. Indeed, tris(oxazoline) **8** that differs from **4** in the frame show a significant increase in both the binding affinity and selectivity, as listed in Table 2.



7 R^1 = Me, R^2 = R^3 = Ph
8 R^1 = Et, R^2 = Ph, R^3 = H
9 R^1 = Et, R^2 = R^3 = Ph

Abstract in Korean:

벤젠에 기초한 삼발이형 트리스옥사졸린이 지금까지 보고된 수용체 중에서 선형 알킬암모늄 이온과 결합하는 가장 선택적이고 가장 강하게 결합하는 수용체로 개발되었다. 2,4,6-트리메틸벤젠 골격에 기초한 여섯 개의 트리스옥사졸린 수용체들 중에서 페닐글리시놀로부터 유도되는 수용체 **4**는 nBuNH$_3^+$ (log K_{ass} = 6.65±0.02)에 대해 가장 큰 결합 상수를 나타내었다. 반면 tBuNH$_3^+$ (log K_{ass} = 3.80±0.01)에 대해서는 다른 수용체와 비슷한 값을 보였다. 이 수용체는 nBuNH$_3^+$에 대해서 tBuNH$_3^+$에 비해 약 700배의 선택성으로 결합하였다. 옥사졸린 고리에 치환기가 없는 트리스옥사졸린 **6**은 입체 장애가 큰 tBuNH$_3^+$ (log K_{ass} = 5.25±0.02)에 대해서도 여전히 큰 결합상수를 나타내었다. 두 수용체 **4**와 **6**은 PhCH$_2$CH$_2$NH$_3^+$ 이온을 물 층으로부터 클로로포름 층으로 거의 완전하게 추출시켰다. 벤젠 골격을 2,4,6-트리메틸벤젠에서 2,4,6-트리에틸벤젠으로 바꾼 경우, 결합력과 선택성에서 놀라운 변화가 관찰되었다. 트리스옥사졸린 **8**은 nBuNH$_3^+$에 대해 10^8 M^{-1}의 결합세기를 보일 뿐 만 아니라, nBuNH$_3^+$/tBuNH$_3^+$ 선택성 또한 2700으로 증가하였다. 이 선택성은 트리스옥사졸린 **9**의 경우 4000배까지 증가하였다. 수용체 **4**와 그 유사체 **7**–**9**가 다른 수용체와 비교해 높은 결합력과 큰 선택성을 보이는 것은 옥사졸린 고리의 페닐 치환체에 의해 주어지는 최적화된 입체 및 전자적인 환경에 의해 설명되어질 수 있다. 이것은 수용체와 손님 분자 착물의 X-선 결정 구조 분석과 ^{1}H NMR 분광학 연구를 통해 확실히 증명되어졌다. 새로운 수용체 계는 구조적 간결성, 합성의 용이성, 구조 변환의 용이성 등의 여러가지 장점을 가지고 있다. 이러한 이점으로 생물학적으로 중요한 아민에 대해 선택적인 수용체들을 만들 수 있을 것이다.

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Table 1. Association constants ($\log K_{ass} \pm \sigma$) of alkylammonium ions (picrate salts) with oxazoline **1**–**6**, obtained by UV spectroscopy.[a]

Receptor	nBuNH$_3^+$	sBuNH$_3^+$	tBuNH$_3^+$	Ph(CH$_2$)$_2$NH$_3^+$	nBuNH$_3^+$/tBuNH$_3^+$[b]
1	4.40 ± 0.05	3.53 ± 0.05	3.00 ± 0.01	4.67 ± 0.08)	25
2	4.40 ± 0.01	3.28 ± 0.02	3.04 ± 0.01	4.38 ± 0.04	23
3	5.28 ± 0.08	4.20 ± 0.02	3.70 ± 0.01	6.61 ± 0.02	38
4	6.65 ± 0.02	6.65 ± 0.02	3.80 ± 0.01	[c]	710
5	4.81 ± 0.01	3.86 ± 0.01	3.23 ± 0.03	5.59 ± 0.09	38
6	6.41 ± 0.03	5.60 ± 0.02	5.26 ± 0.02	[c]	14

[a] Measured in $CHCl_3$ at 25 °C (deviation of minimum two independent determinations). [b] Selectivity factor. [c] Could not be determined due to very large deviations.

Table 2. Association constants ($\log K_{ass} \pm \sigma$) of alkylammonium ions (picrate salts) with oxazoline **7**–**9**, obtained by UV spectroscopy.[a]

Receptor	nBuNH$_3^+$	sBuNH$_3^+$	tBuNH$_3^+$	nBuNH$_3^+$/tBuNH$_3^+$[b]
7	6.30 ± 0.04	4.92 ± 0.05	3.67 ± 0.01	430
8	7.96 ± 0.08	5.94 ± 0.05	4.53 ± 0.01	2700
9	7.77 ± 0.02	5.92 ± 0.03	4.17 ± 0.01	4000

[a] Measured in $CHCl_3$ at 25 °C (deviation of minimum two independent determinations). [b] Selectivity factor.

The association constant observed by tris(oxazoline) **8** toward nBuNH$_3^+$ approaches 10^8 M^{-1}![13] Furthermore, the selectivity ratio of nBuNH$_3^+$/tBuNH$_3^+$ is increased to 2700. This selectivity is even more enhanced to 4000 with hexaphenyl-substituted tris(oxazoline) **9**. By changing the benzene frame, the binding affinity toward BuNH$_3^+$ is raised by up to 20 times. These results demonstrate again the importance of preorganization in the molecular recognition process.

Regarding to the binding mode, the X-ray crystal structure of **4**·PhCH$_2$CH$_2$NH$_3^+$PF$_6^-$ shown in Figure 1 exhibits the tripodal hydrogen bonding.[14] In addition to the hydrogen

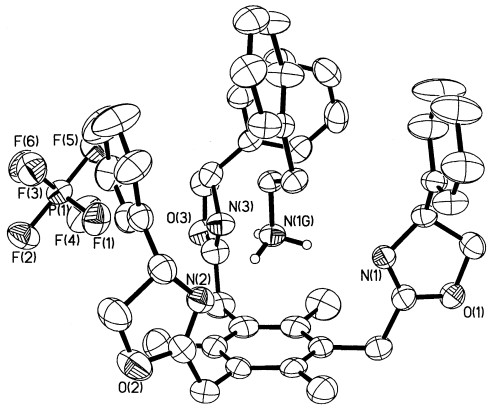

Figure 1. The X-ray crystal structure of **4**·PhCH$_2$CH$_2$NH$_3^+$PF$_6^-$ (except for the NH_3^+ hydrogen atoms, hydrogen atoms have been omitted for clarity). Selected interatomic distances [Å] and angles [°]: N(1G)···N(1) 2.972, N(1G)···N(2) 3.016, N(1G)···N(3) 2.983; N(1)-N(1G)-N(2) 124.1, N(1)-N(1G)-N(3) 109.9, N(2)-N(1G)-N(2) 109.6.

bonds, there exists cation–π interactions between the ammonium ion and the benzene framework that contribute to the stabilization of the complex.[15]

^{1}H NMR spectroscopic studies were performed on 1:1 complexes of nBuNH$_3^+$ with the tris(oxazolines) in CD_3OD/$CDCl_3$ 1:9, which provided an interesting result with regard to the cation–π interactions and an unambiguous evidence for the hydrophobic wall suggested previously. Figure 2 shows spectral changes on complexation.

Particularly notable are that the benzylic protons, more apparently the methyl protons, of the 2,4,6-trimethylbenzene frame exhibit upfield shifts and that their magnitudes depend on the binding affinity. The upfield shift ($-\Delta\delta$) of the methyl protons on complexation is 0.03 for tris(oxazoline) **2**, whereas those for tris(oxazoline) **6** and **4** are 0.15 and 0.14, respectively. Thus, larger upfield shifts are observed for the complexes having larger association constants. One likely explanation for the upfield

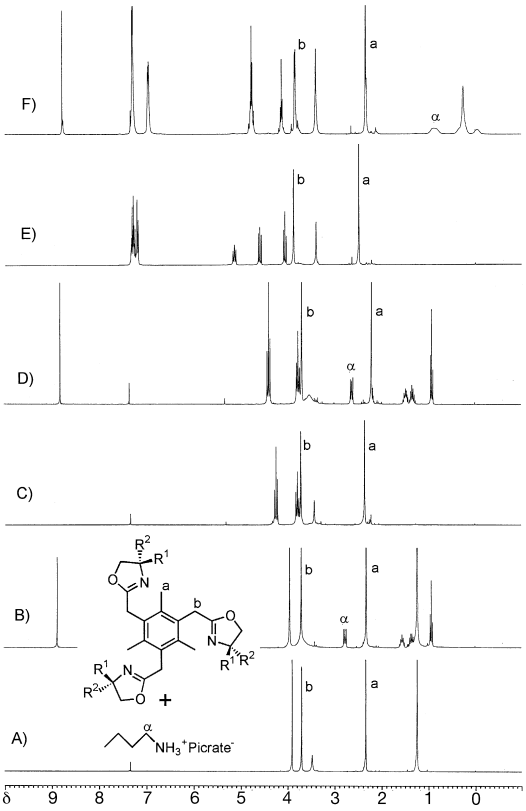

Figure 2. ^{1}H-NMR spectra (300 MHz, $CDCl_3$/CD_3OD 9:1, 25 °C) of tris(oxazoline) receptors (**2**: A, **6**: C, and **4**: E) and their 1:1 complexes of nBuNH$_3^+$ picrate (B, D, and F).

shift is that the cation–π interaction perturbs the delocalization of the benzene π electrons, thus causing a decrease in their deshielding effects.[16] Another interesting point is that the alkyl protons of the guest exhibit dramatic upfield shifts in the case of receptor **4**, compared with the other cases. For example, α-methylene protons of nBuNH$_3^+$ appear at $\delta = 0.87$ in the case of **4**, whereas those in the case of receptors **2** and **6** appear at $\delta = 2.76$ and 2.62, respectively. The dramatic upfield shifts in the case of receptor **4** may be due to the shielding effects by the oxazoline phenyl groups that surround the alkyl chain to form a hydrophobic wall.

Conclusion

We have developed the benzene-based tripodal tris(oxazolines) as the most selective and strong receptors toward linear alkylammonium ions reported to date. The X-ray crystallographic and ^{1}H NMR spectroscopic studies provide unambiguous binding modes both in the solid and in solution states. The new receptor system has several unique features such as ready availability, structural simplicity, and, in particular, versatility in derivatization. By virtue of these advantages, it can be readily tailored as selective receptors toward biologically important amines.

Experimental Section

General: Benzene and dichloromethane were purified by distillation from calcium hydride under nitrogen. Thionyl chloride was distilled under argon before use. Alkylammonium picrates were prepared by neutralization of the appropriate amine with picric acid in methanol and purified by recrystallization from diethyl ether/methanol. Analytical thin layer chromatography was performed using Merck 60 F_{254} precoated silica gel glass plates. Column chromatography was carried out on Merck silica gel 60 (230–400 mesh). Melting points were measured on a Thomas Hoover capillary melting point apparatus and were uncorrected. Optical rotations were measured using Rudolph Research Autopol III digital polarimeter using a sodium lamp (D line, 589 nm) and are reported in degrees with concentration in unit of 10 mg mL^{-1}. Proton and carbon NMR spectra were recorded on an AM-300 Bruker spectrometer. Chemical shifts are reported as δ in ppm downfield from tetramethylsilane ($\delta = 0.0$) using the residual solvent signal as an internal standard: [D_1]chloroform (^{1}H NMR: $\delta = 7.26$; ^{13}C NMR: $\delta = 77.0$). Multiplicity is given as usual. Mass spectral analysis was recorded on Jeol JMS-AX505WA and is reported in units of mass to charge (m/z). Elemental analyses and HR-MS were performed by Seoul Branch Analytical Laboratory of Korea Basic Science Institute.

Synthesis of the tris(oxazolines) 1–7—A representative procedure: Oxalyl chloride (4.3 mL, 50 mmol) and dimethylformamide (0.2 mL, 2.5 mmol) were added at 25 °C to a mixture of (2,4,6-trimethylbenzene)-1,3,5-triacetic acid (10 mmol) in dichloromethane (140 mL). After the reaction mixture was stirred for 18 h, the solvent and excess oxalyl chloride were evaporated under reduced pressure. The crude acid chloride was immediately used for the next step without further purification. A solution of the acid chloride in dichloromethane (40 mL) was added dropwise through a cannula to a stirred solution of an amino alcohol (30 mmol) and triethylamine (4.7 mmol, 34 mmol) in dichloromethane (50 mL) at 0 °C. After the solution was stirred for 12 h at 25 °C, the solvent was evaporated under reduced pressure to give the corresponding crude triamide. To the triamide were added benzene (140 mL) and thionyl chloride (7.2 mL, 100 mmol), and the resulting mixture was vigorously stirred at 25 °C for 18 h. After evaporating excess thionyl chloride and solvent under reduced pressure, the residue was dissolved in dichloromethane/water (200 mL, 1:1 v/v) and then stirred vigorously for 30 min at 25 °C. The organic layer was separated, and the aqueous layer was extracted with dichloromethane. The combined organic layers were washed with brine, dried over $MgSO_4$, and concentrated in vacuo to afford the crude chloromethylamide as a light yellow solid, which was subjected to the next step without further purification. A solution of sodium hydroxide (4.0 g, 100 mmol) in methanol (40 mL) through a cannula was added to a mixture of chloromethylamide dissolved in methanol (100 mL). The resulting mixture was stirred for 30 min at 25 °C and then heated under reflux for 12 h. After being cooled to room temperature, the mixture was concentrated under reduced pressure. The residue was re-dissolved in dichloromethane (20 mL) and neutralized with 1N HCl solution, washed with brine, and dried over $MgSO_4$. After concentration in vacuo, the crude product was purified by column chromatography on SiO_2 and then by recrystallization to afford an analytically pure compound. Similarly, tris(oxazolines) **8** and **9** can be synthesized starting from (2,4,6-triethylbenzene)-1,3,5-triacetic acid. Oxazolines **1** and **3** can be synthesized by a different route reported in the reference [1].

1,3,5-Tris[(4,4-dimethyl-2-oxazolinyl)methyl]-2,4,6-trimethylbenzene (2): Overall yield 45%; $R_f = 0.21$ (ethyl acetate/MeOH 95:5 v/v); m.p. 184–185 °C; ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 3.87$ (s, 6H), 3.69 (s, 6H), 2.37 (s, 9H), 1.24 (s, 18H); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 164.4$, 136.2, 131.0, 79.5, 67.2, 30.7, 28.7, 17.4; MS (EI): m/z (%): 453 (100) $[M]^+$, 382 (51), 310 (37); elemental analysis calcd (%) for $C_{27}H_{39}N_3O_3 \cdot \frac{1}{2}H_2O$: C 70.10 H 8.72, N 9.08; found: C 70.35, H 8.33, N 9.09.

1,3,5-Tris{[4(*S*)-phenyl-2-oxazolinyl]methyl}-2,4,6-trimethylbenzene (4): Overall yield 28%; $R_f = 0.34$ (ethyl acetate/hexanes 3:2 v/v); m.p. 125–126 °C; $[\alpha]_D^{27} = +77.8$ ($c = 1.00$, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): $\delta =$ 7.34–7.21 (m, 15H), 5.16 (dd, $J = 10.1$, 8.3 Hz, 3H), 4.59 (dd, $J = 10.1$, 8.5 Hz, 3H), 4.05 (dd, $J = 8.5$, 8.3 Hz, 3H) 3.87 (s, 6H), 2.51 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 167.0$, 142.5, 135.9, 130.7, 128.6, 127.4, 126.5, 74.8, 69.5, 30.1, 17.3; MS (EI): m/z (%): 597 (100) $[M]^+$, 576 (28); elemental analysis calcd (%) for $C_{39}H_{39}N_3O_3$: C 78.36, H 6.58, N 7.03; found: C 78.13, H 6.70, N 7.41.

1,3,5-Tris{[4(*S*)-phenylmethyl-2-oxazolinyl]methyl}-2,4,6-trimethylbenzene (5): Overall yield 30%; $R_f = 0.24$ (ethyl acetate/hexanes 3:2 v/v); m.p. 139–140 °C; $[\alpha]_D^{27} = -16.7$ ($c = 1.00$, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 7.30-7.16$ (m, 15H), 4.38–4.30 (m, 3H), 4.12 (t, $J = 8.3$ Hz, 3H) 3.94 (t, $J = 7.7$ Hz, 3H), 3.71 (s, 6H), 3.09 (dd, $J = 13.7$, 4.7 Hz, 3H), 2.6 (dd, $J = 13.7$, 8.9 Hz, 3H), 2.38 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 166.6$, 138.3, 136.2, 131.1, 129.7, 128.9, 126.8, 72.0, 67.6, 42.0, 30.5, 17.6; MS (EI): m/z (%): 639 (82) $[M]^+$, 548 (100); elemental analysis calcd (%) for $C_{42}H_{45}N_3O_3$: C 78.84, H 7.09, N 6.57; found: C 79.02, H 7.46, N 6.55.

1,3,5-Tris[(2-oxazolinyl)methyl]-2,4,6-trimethylbenzene (6): overall yield 44%; $R_f = 0.43$ (ethyl acetate/MeOH 4.1 v/v); m.p. 285–290 °C; ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 4.17$ (t, $J = 9.4$ Hz, 3H), 3.75 (t, $J = 9.4$ Hz, 3H) 3.66 (s, 6H), 2.34 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 167.0$, 136.0, 131.1, 67.8, 54.8, 30.3, 17.4; MS (EI): m/z (%): 369 (100) $[M]^+$, 326 (34), 283 (32); HR-MS (EI): calcd for $C_{21}H_{27}N_3O_3$: 369.2052; found: 369.2052.

1,3,5-Tris{[(*S*,*S*)-4,5-diphenyl-2-oxazolinyl]methyl}-2,4,6-trimethylbenzene (7): Prepared similarly with (1*R*,2*S*)-2-amino-1,2-diphenylethanol in overall yield 48%; $R_f = 0.58$ (ethyl acetate/hexanes 1:1 v/v); m.p. 148–149 °C; $[\alpha]_D^{25} = -107.2$ ($c = 0.50$, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 7.37-$ 7.20 (m, 30H), 5.21 (d, $J = 7.3$ Hz, 3H), 5.04 (d, $J = 7.3$ Hz, 3H), 4.06 (s, 6H) 2.69 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 167.1$, 142.7, 141.3, 136.4, 131.4, 129.4, 129.3, 128.8, 128.1, 127.1, 126.0, 89.4, 79.1, 30.9, 18.1; MS (FAB): m/z (%): 826 (58) $[M]^+$, 307 (100); elemental analysis calcd (%) $C_{57}H_{51}N_3O_3$: C 82.88, H 6.22, N 5.09; found: C 82.66, H 6.48, N 5.06.

1,3,5-Tris{[4(*S*)-phenyl-2-oxazolinyl]methyl}-2,4,6-triethylbenzene (8): overall yield 51%; $R_f = 0.25$ (ethyl acetate/hexanes 1:1 v/v); m.p. 63–64 °C; $[\alpha]_D^{25} = -41.4$ ($c = 0.50$, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): $\delta =$ 7.32–7.20 (m, 15H), 5.15 (t, $J = 9.3$ Hz, 3H), 4.58 (dd, $J = 10.2$, 8.4 Hz, 3H), 4.04 (t, $J = 8.4$ Hz, 3H) 3.85 (s, 6H), 2.96 (dd, $J = 7.5$ Hz, 6H), 1.21 (t, $J =$ 7.5 Hz, 9H); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 168.2$, 142.9, 142.7, 130.2, 129.0, 127.8, 127.0, 75.3, 69.9, 29.2, 23.8, 15.1; MS (FAB): m/z (%): 640 (100) $[M]^+$, 307 (61); HR-MS (FAB): calcd for $C_{42}H_{45}N_3O_3$ $[M+H]^+$: 640.3539; found: 640.3544.

1,3,5-Tris{[(*S*,*S*)-4,5-diphenyl-2-oxazolinyl]methyl}-2,4,6-triethylbenzene (9): overall yield 59%; $R_f = 0.65$ (ethyl acetate/hexanes 1:1 v/v); m.p. 81–82 °C; $[\alpha]_D^{25} = -107.4$ ($c = 0.50$, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): $\delta =$ 7.24–7.05 (m, 30H), 5.04 (d, $J = 7.6$ Hz, 3H), 4.93 (d, $J = 7.6$ Hz, 3H), 3.99 (s, 6H), 3.14 (q, $J = 7.4$ Hz, 6H), 1.28 (t, $J = 7.4$ Hz, 9H); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 167.8$, 143.2, 142.7, 130.6, 129.4, 128.7, 128.2, 127.3, 126.6, 126.1, 125.5, 89.4, 79.2, 29.7, 24.0, 15.6; MS (FAB): m/z (%): 868 (100) $[M]^+$, 761 (9), 307 (52); elemental analysis calcd (%) for $C_{60}H_{57}N_3O_3$: C 83.01, H 6.62, N 4.84; found: C 82.69, H 6.87, N 4.80.

Determination of K_{ass}: A mixture of the picrate salt (0.5 mL, 0.015 M in water) and the host (0.1 mL, 0.075 M in $CHCl_3$) in a centrifuge tube was equilibrated for 1 h in a thermostat at 25 °C. After being kept for 1 h, the whole mixture was extracted by Vortex–Genie for 1 min and then centrifuged at 1500 rpm for 1 min. An aliquot of the $CHCl_3$ layer was measured and transferred by micro-syringe into a 5 mL volumetric flask and diluted to the mark with CH_3CN. For a more intensely colored layer 0.01 mL aliquot and for a less intensely colored layer 0.05 mL aliquot were used. The UV absorption of each 5 mL solution was measured at 380 nm

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using Perkin–Elmer HP 8452 UV/Vis spectrometer. Calculation of the binding constant was followed by the literature procedure.[8]

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[14] Crystal data for $\mathbf{4}\cdot C_8H_9NH_3PF_6\cdot CH_2Cl_2$: $0.25\times0.25\times0.25$ mm $C_{48}H_{53}Cl_2F_6N_4O_3P$, $M_r = 949.81$, monoclinic, space group $P2_1$, $a = 11.8497(5)$, $b = 17.5041(7)$, $c = 12.6934(6)$ Å, $\alpha = 90°$, $\beta = 116.465(1)°$, $\gamma = 90°$, $V = 2356.94(18)$ Å^3, $Z = 2$, $T = 223(2)$ K, $\rho_{calcd} = 1.337$ g cm^{-3}, Siemens SMART CCCD diffractometer, $Mo_{K\alpha}$ radiation, 9582 reflections collected, 5795 independent reflections, $R1 = 0.0461$, $wR2 = 0.0921$ $[I > 2\sigma(I)]$, $R1 = 0.0594$, $wR2 = 0.1013$ (all data), GOF = 1.136. Crystallographic data (excluding structure factors) for the structure reported in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication no. CCDC-147263. Copies of the data can be obtained free of charge on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK (fax: (+44) 1223-336-033; e-mail: deposit@ccdc.cam.ac.uk).

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