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Steric and Electronic Effects in Imine-Hemiaminal Ring-Chain Tautomerism

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Abstract:
We have examined a series of 1,3-dihydro-1-isobenzofuranamines that exist in an imine/hemiaminal ring-chain tautomerism. The tautomeric free energies are rationalized in terms of electronic and steric effects. A series of compounds bearing substituents of varying bulk have free energies that correlate well with substituent A values.

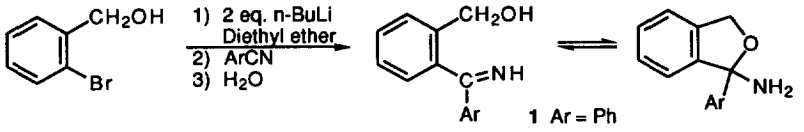
The influence of steric effects in organic reactions is clearly of great importance. Steric hindrance has been termed "the last refuge of the puzzled organic chemist". [1] Many methods of evaluating the steric size of substituent groups have been developed[1-4] but these are often derived from conformational rather than chemical equilibria. Insofar as conformational equilibria allow a measure of substituent size without the influence of electronic effects this may be advantageous. In our efforts to understand the reactivity of molecules and functional groups, the study of steric size using a chemical equilibrium is more useful in determining the interplay of steric and electronic effects. Ring-chain tautomerisms are often convenient systems for the determination of electronic and steric effects associated with ring-forming reactions.[5] From the results, it is often possible to glean valuable information about intermolecular processes, even for intermediates that may not be very stable, such as hemiacetal and hemiaminal species. These latter examples are of considerable interest, as they correspond to the tetrahedral intermediates associated with the hydrolysis of ketals and imines respectively.

We have been engaged in the study of the hydroxy-imine/hemiaminal ring-chain tautomerism shown in Scheme 1. The influence of ortho-substitution on the Ar ring provides a very subtle probe of steric and electronic effects. As substituent R increases in size, the equilibrium constant for the process shown decreases. We have examined equilibria for compounds where R = F, Cl, OCH_3, OCH_2CH_3, CH_3, $CH(OCH_3)_2$, CF_3 and Ph, and where Ar = phenyl, 1- and 2-naphthyl, 9-anthryl and 9-phenanthryl. Equilibrium constants were converted to free energies for correlation with various evaluations of steric size (Table 1).

We have employed hemiaminal precursors to generate substituted isobenzofurans and their homologues. The hemiaminals are easily prepared by the reaction of o-lithiobenzyl alcohols with nitriles (Scheme 1) followed by hydrolysis. In none of the previous examples was there any evidence of any appreciable amount of a chain tautomer.[6] More recently, we have isolated many analogues of **1** that exhibit an imine/hemiaminal ring-chain tautomerism in which both tautomers are observed by proton NMR and whose equilibrium constants are readily measured. Other such systems have been reported,[5,7-16] by comparison with which our

example (Scheme 1) is novel in two principal respects: it involves an N-unsubstituted imine in equilibrium with an amino hemiaminal and it involves an *exo*-trig rather than an *endo*-trig ring closure.

With easy access to a variety of hemiaminals that exhibit ring-chain tautomerism, it was possible to assess the influence of structure on the equilibria. We first examined a series of hemiaminals in which the aryl substituent was a polycyclic aromatic system (Table 1). When Ar is phenyl, only the ring tautomer is observed in solution ($CDCl_3$). The proton spectrum shows an AB quartet centered at ca. 5.3 ppm for the aliphatic protons of the ring and a broad singlet for the NH_2 group. When Ar is 1-naphthyl, both ring and chain tautomers are clearly evident. In addition to signals characteristic of the ring tautomer there is a singlet (or doublet if OH coupled) at approximately 4.9 ppm (CH_2OH) and a broad singlet downfield of the aromatic region that is typical of an imine (C=N-H) proton.[17] The ^{13}C spectrum of the tautomeric mixtures exhibit signals at 100 ppm and 180 ppm due to the hemiaminal and imine carbons respectively.



Scheme 1

Table 1. Tautomerism Free Energies for Different Aryl Substituents

No.	Ar	K_{eq}	$\Delta G°$ (TFE) (kcal/mol)
1	Ph	large	
2	2-Na	large	
3	1-Na	0.52	0.38
4	9-Phenanthryl	0.51	0.40
5	9-Anthryl	small	

A shift towards the chain tautomer in **3** can be explained by steric interactions of the aryl substituent's peri-proton that destabilize the ring tautomer and are absent in the chain compound. Compound **4**, which has the same steric influence as **3**, has a similar equilibrium constant. In **1** and **2**, this steric interaction is diminished and the cyclic tautomer is favoured. Such steric effects have been reported in other tautomeric systems.[18] This effect is additive - when two peri-interactions are present (as in **5**) then the equilibrium is shifted further towards the chain tautomer, an effect which has also been observed for a similar ketone/hemiketal tautomerism.[19]

The results in Table 1 show that larger π-systems (in the Ar substituent) do not significantly enhance the stability of the imine tautomer in our examples. Despite attachment to successively larger π-systems, both **3** and **4** have very similar equilibrium constants. Limited coplanarity of the aryl substituent with the imine would account for the lack of any stabilizing effect. Molecular modeling indicates that steric interactions will limit orbital overlap of the aryl substituents with the imine, particularly on the N-H substituted side of the imine. Comparable conclusions have been drawn based on UV spectral data.[20] The optimum dihedral angle between the C=N and aryl ring is approximately 43° on the NH side and 20° on the other side for a methyl

substituted example (Figure 1). If the hydrogen atom of the imine is swung over to the other side, then the angles are reversed. The former structure is more likely on the basis of an O-H-N hydrogen bond.

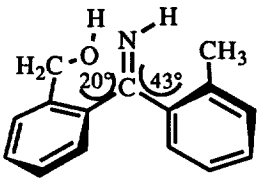
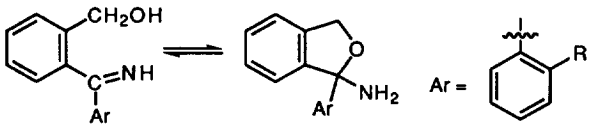


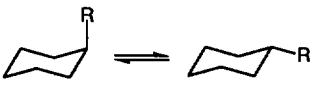
Figure 1.

In order to probe further the steric effects noted in Table 1, we prepared examples in which the aryl group consisted of phenyl rings with different ortho-substituents (Table 2). As the results in Table 1 would predict, there is a general increase in the proportion of chain tautomer as the steric bulk of R increases. Equilibrium constants for R equal to OCH_3 and OCH_2CH_3 are similar despite the fact that the latter has more atoms and might be expected to appear significantly larger. The apparent size similarity of such groups has been attributed to conformations that point the group (or part of it) away from the steric interaction.[21] The small differences observed have been rationalized in terms of restricted rotomer populations leading to a slight entropy decrease.[22] This would also account for the similarity of CH_3 and $CH(OCH_3)_2$.

Table 2: Tautomerism Free Energies for Substituted Aryl Rings



TFE = -ΔG° for ring/chain tautomerism



A value = -ΔG° for equatorial/axial conformers of monosubstituted cyclohexanes

R	No.	K_{eq}	TFE (ΔG) (kcal/mol)	A value[a]	Van der Waals radii (Å) [26]
H	**1**	> ca. 50		0	1.2
Ar = 2-Naphthyl	**2**	> ca. 50		0	1.2
F	**6**	> ca. 50		0.15	
OCH_3	**7**	5.5	-1.0	0.60	1.52
OCH_2CH_3	**8**	3.2	-0.69	0.94[b]	1.52
Cl	**9**	2.2	-0.47	0.43	1.75
Ar = 1–Naphthyl	**3**	0.52	0.39	1.59[c]	
Ar = 9-Phenanthryl	**4**	0.51	0.40	1.59[c]	
CH_3	**10**	0.38	0.58	1.70	2.23
$CH(OCH_3)_2$	**11**	0.35	0.62	1.7[d]	2.2
CF_3	**12**	0.10	1.36	2.1	2.74
Ph	**13**	0.17	1.06	2.8	

[a]These are the "best values" as compiled by Hirsch.[27] [b]Average of two values.[28] [c]Average of two values for vinyl. [d]Value for methyl.

In these equilibria, it is possible that a mixture of steric and electronic effects operate. Electron-donating substituents would be expected to stabilize the chain tautomers by electron-donation to the imine while electron-withdrawing groups would have a destabilizing effect. Electronic effects have been studied for other imine/hemiaminal systems and they exhibit linear correlations with σ^+ parameters.[10,13-16,23-25] The results in Table 1 suggest that substituents acting through the arene π-system (methoxy and ethoxy) might exert only a weak stabilizing influence that would be offset by their electron-withdrawing character. Electron-withdrawing groups that operate inductively would still be expected to have a destabilizing effect. In an effort to determine whether steric or electronic effects are dominating, the equilibrium constants in Table 2 were converted into free energies so that correlations with various evaluations of steric size would be possible.

Over a wide range of substituents there is a good correlation between the tautomerism free energies (TFEs) and A values of the corresponding substituents (Figure 2).[22,27,28] For R equal to OCH_3, OCH_2CH_3, vinyl (approximated by **3** and **4**), CH_3 and CF_3, a plot of TFE versus A value is linear with an r^2 value of 0.99 (Figure 2). The y intercept in Figure 2 (an A value of 0 corresponding to a hydrogen atom substituent) allows prediction of an equilibrium constant of 45 for **1**. This corresponds to a very small amount of chain tautomer and, because of the detection limits of NMR, no chain tautomer is observed and we cannot evaluate an equilibrium constant for **1**. The additional benzo ring-fusion of the 2-naphthyl substituent does not present any additional steric influence over that of a phenyl substituent. One would expect, therefore, that **1** and **2** would have similar equilibrium constants.

The slope of the line indicates that the tautomerism is more sensitive to substituent size than axial/equatorial conformational changes in cyclohexane. The good correlation with A values implies that electronic effects do not play a significant role in determining the value of the equilibrium constants and that steric effects are principally responsible for the relationship between K_{eq} and R.

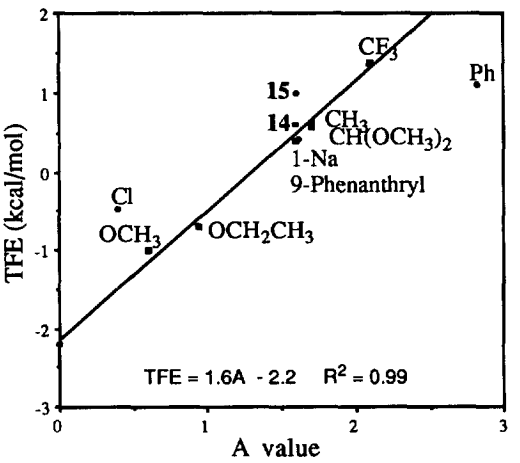


Figure 2: TFEs vs. A values

TFE values also correlate smoothly with the Van der Wäals radii of Bondi[26] if the r_{max} values of Charton for methyl and trifluoromethyl are used (Figure 3).[29] This plot is not linear, nor is there any reason to expect it to be. It does, however, show a smooth increase in TFE with van der Waals radii over a good range of substituent size. The improved correlation with r_{max} values implies that the steric influence of the methyl group does not involve "cogwheel" effects that have been observed in other systems.[30]

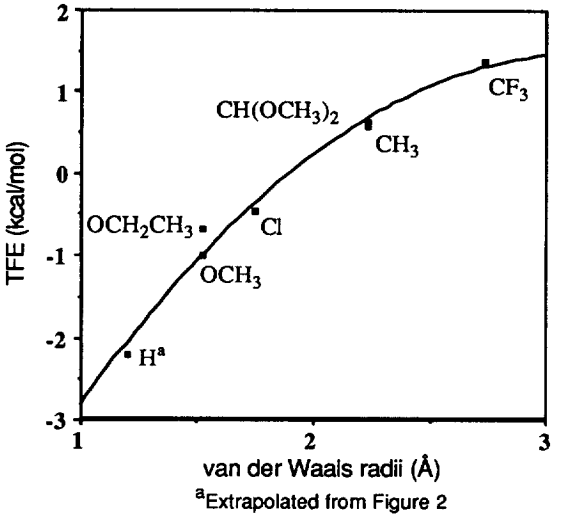


Figure 3: TFEs vs. van der Waal Radii

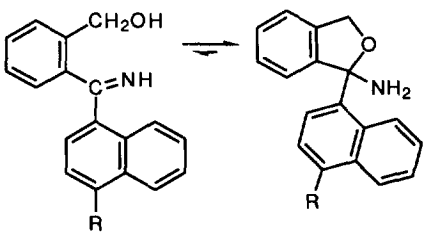
Three substituents, F, Cl and Ph, do not correlate with A values. The case of R equal to Cl is understandable since Cl, and the larger halogens, have A values that do not simply correlate with steric bulk.[22] For the halogen series, as the C-X bond-length increases the substituent rises above the 1,3-diaxial hydrogens, decreasing the interactions that account for the magnitude of A values. This has been cited as a limitation in the ability to apply A values to other systems.[1] In our tautomerism, the longer C-X bond length would be expected to increase the magnitude of the steric interaction. A much better correlation between the TFE of **9** and van der Waals radius of Cl is observed (Figure 3).

The data point for **6** (R equals F) lies somewhere below the line in Figure 2. The Hammett σ_p constant of F is small due to a balance of electronegativity versus π-donation. If we assume that an ortho-substituted F atom has similar electronic properties then one might expect to see only a steric effect. If the substitutents size, slightly greater than that of H, prevents co-planarity of the Ar ring with the imine as described above, then an electron-withdrawing inductive effect would destabilize the imine tautomer and give the observed preference of cyclic tautomer. If this is true for F, however, it should also be true for CF_3 and yet this latter example correlates on the basis of only a steric effect. It is not clear, therefore, why this substituent is anomalous.

The correlation in Figure 2 also breaks down for R equal to Ph (**13**). Considering the different nature of the steric interactions in the two equilibria (tautomerism versus cyclohexane conformational equilibria) it is

not surprising that a topologically complex substituent might have a very different influence. Modeling of the cyclic tautomer of **13** indicates that the most stable conformer has the phenyl substituent (attached to the Ar ring) poised face-down over the CH_2O group. Consistent with this, the diastereotopic protons of the CH_2 appear at 3.82 and 4.82 ppm in the proton NMR spectrum, well-upfield of any other examples. In this conformation, the Ph substituent presents only the electron cloud of the aromatic ring. In the cyclic tautomer of **12**, (R equals CF_3) the trifluoromethyl substituent has no orientation in which a fluorine does not point toward the furan ring. On this basis, it is possible to understand why trifluoromethyl has a larger TFE than does phenyl.

We were able to assess the magnitude of an electronic effect by observing the equilibrium of **14** (Figure 4). In this case, the methoxy substituent can, in principle, exert an electronic effect while steric interactions of the naphthalene ring allow observation of both tautomers. A shift in equilibrium consistent with electron-donation of the methoxy group is observed, but is small. This example is included in Figure 2 and its data point lies very near the line.



No.		Keq
3	R = H	0.52
14	R = OCH_3	0.37

Figure 4. Comparison of **3** and **14.**

As stated above, the data in Table 1 suggest that additional conjugation to larger aryl substituents does not seem to stabilize the imine tautomer to any observable degree. We examined the effect of extending the aromatic system fused to the furan ring (also conjugated to the imine in the chain tautomer). In several hemiketal/ketone tautomerisms, linearly extending the π-system of the ring-fusion results in a shift towards the chain tautomer.[6,18,31] Comparison of the equilibrium constants of **14** and **15** show that in this case also, there is a significant shift towards the chain tautomer. This could be a product of the better overlap of the aryl ring on one side of the imine than the other, as discussed above (Figure 1).

Angular ring-fusion (as in **16**) shifts the equilibrium substantially toward the ring tautomer. The cyclic tautomer can adopt a stable conformer in which the angular benzo-ring is staggered with respect to the amino and aryl substituents. This has been observed for other systems.[32] The proton NMR spectrum of **16** is unusual in that the AB quartet of the CH_2O group and the methoxy resonances exhibit line-broadening due to an exchange process on the NMR time scale. Warming the sample or addition of an acid catalyst causes additional broadening. The exchange process may be racemization of **16** via the acyclic tautomer. This interconversion is slow (on the NMR time scale) for all other examples and it is not clear why this particular example should be unique. It is possible that both tautomers are destabilized by the size of the acetal substituent relative to the transition state for ring-opening and ring-closing, lowering the activation barriers of both processes.

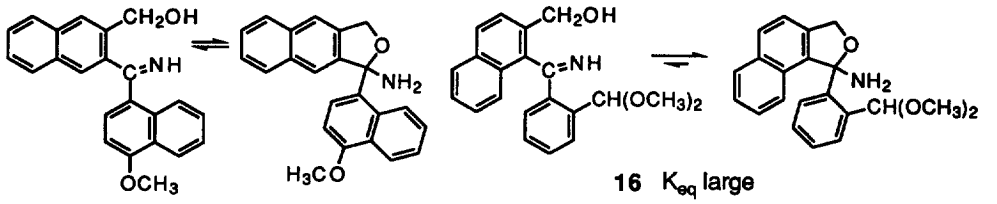


Figure 5. Effects of Ring-fusion to the Isobenzofuran ring

The IR spectra show that most compounds exist as the cyclic tautomer in the solid state. Spectra exhibit two weak bands in the 3200-3400 cm-1 range attributable to symmetric and asymmetric N-H stretches. In contrast, solution IR spectra of several compounds (**4**, for example) have strong O-H stretching bands. Only compounds **5**, **12** and **13**, which display the greatest proportions of acyclic tautomer in solution, exist as the acyclic tautomer in the solid state. These all exhibit strong O-H bands in the IR spectra of the solids.

In principle, all of the hemiaminals described in this paper are potential precursors to aryl-substituted isobenzofurans. We are interested in determining how steric effects may influence the formation and subsequent reaction of such isobenzofurans. Of particular interest, for example, is comparison of **4** and **5**. The isobenzofuran derived from **5**, for example, has both faces blocked by the anthryl substituent. We have been able to trap Diels-Alder adducts (using DMAD and methyl acrylate) of **4** but have had no success trapping the isobenzofuran derived from **5**. Compound **16** is a precursor to 1-[2-(dimethoxymethyl)phenyl]naphtho[1,2-c]furan which, like the parent naphtho[2,3-c]furan,[33] is isolable. We will report on these experiments at a future time.

Experimental Section

Solvents were used without additional purification with the exception of diethyl ether and THF, both of which were distilled from sodium metal prior to use. All organic starting materials were purchased from the Aldrich Chemical Co. unless noted otherwise. Melting points were performed in open capillaries and are uncorrected. NMR spectra were recorded on a Brüker AC-250 NMR spectrometer at an ambient temperature of 298K. Spectra which were used for the calculation of equilibrium constants were run with a routine delay of 10 seconds between pulses. Solutions were run as dilute solutions in $CDCl_3$ unless otherwise noted. Typically, the CH_2 resonances of the ring and chain forms were compared. IR spectra were recorded on a BOMEM MB-102 FTIR. Mass spectra were performed by the Mass Spectroscopy Lab, Department of Chemistry, University of Alberta. Elemental analyses were performed by M-H-W Laboratories, Phoenix Arizona. Molecular modeling calculations (MM+ and MNDO) were performed using HyperChem© release 4.5, Hypercube, Inc., #7-419 Phillip Street, Waterloo, Ontario, N2L 3X2, Canada.

The preparation of compound **1** has been reported.[6] A typical preparation of the novel hemiaminals is given for **2**. Those cases in which THF was used as the reaction solvent are noted. Recrystallization solvent and unoptimized yields are given for all examples. Preparations that deviated from that of **2** are given in full. In some cases, proton NMR signals are attributed to the chain (RO) or ring (RC) tautomer for clarification.

1,3-Dihydro-1-(2-naphthyl)-1-isobenzofuranamine, 2. In a 2-necked 250 mL round bottom flask under nitrogen, 0.7 g (3.74 mmol) of 2-bromobenzylalcohol was dissolved in 125 mL of dry diethyl ether and cooled to -80°C for 5 minutes. Using a syringe, 3.3 mL of 2.5 M n-BuLi (8.2 mmol) was added and allowed to stir for 10 minutes. The reaction was placed in an ice bath and warmed to 0°C for 10 minutes. Following metalation, 0.64 g (4.2 mmol) 2-cyanonaphthalene (purchased from ICN Pharmaceuticals, Plainview NY) was added and the mixture was allowed to stir at 0°C for an additional 30 minutes. Distilled water was added to the reaction flask (100 mL). The mixture was extracted with diethyl ether and the ether layer dried over $MgSO_4$. This was filtered and the solvent removed under vacuum to give a yellow/brown oil which was crystallized from toluene to give 0.55 g of **2** (35% yield): m.p. 111-112°; ^{1}H NMR (250 MHz, $CDCl_3$) δ 2.51 (br s, 2H), 5.24 and 5.31 (ABq, J=13 Hz, 2H), 7.17-7.29 (m, 3H), 7.39-7.46 (m, 3H), 7.71-7.86 (m, 4H), 8.19 (s, 1H); ^{13}C NMR (62.5 MHz, $CDCl_3$) δ 70.91, 99.38, 121.02, 123.34, 124.04, 124.31, 125.95, 126.90, 127.40, 127.67, 127.98, 128.36, 132.83, 132.97, 138.62, 142.14, 143.29; IR ($CHCl_3$) 3397.8 and 3331.2 (N-H), 2975.3, 2858.3, 1642.1, 1460.6, 1356.9, 1013.5, 969.1, 944.6, 893.6, 860.2, 567.5; (KBr) 3387.7 and 3294.6 (N-H), 1601.0, 1458.3, 1006.9, 972.2, 933.6, 887.3, 763.9, 729.1, 572.9, 480.3, 435.9 cm^{-1}; MS (EI) *m/e* 261 (M+, 20), 245 (48), 244 (100), 243 (14), 216 (14), 215 (60), 134 (23), 107.5 (16). Analysis calc'd for $C_{18}H_{15}NO$: C, 82.73; H, 5.79; N, 5.36; found: C, 82.65; H, 5.69; N, 5.10.

1,3-Dihydro-1-(1-naphthyl)-1-isobenzofuranamine, 3. The reaction solvent was THF. The product was crystallized from toluene giving 0.49 g of the desired material (35%): m.p. 80-81°; ^{1}H NMR (250 MHz, $CDCl_3$) δ 2.80 (br s, 2H, NH_2), 4.84 (s, 2H, RO CH_2), 5.06 and 5.27 (ABq, J=13 Hz, 2H, RC CH_2), 7.08-7.96 (m, 11H), 8.81 (d, J=8 Hz, 1H, RO aromatic), 10.06 (br s, 1H, RO NH), ; IR (Nujol) 3402.6 and 3273.4 (N-H), 1597.2, 1566.3, 1305.9, 1199.8, 1018.5, 893.1, 781.2, 758.1, 576.8 cm^{-1}; MS (EI) *m/e* 261.4 (M+, 17.44), 244.5 (100.00), 215.3 (73.57), 134.2 (9.62). Analysis calc'd for $C_{18}H_{15}NO$: C, 5.79; H, 82.73; N, 5.36; found: C, 5.83; H, 82.84; N, 5.30.

1,3-Dihydro-1-(9-phenanthryl)-1-isobenzofuranamine, 4. The product was crystallized from toluene giving 0.16 g of the desired material. (12% yield): m.p. 142-144°; ^{1}H NMR (250 MHz, $CDCl_3$) δ 2.85 (br s, 2H, exchanges with D_2O), 4.87 (d, J=7 Hz, 2H), 5.10 and 5.30 (ABq, J=13 Hz, 2H), 6.58 (t, J=7 Hz, 1H, exchanges with D_2O), 7.10-7.91 (m, 9H), 8.62-8.84 (m, 4H), 10.11 (br s, 1H); ^{13}C NMR (62.5 MHz, $CDCl_3$) δ 64.96, 69.98, 100.29, 121.43, 122.26, 122.65, 123.17, 124.19, 125.99, 126.04, 126.11, 126.14, 126.60, 126.74, 127.02, 127.18, 127.23, 127.29, 127.51, 127.56, 127.72, 127.84, 128.64, 128.81, 129.08, 129.23, 129.51, 130.54, 130.58, 130.77, 131.12, 131.31, 131.74, 132.48, 136.51, 138.29, 138.42, 139.94, 141.49, 143.34, 179.91; IR (KBr) 3423.9, 3259.9, 1635.7, 1595.2, 1444.8, 1363.8, 1205.6, 1018.5, 960.6, 920.1, 887.3, 723.4; (solution $CHCl_3$) 3256.3 (br O-H), 2973.9, 2861.8, 1601.1, 1568.0, 1451.8, 1359.3, 1301.2, 1116.4, 1019.7, 958.3, 889.3, 582.1 cm^{-1}; MS (EI) *m/e* 311.1 (M+, 3.79), 294.1 (100), 265.1 (51.80), 203.0 (4.88), 176.1 (1.53), 147.1 (8.38), 131.5 (14.70), 91.0 (4.05), 63.0 (2.08), 44.0 (14.65). Analysis calc'd for $C_{22}H_{17}NO$: C, 84.86; H, 5.50; N, 4.50; found: C, 85.03; H, 5.30; N, 4.52.

2-Hydroxymethylphenyl 9-anthryl imine, 5. A solution of 0.760 g (4.06 mmol) of 2-bromobenzyl alcohol in 35 mL of dry diethyl ether was cooled to -80°C under nitrogen. n-Butyllithium (3.6 mL of 2.5 M, 9.0 mmol) was added dropwise over a period of 10 minutes. The reaction mixture was warmed to 0°C for 5 minutes, 0.91 g (4.48 mmol) of 9-anthracenecarbonitrile was added and the mixture stirred for 20 minutes. Distilled water (20 mL) was added and the mixture transferred to a separatory funnel. A solid was filtered off which proved to be **5**. The organic layer was washed with 100 mL of a saturated $NaHCO_3$ solution, 100 mL

of distilled water, dried over $MgSO_4$, and filtered. The solvent was removed by vacuum and the residues recrystallized from toluene giving 0.70 g of **5** (55% yield): m.p. 206-208°; ^1H NMR (250 MHz, $CDCl_3$) δ 5.01 (d, J=9 Hz, 2H), 6.79 (t, J=9 Hz, 1H, exchanges with D_2O), 6.93 (d, J=9 Hz, 1H), 7.03 (t, J=7 Hz, 1H), 7.36-7.42 (m, 2H), 7.46 (t, J=7 Hz, 2H), 7.51 (d, J=7 Hz, 1H), 7.59 (d, J=7 Hz, 1H), 7.78 (d, J=9 Hz, 2H), 8.06 (d, J=9 Hz, 2H), 8.55 (s, 1H), 10.16 (br s, 1H, exchanges with D_2O); ^{13}C NMR (62.5 MHz, $CDCl_3$) δ 65.18, 125.19, 125.57, 126.84, 127.94, 128.17, 128.61, 131.15, 131.30, 131.43, 132.63, 135.30, 138.31, 141.38, 179.76; IR (Nujol) 3213.6, 1604.9, 1327.1, 1203.7, 1176.7, 1016.5, 885.4, 842.9, 740.7; (solution $CHCl_3$) 3242.5, 2922.6, 1940.5, 1820.5, 1623.9, 1599.9, 1567.0, 1447.9, 1372.1, 1321.9, 1114.8, 1055.0, 1022.5 cm^{-1}; MS (EI) *m/e* 311 (M+, 22), 294 (36), 293 (71), 292 (100), 265 (41), 204 (10), 176 (13), 145 (20), 133 (70). Analysis calc'd for $C_{22}H_{17}NO$: C, 84.86; H, 5.50; N, 4.50; found: C, 85.05; H, 5.45; N, 4.48.

1,3-Dihydro-1-(2-fluorophenyl)-1-isobenzofuranamine, 6. The product was crystallized from a toluene/petroleum ether mixture to give 0.235 g of the desired material (33 % yield): m.p. 78-79°; ^1H NMR (250 MHz, $CDCl_3$) δ 2.62 (bs, 2H, NH_2), 5.07 and 5.21 (ABq, J=13 Hz, 2H, RC CH_2), 7.00-7.08 (m, 2H), 7.20-7.50 (m, 6H); ^{13}C NMR (62.5 MHz, $CDCl_3$) δ 70.57, 98.02, 98.05, 116.55 (d, J = 24 Hz), 120.96, 123.52, 123.58, 123.73, 123.79, 127.57, 127.60, 127.63, 128.71, 129.65, 129.80, 130.67, 130.86, 139.83, 141.82, 160.50 (d, J = 248 Hz); IR (Nujol) 3385.3, 3298.5, 1614.5, 1585.6, 1219.1, 1003.0, 924.0, 769.6, 447.5 cm^{-1}; MS (EI) *m/e* 229.4 (100.00, M+), 213.3 (76.83), 183.2 (69.32), 134.2 (48.70), 77.1 (18.50). Analysis calc'd for $C_{14}H_{12}FNO$: C, 73.35; H, 5.28; N, 6.11; found: C, 73.40; H, 5.28; N, 6.05.

1,3-Dihydro-1-(2-methoxyphenyl)-1-isobenzofuranamine, 7. The product was recrystallized from CCl_4 to give 0.35 g product in 54% yield: m.p. 73° C°; ^1H NMR (250 MHz, $CDCl_3$) δ 3.10 (bs, 2H, RC NH_2), 3.76 (s, 3H, RO CH_3), 3.94 (s, 3H, RC CH_3), 4.64 (s, 2H, RO CH_2), 4.92 and 5.15 (ABq, J=13 Hz, 2H, RC CH_2), 6.76-7.50 (m, 8H), 10.4 (br s, 1H, NH); IR (Nujol) 3394.9, and 3319.7 (N-H), 1592.2, 1242.2, 1016.6, 897.0, 750.4 cm^{-1}; MS (EI) *m/e* 241.5 (22.16, M+), 240.5 (21.42), 225.4 (42.17), 224.3 (100.00), 210.3 (35.04), 209.2 (31.73), 195.2 (17.79), 181.2 (58.07), 165.3 (33.56), 152.3 (45.85), 134.2 (35.96), 77.1 (13.98). Analysis calc'd for $C_{15}H_{15}NO_2$: C, 74.67; H, 6.27; N, 5.80; found: C, 74.50; H, 6.10; N, 6.04.

1,3-Dihydro-1-(2-ethoxyphenyl)-isobenzofuranamine, 8. The product was recrystallized in CCl_4 to give 0.62 g of desired product in 51% yield: m.p. 84.5-85.5°; ^1H NMR (250 MHz, $CDCl_3$) δ 1.12 (t, J=7 Hz, 3H, RO CH_2CH_3), 1.40 (t, J=7 Hz, 3H, RC CH_2CH_3), 3.03 (bs, 2H, RC NH_2), 3.96 (q, J=7 Hz, 2H, RO CH_2CH_3), 4.00-4.18 (m, 2H, RC CH_2CH_3), 4.64 (s, 2H, RO CH_2OH), 4.96 and 5.16 (ABq, 13H, RC CH_2OR), 6.79-7.48 (m, 8H), 10.18 (bs, 1H, RO NH); ^{13}C NMR (62.5 MHz, $CDCl_3$) δ 14.35, 14.74, 63.88, 64.00, 64.58, 70.45, 99.64, 112.47, 112.62, 119.93, 120.48, 120.83, 123.99, 126.85, 127.07, 127.29, 128.36, 128.45, 129.12, 129.80, 129.94, 130.37, 130.63, 130.69, 131.36, 140.49, 142.74, 156.48, 177.53; IR (Nujol) 725.3, 748.1, 758.4, 895.0, 1012.7, 1251.9, 1298.2, 1493.0, 1599.1, 3319.7, 3394.9 cm^{-1}; MS (EI) *m/e* 255.0 (M+, 12.70), 238.1 (100.00), 219.1 (72.09), 209.0 (70.01), 181.0 (38.85), 165.0 (4.72), 153.0 (3.90). Analysis calc'd for $C_{16}H_{17}NO_2$: C, 75.27; H, 6.71; N, 5.49; found: C, 75.37; H, 6.63; N, 5.43.

1,3-Dihydro-1-(2-chlorophenyl)-1-isobenzofuranamine, 9. The product was crystallized from a toluene/pet ether mixture to give 0.43 g of the desired material (43% yield): m.p. 73.5 -75°; ^1H NMR (250 MHz, $CDCl_3$) δ 2.71 (bs, 2H, RC NH_2), 4.71 (s, 2H, RO CH_2), 5.08 and 5.23 (ABq, J=2 Hz, 13H, RC CH_2), 6.18 (bs, 1H, RO OH), 7.05-7.60 (m, 8H), 9.92 (bs, 1H, RO NH); ^{13}C NMR (62.5 MHz, $CDCl_3$) δ 64.67, 70.59, 98.96, 120.88, 123.67, 126.19, 126.23, 127.10, 127.44, 127.49, 128.38, 128.43, 128.66, 129.14, 129.26, 130.15, 130.67, 130.92, 131.06, 131.20, 131.66, 132.83, 137.71, 139.79, 140.17, 140.32, 141.56, 141.76,

177.66; IR (Nujol) 3387.2 and 3296.6 (N-H), 1568.2, 1269.2, 1228.7, 1001.1, 922.0, 765.8, 729.1, 428.2 cm^{-1}; MS (EI) *m/e* 245.5 (20.62, M+), 229.4 (45.59), 210.3 (100.00), 194.2 (41.66), 180.2 (19.75), 165.3 (39.87), 134.2 (79.58), 77.1 (22.09). Analysis calc'd for $C_{14}H_{12}ClNO$: C, 68.44; H, 4.92; N, 5.70; found: C, 68.39; H, 5.16; N, 5.73.

1,3-Dihydro-1-(2-methylphenyl)-1-isobenzofuranamine, 10. The product was recrystallized from toluene/pet ether to give 1.3 g product (76%): m.p. 53-54°; ^1H NMR (250 MHz, $CDCl_3$) δ 2.34 (br s, 2H, RC NH_2), 2.06 (s, 3H, RO CH_3), 2.17 (s, 3H, RC CH_3), 4.70 (s, 2H, RO CH_2), 5.08 and 5.25 (ABq, J=13 Hz, 2H, RC CH_2), 6.47 (bs, 1H, RO OH), 7.07-7.82 (m, 8H), 9.72 (bs, 1H, RO NH); ^{13}C NMR (62.5 MHz, $CDCl_3$) δ 19.68, 20.93, 64.80, 69.72, 120.76, 123.38, 125.34, 126.16, 126.79, 127.60, 127.63, 128.11, 128.31, 129.40, 130.68, 130.86, 131.18, 131.73, 132.28, 134.36, 138.21, 139.52, 141.45, 141.55, 142.87, 180.89; IR (Nujol) 3379.5, 3292.7, 1597.2, 1226.8, 997.3, 902.7, 765.8, 733.0, 721.4, 598.0, 434.0 cm^{-1}; MS (EI) *m/e* 225 (M+, 5), 210 (33), 209 (27), 208 (100), 194 (14), 193 (13), 134 (18), 92 (18). Analysis calc'd for $C_{15}H_{15}NO$: C, 79.97; H, 6.71; N, 6.22; found: C, 80.10; H, 6.50; N, 6.13.

1,3-Dihydro-1-[2-(dimethoxymethyl)phenyl]-1-isobenzofuranamine, 11. The electrophile (2-dimethoxymethyl benzonitrile) was prepared by refluxing 2-cyanobenzaldehyde in 10:1 methanol/trimethylorthoformate with Dowex overnight. The protected nitrile was purified by distillation and used as the electrophile for the preparation of **11**. Product **11** was recrystallized in pet ether/toluene mixture to give 0.245 g of product (49% yield): m.p. 63.5-64.5°; ^1H NMR (250 MHz, $CDCl_3$) δ 3.00 (bs, 2H, RC NH_2), 3.19 (s, 6H, RO methyl groups), 3.30 (s, 3H, RC methyl), 3.34 (s, 3H, RC methyl), 4.71 (s, 2H, RO CH_2), 4.82 and 5.09 (ABq, J=13 Hz, 2H, RC CH_2), 4.99 (s, 1H, RO CH), 6.40 (s, 1H, RC CH), 6.41 (bs, 1H, RO OH), 7.04-7.78 (m, 8H), 9.93 (bs, 1H, RO NH); IR (Nujol) 3396.9 and 3321.6 (N-H), 1637.7, 1246.1, 1209.4, 1066.7, 1000.5, 769.6 cm^{-1}; MS (EI) *m/e* 285.4 (0.20, M+), 268.3 (53.33), 253.4 (94.28), 239.5 (26.40), 222.5 (75.08), 221.5 (100.00), 220.4 (91.42), 209.4 (37.29), 193.3 (85.67), 178.3 (45.61), 165.2 (90.61), 152.3 (16.07), 134.3 (52.52), 89.2 (19.32). Analysis calc'd for $C_{17}H_{19}NO_3$: C, 71.56; H, 6.71; N, 4.91; found: C, 71.54; H, 6.76; N, 4.98.

1,3-Dihydro-1-(2-trifluoromethylphenyl)-1-isobenzofuranamine, 12. The product was crystallized from diethyl ether/hexanes in 32% yield: m.p. 72-73°; ^1H NMR (250 MHz, $CDCl_3$) d 4.72 (br s, 2H, RO CH_2), 5.17 and 4.99 (ABq, J=13 Hz, 2H, RC CH_2), 6.12 (br s, 1H, RO O-H), 7.02 (d, J=8 Hz, 1H, RO), 7.20-7.75 (m, 6H), 7.77 (d, J=7 Hz, 1H, RO), 8.02 (d, J=8 Hz, 1H, RC), 9.87 (br s, 1H, RO N-H); ^{13}C NMR (62.5 MHz, $CDCl_3$) d 64.88 (RO CH_2), 70.21 (RC CH_2), 98.88 (RC OCN), 117.15, 121.28, 123.46, 124.44 (q, J = 274 Hz), 126.75 (q, J = 5 Hz), 127.50, 128.62, 129.25, 129.55, 130.18, 131.27, 131.35, 132.18, 132.50, 137.65, 139.79 (q, J = 2 Hz), 141.75, 177.87; IR (KBr) 3242, 1611, 1315, 1137, 1116, 1027, 770 cm^{-1}; MS (EI) *m/e* 279 (M^+, 4), 263 (20), 262 (100), 233 (15), 214 (14), 210 (24), 193 (42), 183 (12), 165 (55). Analysis calc'd for $C_{13}H_{12}F_3NO$: C, 64.51; H, 4.33; N, 5.02; found: C, 64.51; H, 4.50; N, 4.91.

1,3-Dihydro-1-(2-biphenyl)-1-isobenzofuranamine, 13. This product was crystallized from CCl_4 (21 %): m.p. 98-99°; ^1H NMR (250 MHz, $CDCl_3$) δ 3.82 (d, J=13 Hz, 1H, RC CH_2), 4.41 (s, 2H, RO CH_2), 4.82 (d, J=13 Hz, 1H, RC CH_2), 6.33 (bs, 1H, RO OH), 6.94-7.90 (m, 13H, RO and RC aromatic), 9.81 (bs, 1H, RO NH); ^{13}C NMR (62.5 MHz, $CDCl_3$) δ 64.54, 69.69, 120.73, 123.38, 125.84, 126.81, 126.93, 127.04, 127.34, 127.43, 127.67, 128.05, 128.21, 128.67, 128.80, 129.05, 129.86, 130.43, 130.58, 130.68, 131.26, 132.16, 138.73, 139.91, 140.37, 140.74, 141.26, 142.08, 143.00, 144.05, 180.47; IR (KBr) 3223 (br O-H), 1605, 1451, 1362, 1208, 1026, 747, 700 cm^{-1}; MS (EI) *m/e* 287 (M^+, 4), 270 (70), 269 (34), 253 (46), 252

(100), 239 (38), 165 (15), 119.5 (17). Analysis calc'd for $C_{20}H_{17}NO$: C, 83.60; H, 6.06; N, 4.87; found: C, 83.72; H, 6.06; N, 4.82.

1,3-Dihydro-1-[1-(4-methoxynaphthyl)]-1-isobenzofuranamine, 14. This product was recrystallized in toluene to give 0.584 g product (45% yield): m.p. 110° (dec); ^1H NMR (250 MHz, $CDCl_3$) δ 2.72 (br s, 2H, NH_2), 3.95 (s, 3H, OCH_3 RC), 4.03 (s, 3H, OCH_3 RO), 4.79 (d, J=7 Hz, 2H, CH_2 RO), 5.04 and 5.24 (ABq, J=12 Hz, 2H, CH_2 RC), 6.58 (t, 3H, OH RO), 6.62 (d, 1H, RC), 6.70 (d, J=8 Hz, 1H, RO), 7.09-7.60 (m, 8H, RO and RC), 8.28-8.35 (m, 1H, RO and RC), 8.66 (d, J=8 Hz, 1H, RC), 9.93 (s, 1H, NH RO); ^{13}C NMR (62.5 MHz, $CDCl_3$) δ 55.45, 55.70, 64.93, 69.74, 100.18, 102.04, 102.81, 121.32, 122.46, 122.59, 123.96, 124.70, 124.84, 125.07, 125.57, 125.72, 126.17, 126.47, 126.69, 126.74, 127.40, 127.54, 127.57, 128.42, 130.71, 130.84, 131.15, 131.55, 131.98, 132.30, 132.37, 139.32, 139.77, 141.55, 143.81, 155.62, 156.67, 179.79; IR (Nujol) 3262 and 3191 (N-H), 1601, 1581, 1269, 1229, 1092, 1022, 899, 791, 764, 610 cm^{-1}; MS (EI) *m/e* 291 (M+), 275 (22), 274 (100), 259 (31), 231 (36), 202 (43), 137 (13), 101 (13); Analysis calc'd for $C_{19}H_{17}NO_2$: C, 78.33; H, 5.88; N, 4.81; found: C, 78.21; H, 5.66; N, 4.68.

1,3-Dihydro-1-[1-(4-methoxynaphthyl)]-1-naphtho[2,3-c]furanamine, 15. This product was recrystallized in toluene to give 0.078 g product (17% yield): m.p. 146° (dec); ^1H NMR (250 MHz, $CDCl_3$) δ 3.97 (s, 3H, RC methoxy), 4.08 (s, 3H, RO methoxy), 4.96 (s, 2H, RO CH_2), 5.11 and 5.35 (ABq, J=13 Hz, 2H, RC CH_2), 6.65 (d, 8H, RC aromatic), 6.80 (bs, 1H, RO OH), 6.85 (d, 8H, RO aromatic), 7.35-8.63 (m, 10H); IR (Nujol) 3269.6 (N-H), 1712.9, 1583.7, 1510.4, 1273.1, 1232.6, 1170.9, 1086.0, 1022.3, 908.5, 825.6, 765.8, 719.5, 480.3 cm^{-1}; MS (EI) *m/e* 341.0 (M+, 2.10), 324.0 (78.24), 309.0 (14.07), 281.0 (37.06), 251.9 (32.04), 184.9 (6.84), 162.0 (9.19), 126.0 (31.15), 91.1 (100.00); Analysis calc'd for $C_{23}H_{19}NO_2$: C, 80.92; H, 5.61; N, 4.10; found: C, 81.17; H, 5.81; N, 3.89.

1,3-Dihydro-1-[2-(dimethoxymethyl)phenyl]-1-naphtho[1,2-c]furanamine, 16. In 75 mL of THF was dissolved 2.1 g (8.9 mmol) of 1-bromo-2-naphthalenemethanol. The solution was cooled to -80°C under N_2. Butyllithium (7.6 mL of a 2.5 M solution in hexanes, 19 mmol) was added by syringe and the solution warmed to 0°C for 10 minutes. The electrophile, 2-(dimethoxymethyl)benzonitrile (see preparation of **11**) 1.62 g (9.2 mmol) in 25 mL of THF was added by syringe. The reaction was quenched with 100 mL of water and extracted 3 times with 100 mL portions of diethyl ether. The organic phases were dried over $MgSO_4$, filtered and stripped of solvent. Crystallization from ether gave 1.7 g of **17** (56%): m.p. 112-113°; ^1H NMR (250 MHz, $CDCl_3$) δ 3.18 (br s, NH_2 and OCH_3 5H), 3.40 (s, 3H), 4.98 and 4.25 (br ABq, J=12 Hz, 2H), 6.29 (s, 1H), 7.06-7.14 (m, 2H), 7.25-7.49 (m, 4H), 7.79 (d, J=8 Hz, 1H), 7.88-7.91 (m, 2H), 8.23 (br d, J=7 Hz, 1H); ^{13}C NMR (62.5 MHz, $CDCl_3$) δ 52.47, 54.95, 70.15, 101.10, 119.46, 125.19, 125.72, 126.89, 127.67, 128.01, 128.08, 128.15, 128.66, 129.75, 130.24, 133.79, 136.53, 137.50, 138.12, 140.72; IR (Nujol) 3402 and 3324 (N-H), 1211, 1082, 1062, 1016, 969, 763 cm^{-1}; MS (EI) *m/e* 335 (M^+, 2), 318 (62), 304 (26), 303 (100), 271 (82), 259 (46), 258 (19), 243 (19), 194 (42). Analysis calc'd for $C_{21}H_{21}NO_3$: C, 75.20; H, 6.31; N, 4.18; found: C, 75.02; H, 6.04; N, 4.17.

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