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Supramolecular Adsorption of Alkaloids by Metallosalphen Complexes

Eduardo C. Escudero-Adán,[†] Jordi Benet-Buchholz,[†] and Arjan W. Kleij*[,†,‡]

Institute of Chemical Research of Catalonia (ICIQ), Av. Països Catalans 16, 43007 Tarragona, Spain, and Institució Catalana de Recerca i Estudis Avançats (ICREA), Pg. Lluís Companys 23, 08010 Barcelona, Spain

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Mono and bis-zinc(II)-centered salphen derivatives **1–5** are presented as efficient adsorption materials for pyridine-based alkaloid derivatives. The different alkaloid assemblies were studied by UV–vis and NMR spectroscopy, and high binding constants ($K_s \sim 10^5$) were additionally determined for the supramolecular complexes based on nicotine. X-ray analyses furthermore revealed, together with spectroscopic solution data, a preferential positioning of the nicotine guest(s). Upon binding to bis-Zn^{II}-bis-salphen complexes, the dinicotine assembly provokes a colorimetric change that may be useful for colorimetric analyses. The adsorption/desorption process of nicotine was studied using a polymeric bis-Zn(salphen) complex (**5**) and showed a recycling potential of this type of complexes in the binding of alkaloid compounds.

Introduction

Cigarette smoking is the most common way of tobacco consumption and can be regarded as an addiction with a global health impact. An excessive, long-term inhalation of cigarette smoke has been connected with numerous health problems that span the development of various types of cancer (with lung cancer being the most notorious one) and cardiovascular/respiratory diseases.[1] One of the most well-known components of tobacco is nicotine, with cotinine (Scheme 1) representing a byproduct in the metabolism of nicotine.[2] Structurally related alkaloid species (Scheme 1) and other active species such as the harmala alkaloids are, however, also found in tobacco.[3] Nicotine is a highly toxic substance with a lethal dosage as low as 40−60 mg for an adult human being. In much lower concentrations, however, it acts as a stimulant for the central nervous system giving the consumer, after ingestion, an almost immediate kick via the discharge of the hormone epinephrine (adrenaline). The dependency formation (addictive) properties of tobacco-smoking is hence primarily ascribed to nicotine.[4] While nicotine and its alkaloid derivatives constitute a clear and significant risk, tobacco-specific volatile nitrosamines that are derived from these alkaloids in cigarette smoke are also particularly harmful and carcinogenic.[5] Molecules that are able to reversibly bind these pyridine-containing alkaloids with high stability are therefore particularly interesting as new adsorption materials.

The use of a Zn(II)porphyrin as receptor molecule for nicotine was reported previously,[6] and the porphyrin structure was designed to accommodate a two-point interaction with the nicotine guest (K_s up to 4.6×10^5 M^{-1}) to increase the recognition capability. We recognized the structural resemblance between the porphyrin and salphen [salphen = *N,N′*-phenylenebis(salicylideneimine)] scaffold, since both types

* To whom correspondence should be addressed. E-mail: akleij@iciq.es. Phone: +34-977920247. Fax: +34-977920224.

[†] Institute of Chemical Research of Catalonia (ICIQ).

[‡] Institució Catalana de Recerca i Estudis Avançats (ICREA).

(1) For general facts and information about tobacco please visit http://www.tobaccofacts.org/ or http://www.cdc.gov/tobacco/.

(2) Brown, K. M.; von Weymarn, L. B.; Murphy, S. E. *Chem. Res. Toxicol.* **2005**, *18*, 1792.

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(5) Hoffmann, D.; Adams, J. D.; Piade, J. J.; Hecht, S. S. *IARC Sci. Publ.* **1980**, *31*, 507.

(6) Deviprasad, G. R.; D'Souza, F. *Chem. Commun.* **2000**, 1915.

(7) For the use of salen-based complexes see (a) Larrow, J. F.; Jacobsen, E. N. *Top. Organomet. Chem.* **2004**, *6*, 123. (b) Katsuka, T. *Adv. Synth. Catal.* **2002**, *344*, 131. (c) Cozzi, P. G. *Chem. Soc. Rev.* **2004**, *33*, 410. (d) Canali, L.; Sherrington, D. C. *Chem. Soc. Rev.* **1999**, *28*, 85. (e) McMarrigle, E. M.; Gilheany, D. G. *Chem. Rev.* **2005**, *105*, 1563. (f) Atwood, D. A.; Harvey, M. J. *Chem. Rev.* **2001**, *101*, 37.

(8) The term "salen" is here used as a general name for this type of ligand whereas salphen is used to denote the presence of a bridging phenyl group.

(9) See for instance (a) Kleij, A. W.; Tooke, D. M.; Spek, A. L.; Reek, J. N. H. *Eur. J. Inorg. Chem.* **2005**, 4626. (b) Holbach, M.; Zheng, X.; Burd, C.; Jones, C. W.; Weck, M. *J. Org. Chem.* **2006**, *71*, 2903. (c) Morris, G. A.; Zhou, H.; Stern, C. L.; Nguyen, S.-T. *Inorg. Chem.* **2001**, *40*, 3222.

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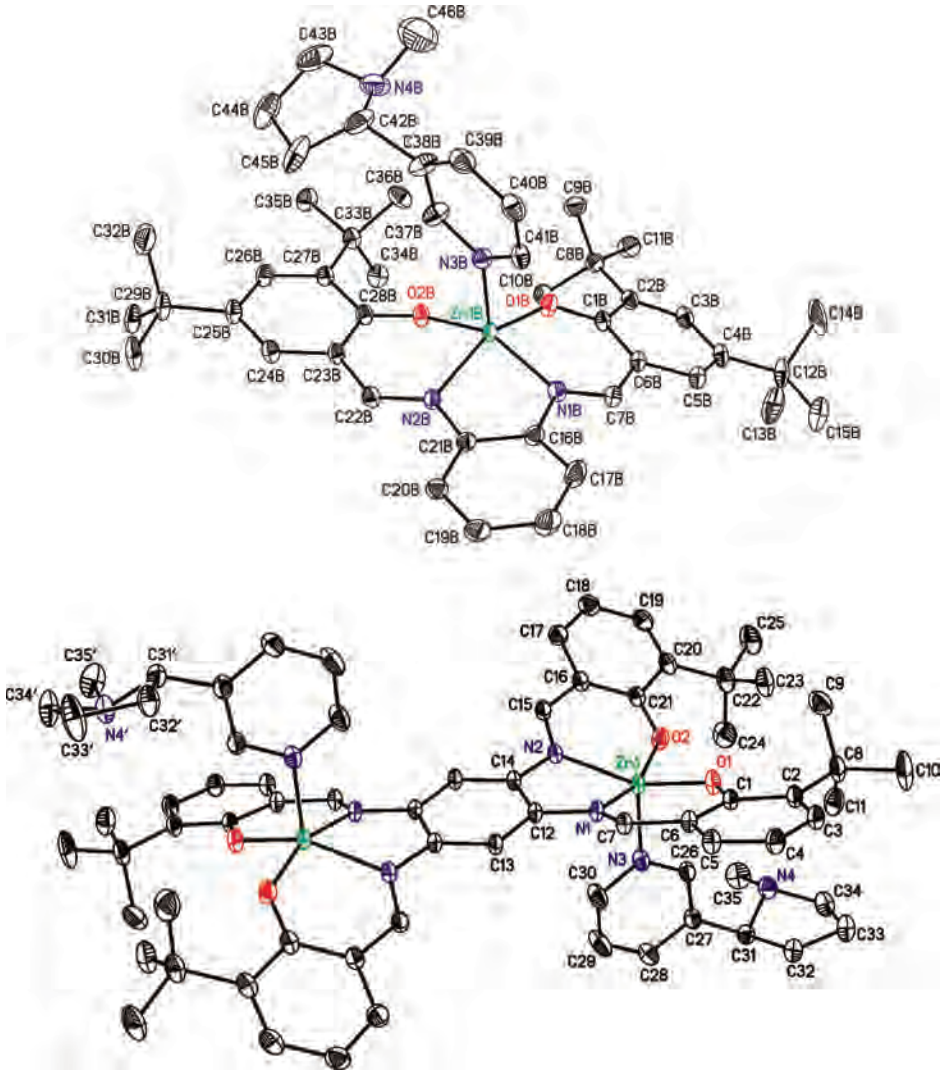
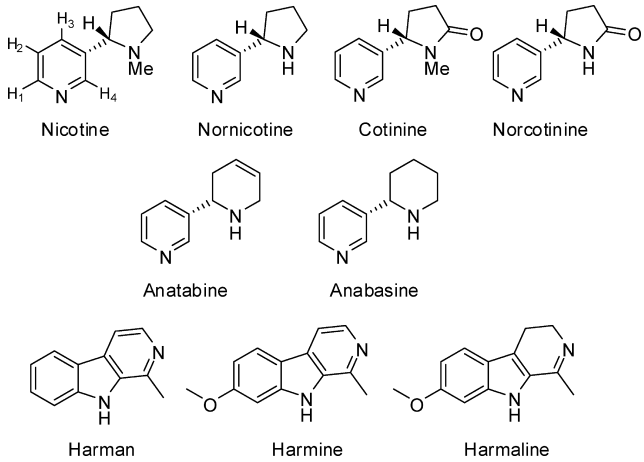


Figure 1. X-ray molecular structures of supramolecular nicotine complexes **1**·nicotine (upper structure) and pseudo centrosymmetric **4**·(nicotine)$_2$; hydrogen atoms and cocrystallized solvent molecules are omitted for clarity.[15]

Scheme 1. Schematic Structures of Nicotine and Its Most Important Alkaloid Derivatives Together with a Selection of Harmala Alkaloids[a]



[a] Please note the general substructural pyridine unit in all compounds except for Harmaline.

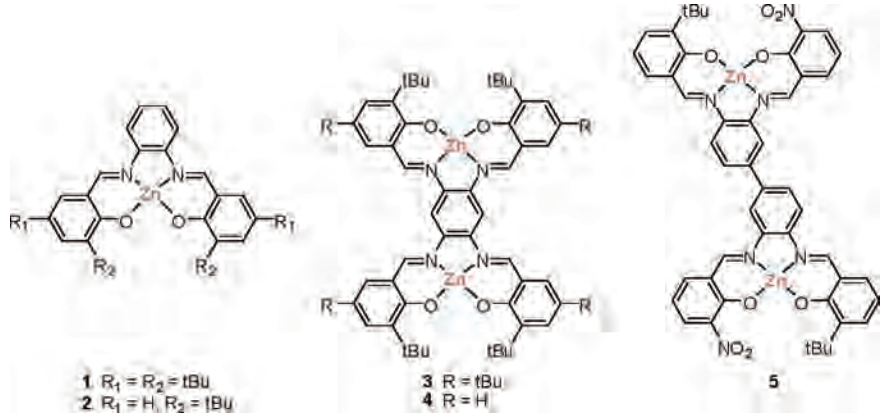
of ligands have a dianionic, tetradentate coordination pocket for various transition metal and main group cations.[7] Salen ligands[8] are characterized by the ease of preparation on a large scale, the versatility in the available structures,[9] and the stability of their complexes because of the presence of a tetradentate coordination geometry. Furthermore, they represent materials that are generated from cheap and accessible reagents. These properties make salen complexes attractive candidates for use as molecular adsorption materials.

Recently, the successful introduction of salen structures in supramolecular applications has initiated renewed interest in

(10) For some illustrative examples see (a) Sun, S.-S.; Stern, C. L.; Nguyen, S.-T.; Hupp, J. T. *J. Am. Chem. Soc.* **2004**, *126*, 6314. (b) Oliveri, C. G.; Gianneschi, N. C.; Nguyen, S. T.; Mirkin, C. A.; Stern, C. L.; Wawrzak, Z.; Pink, M. *J. Am. Chem. Soc.* **2006**, *128*, 16286. (c) Richeter, S.; Rebek, J., Jr *J. Am. Chem. Soc.* **2004**, *126*, 16280. (d) Breinbauer, R.; Jacobsen, E. N. *Angew. Chem., Int. Ed.* **2000**, *39*, 3604. (e) Ma, C.; Lo, A.; Abdolmaleki, A.; MacLachlan, M. J. *Org. Lett.* **2004**, *6*, 3841. (f) Ma, C.; MacLachlan, M. J. *Angew. Chem., Int. Ed.* **2005**, *44*, 4178.

(11) (a) Kleij, A. W.; Lutz, M.; Spek, A. L.; van Leeuwen, P. W. N. M.; Reek, J. N. H. *Chem. Commun.* **2005**, 3661. (b) Kleij, A. W.; Kuil, M.; Tooke, D. M.; Lutz, M.; Spek, A. L.; Reek, J. N. H. *Chem.—Eur. J.* **2005**, *11*, 4743. (c) Kleij, A. W.; Kuil, M.; Lutz, M.; Tooke, D. M.; Spek, A. L.; Kamer, P. C. J.; van Leeuwen, P. W. N. M.; Reek, J. N. H. *Inorg. Chim. Acta* **2006**, *359*, 1807. (d) Kleij, A. W.; Kuil, M.; Tooke, D. M.; Spek, A. L.; Reek, J. N. H. *Inorg. Chem.* **2007**, *46*, 5829. (e) Kleij, A. W.; Reek, J. N. H. *Chem.—Eur. J.* **2006**, *12*, 4218. (f) Escudero-Adán, E. C.; Benet-Buchholz, J.; Kleij, A. W. *Inorg. Chem.* **2007**, *46*, 7265.

Scheme 2. Schematic Structures of Zn-Salphen Complexes **1**–**5**



these ligand systems as molecular building blocks,[10] and we are currently particularly interested in the application potential of readily available Lewis-acidic Zn(II)-salphen complexes.[11] The high Lewis-acid character of these latter derivatives was successfully utilized in the binding of simple N-donor guest molecules.[12] We set out to explore the binding features of Zn(salphens) with more functional and relevant N-heterocycles such as alkaloids (Scheme 1) and, in particular, of nicotine as this alkaloid species is main responsible for the addictive nature of smoking.[4] An efficient adsorption on Zn(salphen) structures might offer opportunities to selectively lower the content of nicotine and structurally similar alkaloids (Scheme 1) in tobacco, thereby making smoking potentially less toxic and addictive. The use of electronically connected Zn(II) centers in multisalphen derivatives may then be used to vary the strength of association of the guest molecule and thus the reversibility of the binding process (cf., desorption). Alternatively, variation of the steric and/or electronic properties of such bis-salphen complexes[13] also provides a tool to fine-tune the adsorption process.

Results and Discussion

Zn(II)salphens **1**–**3** and **5** (Scheme 2) were prepared in high yield by reported methods,[9a,11b,13] and characterized in full by a combination of analytical and spectroscopic techniques. Compounds **1**–**5** were investigated for their binding efficiency with various alkaloid derivatives including nicotine, and the supramolecular assemblies were analyzed by NMR, UV–vis, and single crystal X-ray analysis. As a representative example for these alkaloids (Scheme 1), crystals were obtained from acetonitrile solutions of the respective salphen complex (i.e., **1** and **4**) in the presence of nicotine. The bulk presence of this solvent does not interfere with nicotine coordination to the metal complex since acetonitrile binding to Zn(II)salphen complexes is known to be relative weak.[14]

Table 1. Selected Bond Distances (Å) and Angles (°) for Compounds **1**·Nicotine and **4**·(Nicotine)$_2$[a]

1·nicotine		**4**·(nicotine)$_2$	
Distances			
O(1B)−Zn(1B)	1.9590(2)	Zn(1)−O(1)	1.9664(10)
O(2B)−Zn(1B)	1.9643(16)	Zn(1)−O(2)	1.9701(10)
N(1B)−Zn(1B)	2.0698(19)	Zn(1)−N(2)	2.0717(10)
N(2B)−Zn(1B)	2.1100(2)	Zn(1)−N(3)	2.0788(12)
N(3B)−Zn(1B)	2.1160(17)	Zn(1)−N(1)	2.1145(11)
Angles			
O(2B)−Zn(1B)−N(2B)	87.83(7)	O(1)−Zn(1)−N(2)	149.09(5)
O(1B)−Zn(1B)−N(2B)	155.60(7)	O(1)−Zn(1)−N(1)	88.00(4)
O(2B)−Zn(1B)−N(1B)	153.15(7)	O(2)−Zn(1)−N(1)	161.84(4)
O(1B)−Zn(1B)−N(1B)	89.44(8)	O(2)−Zn(1)−N(2)	89.11(4)
N(2B)−Zn(1B)−N(3B)	97.06(8)	O(1)−Zn(1)−N(3)	103.16(5)
N(1B)−Zn(1B)−N(3B)	102.32(7)	O(2)−Zn(1)−N(3)	94.67(5)
		N(3)−Zn(1)−N(1)	100.90(4)
		N(2)−Zn(1)−N(3)	106.34(5)

[a] Estimated standard deviations in parentheses.

The structures of **1**·nicotine and **4**·(nicotine)$_2$ are shown in Figure 1, and relevant structural/crystallographic data is collected in Tables 1 and 2 (see also the Experimental Section).

In both structures, the nicotine guest is coordinating via the N_{pyr} atom to afford an approximate square pyramidal coordination geometry around the central Zn atoms (see also Tables 1 and 2), comparable to earlier reported Zn(salphen) structures.[9a,11b,f] There seems to be a preferred positioning of the nicotine molecule in the assembled structure with the pyrrolidine ring pointing away from the phenyl bridge of the salen structure, bringing one of the *ortho* protons of the pyridine ring in close proximity of this connecting benzene ring. The structure **4**·(nicotine)$_2$ represents to our knowledge the first example of a receptor molecule that can simultaneously bind two nicotine molecules, and in the present case, the nicotine guests are in an *anti*-orientation with respect to the bis-salphen plane.

The assemblies **1**·nicotine and **3**·(nicotine)$_2$,[16] together with a series of reference structures based on a pyridine framework, were also investigated by ^{1}H NMR performed in d_6-acetone[17]

(12) For a representative, recent example of the use of Zn(salens) in the binding/recognition of N-donor molecules see Dalla Cort, A.; Mandolini, L.; Pasquini, C.; Rissanen, K.; Russo, L.; Schiaffino, L. *New J. Chem.* **2007**, *31*, 1633.

(13) Curreli, S.; Escudero-Adán, E. C.; Benet-Buchholz, J.; Kleij, A. W. *J. Org. Chem.* **2007**, *72*, 7018.

(14) The presence of bulk acetonitrile does not interfere with the pyridine coordination, and only coordination of the latter is observed by NMR. Preferential crystallization of the pyridine adducts takes place, even when very small relative amounts of pyridine are used (≤1% v/v in acetonitrile).

(15) For **1**·nicotine, only one of the crystallographically independent molecules is shown. For both structures, the disorder in the 5-membered pyrrolidine rings is not shown.

(16) We used assembly **3**·(nicotine)$_2$ instead of **4**·(nicotine)$_2$ for the ^{1}H NMR studies, as the latter is sparingly soluble in d_6-acetone.

Table 2. Crystallographic Data and Structure Refinement for Complexes **1**·Nicotine and **4**·(Nicotine)$_2$

	1·nicotine	**4**·(nicotine)$_2$
empirical formula	$C_{94}H_{123}N_9O_4Zn_2$	$C_{70}H_{82}N_8O_4Zn_2$
formula weight	1573.75	1230.18
temperature, K	100(2)	100(2)
wavelength, Å	0.71073	0.71073
crystal system, space group	triclinic, $P\bar{1}$, pseudo centrosymmetric	Triclinic, $P\bar{1}$, pseudo centrosymmetric
unit cell dimensions	a = 16.7428(7) Å, α= 74.724(2)° b = 17.3403(7) Å, β = 65.086(2)° c = 17.5030(7) Å, γ = 85.266(2)°	a = 11.6161(11) Å, α= 78.037(4)° b = 11.7161(10) Å, β= 81.872(4)° c = 14.7077(12) Å, γ = 70.692(4)°
volume, Å^3	4443.5(3)	1842.3(3)
Z	2	1
density (calculated), Mg/m^3	1.176	1.109
absorption coeff., mm^{-1}	0.593 mm^{-1}	0.698 mm^{-1}
F(000)	1684	650
crystal size, mm^3	0.40 × 0.40 × 0.30	0.20 × 0.20 × 0.10
θ range for data collection, °	2.73° to 37.84°	2.84° to 39.75°
index ranges	$-28 \le h \le 5$, $-29 \le k \le 29$, $-29 \le l \le 30$	$-20 \le h \le 16$, $-20 \le k \le 20$, $-26 \le l \le 26$
refl. collected/ independent	86437, 35072 [R(int) = 0.0342]	21061 [R(int) = 0.0347]
completeness to θ = 37.84°	73.3%	93.8%
absorption correction	SADABS (Bruker−Nonius)	SADABS (Bruker−Nonius)
max. and min. transmission	0.8421 and 0.7972	0.9335 and 0.8730
refinement method	full-matrix least-squares on F^2	full-matrix least-squares on F^2
data/restraints/parameters	35072/158/1170	21061/0/440
goodness-of-fit on F^2	1.115	1.075
Final R indices [$I > 2\sigma(I)$]	R1 = 0.0707, wR2 = 0.1874	R1 = 0.0476, wR2 = 0.1453
R indices (all data)	R1 = 0.0901, wR2 = 0.1972	R1 = 0.0573, wR2 = 0.1494
larg. diff. peak, hole, e·Å^{-3}	1.711 and –0.689	0.841 and −0.474

to study the assembly formation in solution and to compare the NMR features with the reference materials. In this relatively polar solvent, significant chemical shift changes were noted for the pyridyl fragment of the different alkaloids/compounds (Figure 2, Table 3). In the case of **1**·nicotine and **3**·(nicotine)$_2$, the expected stoichiometry [1:1 in the case of **1**·nicotine and 1:2 in the case of **3**·(nicotine)$_2$, the crystalline materials were used] was confirmed by signal integration. The largest (upfield) shift was noted for H_2 ($\Delta\delta = -0.33$ ppm, Figure 2), while for the other pyridine-H (H_1, H_3, and H_4) only moderate shifts were observed ($\Delta\delta = \pm$ 0.03–0.09 ppm). The use of a noncoordinating solvent such as CD_2Cl_2 for assembly **1**·nicotine produced, as may be expected, even larger shifts for H_2 ($\Delta\delta = -0.38$ ppm) and H_1 ($\Delta\delta = -0.12$ ppm). Such upfield shifts have also been encountered for pyridine complexation to similar Zn(salphen) derivatives[11] and are diagnostic for its complexation to the Zn metal center in solution. The observed upfield shifts for the *ortho* protons are the result of the sum of the electronic effect upon complexation of the N_{pyr} atom to the Zn complex and the shielding effect of its aromatic groups. This type of shielding phenomenon is well-documented in Zn(II)porphyrin chemistry, although pyridine complexation in these cases leads to significantly larger upfield NMR shifts. The considerable upfield shifts are thus in line with the crystallographic results and the molecular modeling studies performed for this assembly[18] and confirm the presence of pyridyl−Zn coordinative interactions in solution. Furthermore, NOE spectroscopy carried out for **1**·nicotine in CD_2Cl_2 showed also a much stronger NOE contact between H_1 and the 3-positioned *t*-Bu groups of the imine ligand than H_2 (Supporting Information). This suggests that in solution the nicotine guest may exert a preferential position. As for **1**·nicotine, for the assembly **3**·(nicotine)$_2$ similar but somewhat smaller shifts were noted for H_2 ($\Delta\delta = -0.18$ ppm) and for the other pyridyl protons ($\Delta\delta = \pm$ 0.05–0.07 ppm). The other pyridine-containing compounds showed similar NMR spectroscopic features (Table 3), with significant upfield shifts noted for the *ortho*-positioned groups (H or Me) attached to the pyridine ring. These shifts thus again confirm the presence of the expected 1:1 and 1:2 assembled structures in solution. Please note the larger shifts reported for H_3 and H_4 of assembly **5**·(nicotine)$_2$, which is a result of the higher Lewis acidity of the metal center because of the presence of the electron-withdrawing NO_2 groups. Another interesting observation is the shifts that were determined for the nornicotine and norcotinine assemblies in which the pyrrolidine−NMe group is absent. In these cases, both the H_1 as the H_2 hydrogens undergo a similar upfield shift upon coordination, whereas in the former case also upfield shifts were noted for both H_3 and H_4. This points at a larger degree of free rotation of the pyrrolidine ring around the Zn−N_{pyr} bond upon complexation, which is obviously less pronounced for norcotinine as a result

(17) The NMR experiments were carried out by mixing the components in the appropriate stochiometry in d_6-acetone following NMR analysis, except for the crystallized assemblies **1**·nicotine and **3**·(nicotine)$_2$, and crystallized complexes **1**·pyridine, **1**·(2,5-lutidine), and **1**·(2-picoline) which were used directly after their respective isolation.

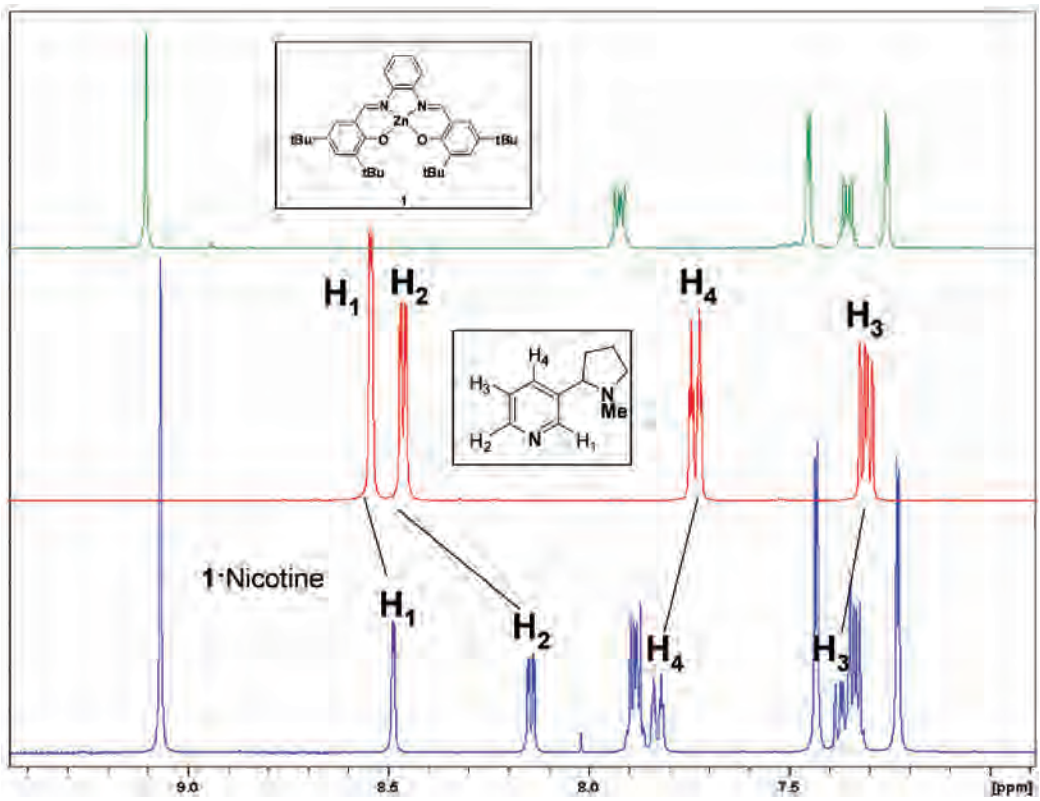
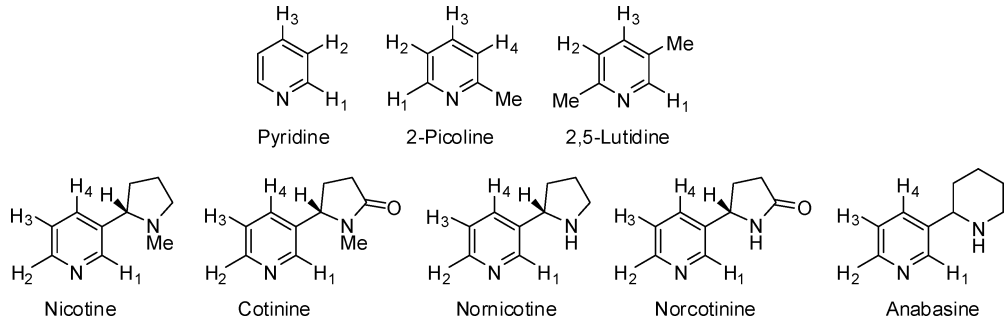


Figure 2. Representative NMR spectra for the complex induced shifts that occur upon coordination of alkaloid species to complex **1**; the presented spectra refer to nicotine coordination.

Table 3. Assembly Formation between Zn(Salphen) Complexes **1**, **3**, and **5** and Various Pyridine-Based Compounds (See below) in d_6-Acetone: Complex induced NMR Shifts



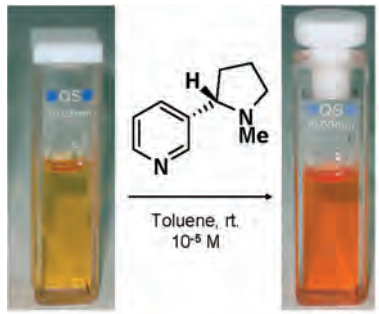
assembly:	H_1	H_2	H_3	H_4	Me
1·Nicotine	−0.08	−0.33	+0.03	+0.09	−0.19
1·Nornicotine	−0.36	−0.26	−0.25	−0.16	
1·Cotinine	−0.12	−0.19	+0.04	+0.11	−0.16
1·Norcotinine	−0.22	−0.15	+0.09	+0.12	
1·Anabasine	−0.10	−0.31	−0.10	+0.07	
1·Pyridine	−0.21	+0.12	+0.16		
1·(2-Picoline)	−0.03	+0.11	+0.05	+0.05	−0.10
1·(2,5-)Lutidine	+0.15	+0.02	+0.10		−0.30
3·$(Nicotine)_2$	−0.05	−0.18	+0.07	+0.05	−0.14
5·$(Nicotine)_2$	+0.07	−0.19	+0.14	+0.19	−0.16

of the presence of a relatively more rigid pyrrolidine ring.

With nicotine being an illustrative example of the alkaloid family, the binding properties between nicotine and complexes **1**–**4** were then primarily investigated by UV–vis titrations carried out in toluene solutions, and additional titration of **1** with cotinine and anabasine was carried out to estimate a possible difference in binding efficiency between nicotine and the other alkaloid species by the metallo-host. Host solutions of approximate 10^{-5} M were freshly prepared and directly titrated with nicotine-containing host solutions. The binding constants were fitted against the appropriate stoichiometries[19] and are summarized in Table 4. Typical UV–vis titration data are presented in the Supporting Information, Figures S1 and S2. As evident from the titration experiments, the binding of nicotine and related alkaloids to the Zn-salphen complex is high, typically up to an order

(18) Modeling studies were performed with a CAChe 7.5 WorkSystem using the implemented MM2 parameter set.

Table 4. Titration Data for Zn(Salphen) Complexes **1**–**4** with Pyridine and Alkaloids Nicotine, Cotinine, and Anabasine:[a] A Typical Color Change Is Shown below upon Titration of **3** with Nicotine (See from Left to Right)



[H]	[H]−[G][b]	K_1 (10^5 M^{-1})	K_2 (10^5 M^{-1})
1	1·[Pyr]	5.27	
1	1·[Nic]	1.53	
1	1·[Cot]	1.68	
1	1·[Ana]	1.19	
2	2·[Nic]	1.13	
3	3·$[Nic]_2$	2.08[c]	1.34[c]
4	4·$[Nic]_2$	1.88[c]	1.25[c]

[a] All experiments were performed with freshly prepared solutions. [b] [Pyr] = pyridine, [Nic] = nicotine, [Ana] = anabasine, and [Cot] = cotinine. [c] Statiscally corrected microscopic binding constant.

of 10^5. For both **3** and **4**, the second binding of nicotine is around two times smaller[20] as compared to the first binding (Table 4), a result that points at an electronic communication between the individual chromophores. This is also supported by the UV–vis spectrum for both **3** and **4** which shows absorption maxima at much longer wavelengths (498 and 490 nm, respectively) than observed for **1** (427 nm) and **2** (408 nm). Interestingly, upon addition of nicotine to compounds **3** or **4**, an increasing colorimetric shift is noted, which may be useful for sensing purposes. Comparison between the binding of nicotine, anabasine, and cotinine at the Zn-center in complex **1** reveals a rather similar association constant (Table 4) as may be expected from the small differences in molecular size/shape while pyridine binds about 4–5 times more strongly to the Zn(salphen) complex **1**.

We then also examined the effectiveness of the nicotine binding to and decomplexation from bis-Zn(salphen) **5**[13] to demonstrate the adsorption potential of such complexes for alkaloid derivatives resembling nicotine (see Figure 3). The choice for bis-salphen complex **5** is based on the dimer formation of the Zn(salphen) units when insufficient steric bulk is present on the 3 and 3′ positions of the salphen backbone.[11c] This derivative is assumed to be polymeric and has a low solubility in most common organic solvents. In solution, the polymeric structure may be disrupted upon addition of suitable donor systems (such as pyridines) affording **5** as a monomeric structure. Indeed, complex **5** is virtually insoluble, but in the presence of nicotine it dissolves readily. This implies that coordination of the pyridine unit takes place, and monomeric **5** is formed. When the reaction was carried out in acetone, the initial suspension of **5** was converted into a clear solution where after an orange solid precipitated. NMR analysis of this product carried out in d_6-dmso revealed that the assembly **5**·(nicotine)$_2$ had been isolated in 82% isolated yield. The 1:2 assembly could be readily dissolved in tetrahydrofuran (THF), and we envisioned that the nicotine guests could be desorbed by treatment with MeI to prevent pyridine coordination by N-alkylation. Addition of the alkyl halide (excess) to a solution of **5**·(nicotine)$_2$ in THF gave rise to a suspension, and after 5 h the mixture was filtered and concentrated to yield an orange solid, which was then analyzed by ^{1}H NMR (d_6-dmso). The spectrum showed that under the applied conditions the total amount of (alkylated) nicotine derivatives[21] was significantly reduced to 34% of the original content, and a mass balance calculation provided an 82% recovery of the adsorption material **5**.[22]

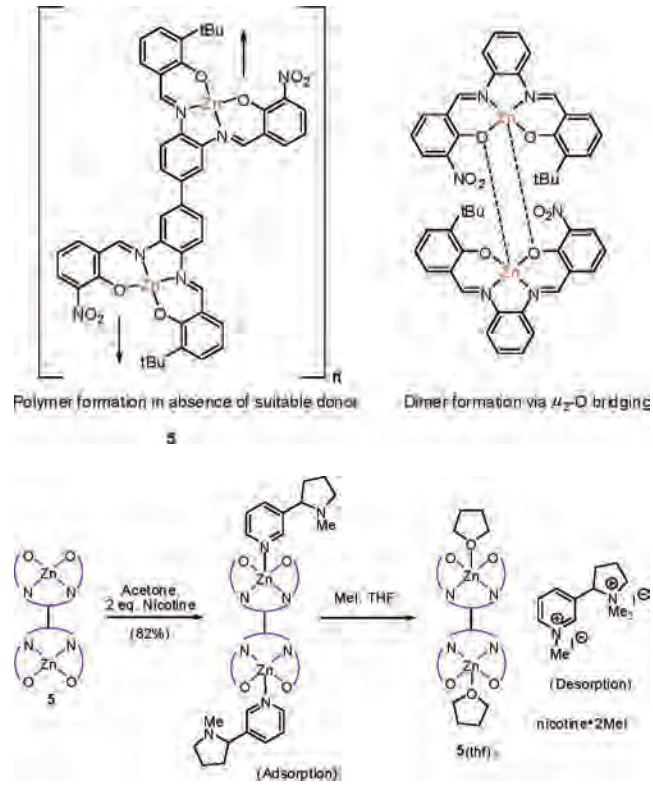


Figure 3. Adsorption and desorption of nicotine using the bis-Zn(salphen) complex **5**.

Conclusion

In summary, we here present new adsorption materials for functional N-heterocycles based on the nicotine alkaloid family

(19) For the software details see Bisson, A. P.; Hunter, C. A.; Morales, J. C. *Chem.—Eur. J.* **1998**, *4*, 845.

(20) The electronically connected Zn metal centers in **3** and **4** are apparently as Lewis acidic as their corresponding mono-Zn complexes **1** and **2**. However, this electronic connection gives rise to a lower binding constant for the second molecule of nicotine.

(21) Treatment of nicotine with MeI in THF gives precipitation of a yellowish solid analyzed as a mixture of three components, that is, both the mono-methylated species as well as the doubly methylated compound (based on MS and ^{1}H NMR data). The latter could be exclusively obtained by in situ treatment of the crude product with excess MeI in DMSO-d_6 (Supporting Information). The nicotine desorption process from **5** could therefore be followed using these reference data and showed the complete absence of the *bis*-alkylated species nicotine·2MeI. Please note that also no free nicotine was observed after the MeI treatment, a result that points at a high level of nicotine desorption.

using readily available (multicentered) Zn(salphen) complexes. The efficient binding of (multiple) alkaloid guests via their respective pyridine N-atoms using a single-point interaction has been clearly demonstrated using UV–vis and NMR spectroscopy and X-ray diffraction. Furthermore, the analytical data suggest that upon complexation with the salphen hosts, the alkaloid guest(s) may acquire(s) a preferred geometrical position both in solution as well as in the solid state, and this is related to the structural nature of the 3-positioned group on the pyridine ring. The difference in nicotine binding affinity between compounds **1** and **2** compared with **3** and **4** demonstrates that the nicotine desorption process[23] will be a function of the Zn(salphen) structure. We have shown, as a proof of principle, that the desorption of nicotine from a bissalphen complex (**5**) can be readily achieved[24] and thus recycling of the adsorption material can be potentially realized. In this respect, it is of interest to examine the affinity of such alkaloids for other types of macrocyclic Zn(salphen) structures[10e,f] that will show similar binding properties but have an even larger separation potential as referred to **5**.[25] Future studies are ongoing to explore in detail the application potential of such composites.

Experimental Section

General Comments. (*S*)-(−)-Nicotine (Fluka, ≥99%), (±)-nornicotine (Sigma, 99%), (−)-cotinine (Fluka, ≥96%) and DL-anabasine (Aldrich) were purchased from commercial sources with a purity of at least 96%. Compounds **1**–**3**[9a,11b] were prepared using previously reported methods. Elemental analyses were performed at the Unidad de Análisis Elemental from the University of Santiago de Compostela (Spain). All NMR measurements were carried out on a Bruker-400 MHz spectrometer at ambient temperature unless stated otherwise, and chemicals shifts are given in ppm versus TMS. Mass spectrometric data were gathered by the Research Support unit of the ICIQ, and MALDI-TOF experiments carried out with DCTB [= *trans*-2-{3-(4-*t*-butyl-phenyl)-2-methyl-2-propenylidene}malononitrile] as matrix.

Synthesis of Ligand Precursor to Bissalphen Complex (4). To a mixture of 1,2,4,5-tetraaminobenzene tetrahydrochloride (0.13 g, 0.46 mmol) in MeOH (25 mL) was added 3-*tert*-butyl-salicylaldehyde (0.36 g, 2.02 mmol). In due course an orange precipitate was noted which was filtered off after 18 h and dried to give the tetraimine product as a yellow to orange solid (0.25 g, 0.32 mmol, 70%). ^{1}H NMR ($CDCl_3$): δ = 13.64 (s, 4H), 8.78 (s, 4H), 7.43 (d, ^3J = 7.6 Hz, 4H), 7.31 (d, ^3J = 7.6 Hz, 4H), 7.19 (s, 2H), 6.90 (t, ^3J = 7.6 Hz, 4H), 1.45 (s, 36H). ^{13}C{^{1}H} ($CDCl_3$): δ = 164.5, 161.0, 141.7, 138.1, 131.1, 131.0, 119.2, 118.5, 111.0, 35.1, 29.5. MALDI-TOF-MS: *m*/*z* 780 (M + H)$^+$. Anal. Calcd for $C_{50}H_{58}N_4O_4$: C, 77.09; H, 7.50; N, 7.19. Found: C, 78.63; H, 7.64; N, 7.27.

Synthesis of Bissalphen Complex (4). To a suspension of the tetraimine ligand precursor (see above, 101.1 mg, 0.130 mmol) in MeOH (150 mL) was added $Zn(OAc)_2\cdot 2H_2O$ (93.4 mg, 0.426 mmol) dissolved in MeOH (5 mL). The mixture was gently heated until a clear deep orange to red solution was obtained. After cooling an orange/red suspension was obtained which was filtered after 16 h to yield a bright red solid (93.0 mg, 0.103 mmol, 79%). ^{1}H NMR (DMSO-d_6): δ = 9.22 (s, 4H), 8.39 (s, 2H), 7.37 (d, ^3J = 6.8 Hz, 4H), 7.26 (d, ^3J = 7.2 Hz, 4H), 6.51 (t, ^3J = 7.5 Hz, 4H), 1.51 (s, 36H). ^{13}C{^{1}H} (DMSO-d_6+5% d_5-pyridine): δ = 172.3, 162.5, 141.6, 138.4, 134.4, 130.5, 119.6, 112.4, 103.2, 35.1, 30.7. MALDI-TOF-MS: *m*/*z* 906 (M)$^+$. Anal. Calcd. for $C_{50}H_{54}N_4O_4Zn_2$: C, 66.30; H, 6.01; N, 6.19. Found: C, 65.98; H, 6.14; N, 6.64.

Synthesis of Bissalphen Complex (5). This complex was prepared by an improved and modified procedure.[13] To a solution of the symmetrical diimine species derived from 3,3′-diaminobenzidine and 3-*tert*-butylsalicylaldehyde[13] (56.0 mg, 0.105 mmol) in $CHCl_3$ (20 mL) was first added a solution 3-nitro-salicylaldehyde (79.7 mg, 0.477 mmol). Thereafter, a solution of $Zn(OAc)_2\cdot 2H_2O$ (97.9 mg, 0.446 mmol) was added, and the mixture was stirred for 18 h. Concentration and trituration of the crude with MeOH afforded, after drying, an orange solid (97.4 mg, 0.101 mmol, 97%) identified as pure **5**. ^{1}H NMR (DMSO-d_6): δ = 9.30 (s, 2H), 9.01 (s, 2H), 8.33 (s, 2H), 8.01 (d, ^3J = 8.6 Hz, 2H), 7.94 (d, ^3J = 8.3 Hz, 2H), 7.86 (d, ^3J = 7.7 Hz, 2H), 7.81 (d, ^3J = 7.8 Hz, 2H), 7.31 (d, ^3J = 7.1 Hz, 2H), 7.25 (d, ^3J = 7.2 Hz, 2H), 6.65 (t, ^3J = 7.7 Hz, 2H), 6.48 (t, ^3J = 7.5 Hz, 2H), 1.46 (s, 18H).

Synthesis of Crystalline Assemblies 1·(2,5-Lutidine) and 1·(2-Picoline). General procedure: Complex **1** (typically 20–30 mg in repeated experiments) was dissolved in hot CH_3CN and then an excess of 2,5-lutidine/2-picoline was added. The orange solution was then allowed to cool to room temperature after which orange crystals quickly deposited. The crystalline material was isolated by decantation and vacuum-dried. The 1:1 assemblies were then analyzed by NMR and MS. For **1**·(2,5-lutidine): ^{1}H NMR (d_6-acetone, 400 MHz): δ = 9.00 (s, 2H, CH=N), 8.45 (s, 1H, pyr−H), 7.82–7.84 (m, 2H, ArH), 7.56 (d, ^4J = 1.8 Hz, ^3J = 7.9 Hz, pyr−H), 7.45 (d, ^4J = 2.7 Hz, 2H, ArH), 7.32–7.34 (m, 2H, ArH), 7.24 (d, ^4J = 2.7 Hz, 2H, ArH), 7.13 (d, ^3J = 7.9 Hz, 1H, pyr−H), 2.27 (s, 3H, NMe), 2.14 (s, 3H, NMe), 1.53 (s, 18H, $C(CH_3)_3$), 1.33 (s, 18H, $C(CH_3)_3$). MS (MALDI-TOF, DCTB): *m*/*z* = 852.5 (M − pyr + DCTB)$^+$, 708.4 (M)$^+$, 602.4 (M − pyr)$^+$. Anal. Calcd for $C_{43}H_{55}N_3O_2Zn$: C, 72.61; H, 7.79; N, 5.91. Found: C, 72.26; H, 7.99; N, 5.95. For **1**·(2-picoline): ^{1}H NMR (d_6-acetone, 400 MHz): δ = 9.01 (s, 2H, CH=N), 8.45 (d, ^3J = 4.6 Hz, 1H, pyr−H), 7.81–7.83 (m, 2H, ArH), 7.73 (dt, ^4J = 1.6 Hz, ^3J = 7.7 Hz, 1H, pyr−H), 7.46 (d, ^4J = 2.6 Hz, 2H, ArH), 7.31–7.33 (m, 2H, ArH), 7.27 (d, ^3J not resolved, 1H, pyr−H), 7.25 (d, ^4J = 2.7 Hz, 2H, ArH), 7.19 (t, ^3J = 5.7 Hz, 1H, pyr−H), 2.39 (s, 3H, NMe), 1.52 (s, 18H, $C(CH_3)_3$), 1.33 (s, 18H, $C(CH_3)_3$). MS (MALDI-TOF, DCTB): *m*/*z* = 1102.6 (M − pyr + 2 DCTB)$^+$, 852.4 (M − pyr + DCTB)$^+$, 602.3 (M − pyr)$^+$. Anal. Calcd for $C_{42}H_{53}N_3O_2Zn$: C, 72.34; H, 7.66; N, 6.03. Found: C, 72.08; H, 7.98; N, 6.17.

(22) Although a complete removal of the nicotine derivatives was not yet achieved as a result of the partial solubility of the mono-methylated nicotine derivatives in THF, the results show that reuse of the adsorption material should be feasible.

(23) NMR studies carried out for **1**·nicotine in d_8-THF (see the Supporting Information) indicate that nicotine binding is still present, but because of the more dynamic character of the N_{pyr}−Zn bond, desorption should be feasible in coordinating solvents. This is in line with the desorption studies carried out with **5** in THF; the more dynamic character of the alkaloid binding allows the nicotine guest to be irreversibly converted into alkylated derivatives without affecting the Zn(salphen) structure. See also: Singer A. L.; Atwood, D. A. *Inorg. Chim. Acta* **1998**, *277*, 157.

(24) No demetalation was observed in **5** under the experimental conditions as shown in our previous work with Zn(salphen) complexes that were treated with N-unprotected (benz)imidazole or purine ligands. Some care should be taken with the kinetic stability of the complexes under various experimental conditions, for example, in the absence of suitable donor solvents. See Escudero-Adán, E. C.; Benet-Buchholz, J.; Kleij, A. W. *Dalton Trans.* **2008**, 734–737.

(25) For an example of a Zn(salen)-based polymeric compounds see Kwok, C.-C.; Yu, S.-C.; Sham, I. H. T.; Che, C.-M. *Chem. Commun.* **2004**, 2758.

(26) For similar *pseudo*-centrosymmetrically resolved structures consult (a) Brock, C. P.; Dunitz, J. D. *Chem. Mater.* **1994**, *6*, 1118. (b) Marsh, R. E. *Acta Crystallogr.* **2005**, *B61*, 359. (c) Flack, H. D.; Bernadelli, G.; Clemente, D. A.; Linden, A.; Spek, A. L. *Acta Crystallogr.* **2006**, *B62*, 695.

Synthesis of the Assembly 5·(Nicotine)$_2$. A suspension of **5** (43.7 mg, 0.0455 mmol) in acetone (1.5 mL) was treated with a solution of nicotine (14.8 mg, 0.0912 mmol) dissolved in acetone (0.5 mL). The suspension was immediately converted into a clear orange solution, after which an orange solid precipitated. The solid was isolated by filtration and dried to furnish an orange solid (48.0 mg, 0.0373 mmol, 82%). The 1:2 stochiometry was fully supported by ^{1}H NMR analysis in d_6-dmso, while a low-concentration ^{1}H NMR analysis could be performed in d_6-acetone. ^{1}H NMR (d_6-acetone): δ = 9.27 (s, 2H, CH=N), 9.03 (s, 2H, CH=N), 8.61 (s, 2H, nicotine−Pyr−H$_1$), 8.31 (s, 2H, ArH), 8.28 (d, ^3J = 4.8 Hz, nicotine−Pyr−H$_2$), 7.99 (d, ^3J = 8.6 Hz, 2H, ArH), 7.93 (d, ^3J = 8.1 Hz, 2H, nicotine−Pyr−H$_4$), 7.90 (d, ^3J = 8.4 Hz, 2H, ArH), 7.82 (d, ^3J = 7.7 Hz, ^4J = 1.6 Hz, 2H, ArH), 7.69 (d, ^3J = 7.0 Hz, ^4J = 1.4 Hz, 2H, ArH), 7.45–7.49 (m, 2H, nicotine−Pyr−H$_3$), 7.30 (d, ^3J = 7.2 Hz, ^4J = 1.3 Hz, 2H, ArH), 7.24 (d, ^3J = 7.8 Hz, 2H, ArH), 6.59 (t, ^3J = 7.7 Hz, 2H, ArH), 6.48 (t, ^3J = 7.5 Hz, 2H, ArH), 3.15 (t, ^3J = 8.0 Hz, 2H, pyrrolidine−H), 3.09 (t, ^3J = 7.3 Hz, 2H, pyrrolidine−H), 2.27 (q, ^3J = 8.8 Hz, 2H, pyrrolidine−H), 2.10–2.18 (m, 2H, pyrrolidine−H), 1.97 (s, 3H, NMe), 1.68–1.85 (br m, 4H, 2 × pyrrolidine−H), 1.49 (s + m, 18H + 2H, C(CH$_3$)$_3$ + pyrrolidine−H). MS (MALDI-TOF, DCTB): *m/z* = 1457.6 (M − 2 pyr + 2 DCTB)$^+$, 1208.5 (M − 2 pyr + DCTB)$^+$, 981.4 (M – 2 pyr + Na)$^+$, 958.3 (M − 2 pyr)$^+$. Anal. Calcd for $C_{68}H_{68}N_{10}O_8Zn_2$: C, 63.60; H, 5.34; N, 10.91. Found: C, 63.35; H, 5.05; N, 11.03.

Desorption Studies with 5·(Nicotine)$_2$. A solution of **5**·(nicotine)$_2$ (9.1 mg, 0.0071 mmol) in THF (0.5 mL) was treated with MeI (0.5 mL, excess) at room temperature. After 5 h, the suspension was filtered and the orange solution concentrated. The orange, solid product (6.5 mg) was then analyzed by ^{1}H NMR (d_6-dmso). Signal integration was used to calculate the mass balance and showed 82% mass recovery for complex **5**. As a pure, reference material, nicotine·2MeI was prepared in situ (d_6-dmso). ^{1}H NMR (nicotine·2MeI, d_6-dmso): δ = 9.38 (s, 1H, Pyr−H$_1$), 9.17 (d, ^3J = 6.1 Hz, 1H, Pyr−H$_2$), 8.88 (d, ^3J = 8.2 Hz, 1H, Pyr−H$_4$), 8.31 (dd, ^3J = 6.1 Hz, 1H, Pyr−H$_3$), 5.14 (dd, ^3J = 8.3 Hz, 1H, pyrrolidine−H), 4.42 (s, 3H, N$_{pyr}$−Me), 3.88–3.94 (m, 1H, pyrrolidine−H), 3.73–3.80 (m,1H, Pyr−H$_2$), 3.20 (s, 3H, NMe), 2.89 (s, 3H, NMe), 2.72–2.82 (m, 1H, pyrrolidine−H), 2.49–2.58 (m, 1H, pyrrolidine−H), 2.22–2.31 (m, 1H, pyrrolidine−H).

Titration Experiments. All experiments were carried out with freshly prepared solutions of the respective Zn(salphen) complex (host solutions of approximate 10^{-5} M) in toluene (predried on $MgSO_4$). Data were collected at ambient temperature on a Shimadzu PharmaSpec UV-1700 spectrophotometer between 300 and 800 nm, and the data set was fitted against the expected stoichiometries using software provided by Prof. C. A. Hunter.[19] The nicotine guest was dissolved in the host solution and subsequently added in small aliquots to the host solution.

X-ray Structure Refinement for Assemblies 1·Nicotine and 4·(Nicotine)$_2$. The compounds **1**·nicotine and **4**·(nicotine)$_2$ crystallize as *pseudo* centrosymmetric structures. This phenomenon has been observed for many structures.[26] Since the nicotine molecules are pure, chiral components (*S*-nicotine), the structures should be normally refined in a noncentrosymmetric space group (in both cases *P*1). But, if a noncentrosymmetric space group is used for refinement, in both cases it is observed that some of the atoms are showing correlation effects and negative atomic displacements parameters (ADP). In the case of using a centrosymmetric space group $P\bar{1}$, the correlation effects can be avoided and no negative ADPs were observed. Upon using centrosymmetric space groups for both structures, the nicotine ligands were refined as disordered in two overlapping structures which should always correspond to *S*-nicotine. This can be explained considering that in the inverted structure (or part of the structure) the nicotine molecule adopts another orientation conserving its stereochemistry. Therefore, the centrosymmetric space group $P\bar{1}$ was considered the best choice for describing the structures of **1**·nicotine and **4**·(nicotine)$_2$.

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Supporting Information Available: Crystallographic details for **1**·nicotine and **4**·(nicotine)$_2$ in CIF-format, and detailed experimental and analytical data and relevant NMR spectra (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

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