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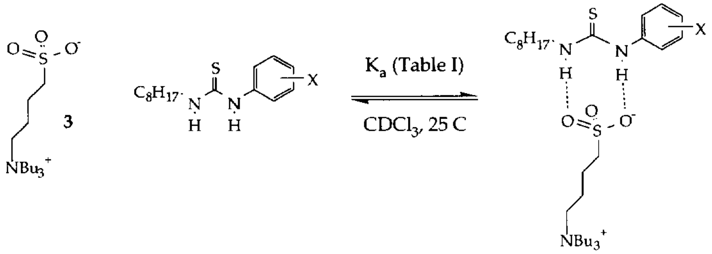
Experimental and Theoretical Studies of Substituent Effects in Hydrogen Bond Based Molecular Recognition of a Zwitterion by Substituted Arylureas.

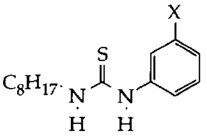
Craig S. Wilcox*, Eun-il Kim, David Romano,
Lung Huang Kuo, Arthur L. Burt, and Dennis P. Curran
Department of Chemistry, University of Pittsburgh
Pittsburgh, Pennsylvania 15260

Abstract: Electron withdrawing groups have a strong effect on hydrogen bonding to aryl ureas. The effect of para substituents modestly exceeds the effect of meta substituents. Among common substituent parameters, σ^- ($\rho = 1.77$, $r^2 = 0.988$) is found to be the best predictor for the observed effects of para substituents in aryl ureas. Semi-empirical and *ab initio* methods are used to calculate charge distributions in substituted benzene derivatives and in these ureas. A comparison of experimental and predicted (AM1, STO3G, 321-G*, 631-G**) dipole moments of benzene derivatives is presented. It is shown that calculated surface electric potentials for these thioureas successfully predict the relative hydrogen bonded association energies.

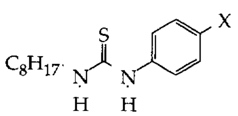
There have been reports in the past few years showing that substituents can have strong effects on association constants in host-guest systems involving hydrogen bond formation. An important example was reported by Etter, who described the excellent hydrogen bonding properties of 1,3-bis-(*m*-nitrophenyl)urea.[2] Hamilton and Whitlock both observed that donor substituents on pyridine rings enhance the binding of acidic substrates that associate through H-bond formation.[3,4] Recent experiments involving substitutions in RNA hairpin structures have led to the proposal of a strong "context dependence for the free energy of hydrogen bond formation".[5] Here we report results of a systematic study of substituent effects in arylurea binding to a zwitterion in chloroform solution. Empirical and theoretical approaches to predicting association energies are evaluated.



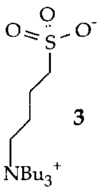
We have recently been investigating N-arylureas for binding of ionic species and neutral molecules.[6,7] Substituents in this system have a large effect on binding. In order to further illuminate the cause of the effect of substituents in N-arylurea hydrogen bonding, a series of N-octyl-N'-arylthioureas were examined. One meta-substituted thiourea (**1**) and a series of para-substituted thioureas (**2a-2h**) were prepared by standard methods. (Experimental Section) Association constants (K_a) for binding of these ureas to 4-tributylammonium-1-butanesulfonate (**3**) were measured in $CDCl_3$ at 25 °C by NMR spectroscopy.[8] (Table 1)



1, X=NO_2



2a, X=H **2e**, X=$COOC_2H_5$
2b, X=NO_2 **2f**, X=C_6H_5
2c, X=CN **2g**, X=OC_2H_5
2d, X=CF_3 **2h**, X=$N(CH_3)_2$



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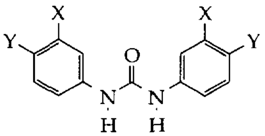
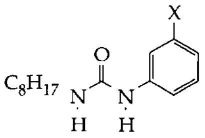
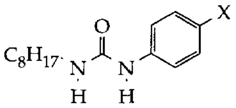


4, X=NO_2, Y=H
5, X=H, Y=NO_2



6, X=NO_2



7, X=NO_2

Etter observed that 1,3-bis-(m-nitrophenyl)urea (**4**) formed crystalline complexes with moderate hydrogen bond acceptors but 1,3-bis-(p-nitrophenyl)urea (**5**) did not form such crystals. On this basis it was hypothesized that the meta effect was unique. It was further suggested that the effect of a meta nitro group on an ortho C-H bond might lead to enhanced C(H)···O interactions.[2] Such interactions would inhibit intermolecular hydrogen bonding to the carbonyl group and this effect might explain the unique behavior of the meta-nitro arylureas in those cocrystallization experiments.

The effect of a nitro group meta to the urea in our molecules is to increase the binding constant and this agrees with Etter's observations. The meta nitro group increases the binding energy from -2.3 kcal/mol (**2a**, Table 1) to -4.5 kcal/mol (**1**, Table 1). In regard to the relative effectiveness of meta and para substituents, however, the results of these binding experiments provide an interesting contrast with the cocrystallization experiments. In cocrystallizations, the para substituted urea failed to form complexes with moderate hydrogen bond accepting groups.

Table 1. Association constants for aryl ureas binding to zwitterion **3** at 25 °C in $CDCl_3$.

Urea receptor	$K_a^{1:1}$ (M^{-1})	ΔG^o (kcal/mol)	Dipole Moment (D) [AM1/631G*]
1 (X = NO_2)	$2.1 \pm 0.8 \times 10^3$	-4.5	b
2a (X = H)	$4.5 \pm 0.2 \times 10^1$	-2.3	4.72
2b (X = NO_2)	$6.6 \pm 0.8 \times 10^3$	-5.2	9.08
2c (X = CN)	$3.4 \pm 0.3 \times 10^3$	-4.8	8.53
2d (X = CF_3)	$5.8 \pm 0.8 \times 10^2$	-3.7	7.42
2e (X = $COOC_2H_5$)	$5.9 \pm 0.5 \times 10^2$	-3.8	6.10[a]
2f (X = C_6H_5)	$7.4 \pm 0.3 \times 10^1$	-2.5	4.74
2g (X = OC_2H_5)	$3.1 \pm 0.4 \times 10^1$	-2.0	4.53[a]
2h (X = NMe_2)	$1.0 \pm 0.9 \times 10^1$	-1.4	4.04
6 (X = NO_2)	$6.3 \pm 5.9 \times 10^3$	-5.2	b
7 (X = NO_2)	$1.5 \pm 0.5 \times 10^4$	-5.7	b

[a] Average of two principle conformers, weighted by population. [b] Not calculated.

For binding by 1:1 complexation to the zwitterion **3**, however, the para-nitro thiourea **2b** is *more* effective than the meta-nitro thiourea. The difference is not large, but the association energy increases by -0.7 kcal/mol, to a total of -5.2 kcal/mol, in going from the meta to the para derivative. A C(H)...S interaction in the thioureas might be less important than the C(H)...O interactions that Etter proposed, so we prepared oxyureas **6** and **7**. Here, too, the para derivatized urea has the greater affinity for this zwitterion. For binding to zwitterion **3**, the oxyurea association constants are about 3 times larger than the analogous thiourea association constants.[9]

The trend found is that introduction of electron withdrawing substituents leads to stronger binding. Strongly donating substitutents decrease binding relative to **2a**, the urea with no substituent. The binding affinities correlate poorly with σ_p. A plot of $\log(K/K_H)$ versus σ_p gives $\rho = 1.96$, $r^2 = 0.935$. A better linear free energy relationship is found using σ_m ($\rho = 3.29$, $r^2=0.968$) and this suggests that inductive or field effects play a role in the observed changes in binding.[10] Correlation is best with σ^- ($\rho = 1.77$, $r^2 = 0.988$).[11] (Figure 1a) The fact that meta substituents have nearly as large an effect as para substituents suggests that field effects of the substituents may be important. We used a two parameter regression model to fit a plot of $\log(K/K_H)$ versus $f\mathcal{F} + r\mathcal{R}$, where $\mathcal{F}$ and $\mathcal{R}$ are the field and resonance parameters recommended by Swain, et al.[12] (Figure 1b) The correlation is acceptable ($r^2 = 0.983$), but improvement is to be expected for a two parameter regression. Following Swain's treatment, the coefficients of this regression analysis ($f = 1.61$, $r = 0.52$) can be interpreted to mean that 24% of the observed effect is due to resonance interactions. This can be compared to σ^-, which is said to be 59% due to resonance, σ^+ (62% resonance),

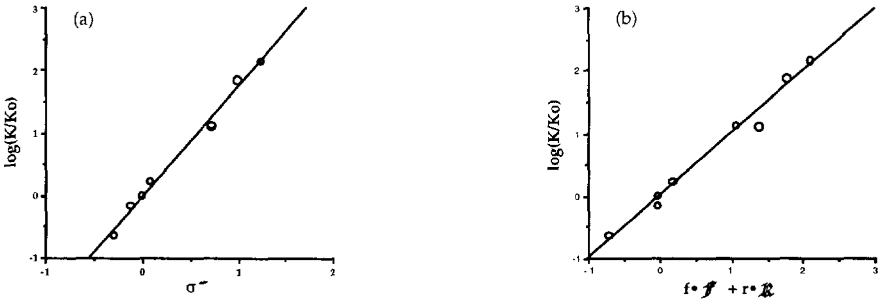


Figure 1. Linear free energy relationships for relative association constants (Table 1) based on (a) σ^- and (b) Swain's two parameter regression.

σ_p (38% resonance), and σ_m (20% resonance). Dividing observed effects among resonance and field contributions has been criticized, and we feel that this type of analysis should be considered only to provide additional qualitative evidence that both field and resonance effects are significant in affecting hydrogen bonding in these systems.[13]

For this system the acidity of substituted phenols (σ^-) best correlates with the observed binding constants. Although correlation with σ^- is excellent, this cannot be taken as evidence that deprotonation occurs upon binding. The UV spectra of these hosts show only the expected bathochromic shift induced by binding of the zwitterion **3** (Table 2, Experimental Section) and no deprotonation is observed. Nevertheless acidity (when known) may be a useful parameter for predicting relative binding of other arylurea based host-guest systems. It is interesting to consider how the value of ρ may vary in other binding events involving less charged hydrogen bond acceptors. The magnitude of ρ may vary with basicity and charge of the guest.

What is the origin of these changes in assocation constant and how may they be predicted? Introduction of nitro or cyano groups in these ureas has several results. Geometry will be only slightly changed, but the charge distribution in the molecules is greatly affected, and the direction and magnitude of the dipole moment will therefore change. Because the zwitterion also has a substantial dipole moment, increasing the dipole moment of the urea will affect the association energy. However, while dipole-dipole interactions do influence the observed binding, *a subset of short range coulombic effects in the vicinity of intermolecular contact will dominate the binding.* The field effect of the substituent has an important role in modifying the electrostatic potential (electric field) in the vicinity of the hydrogen bonding functional group. We think that when a nitro or cyano group is introduced in the meta or para position the overall dipole changes, but the most important effect is that the electric potential at the molecular surface adjacent to the N-H bonds becomes more positive due to changes in local electric field caused by through-space field substituent effects and by electron redistribution.

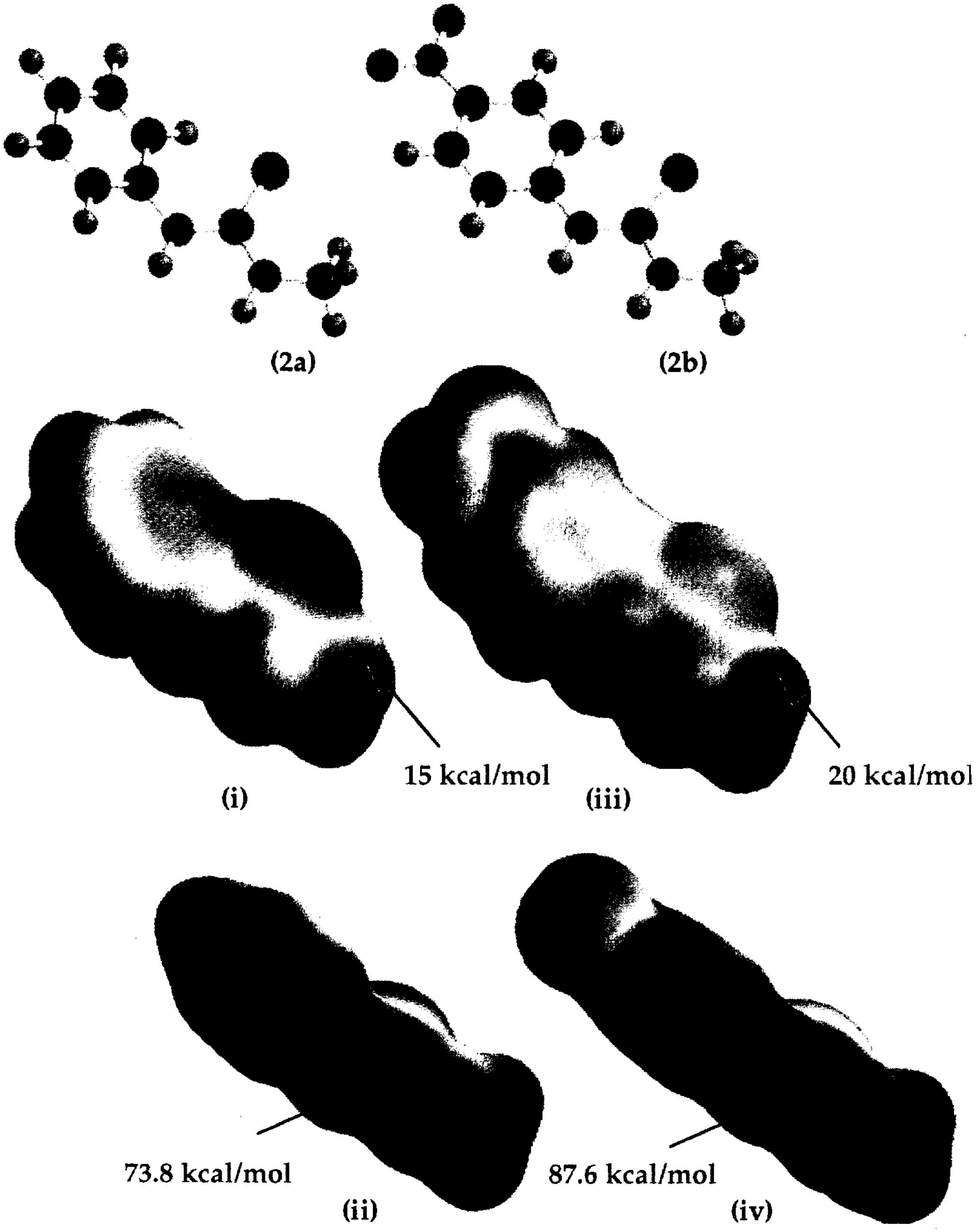


Figure 2. (*i, ii*) Two views of receptor **2a** showing electrostatic potential (AM1 geometry optimization/631-G* HF potentials) mapped onto the total electron density surface. Ball-and-stick figures (top) are presented for comparison. (*iii, iv*) Two comparable views of the nitro group containing receptor **2b**. The color scale is constant for all four surfaces.

To illustrate some of these effects, we used Hartree-Fock (HF) methods (631G* basis set) to calculate the electrostatic potential energy in the vicinity of thioureas **2a** and **2b**.[14] Figure 2 presents, in addition to ball-and-stick representations of **2a** and **2b**, two views (**i** and **ii**) of the total molecular electron density surface of 1-methyl-3-phenylurea (**2a**) and two comparable views (**iii** and **iv**) of 1-methyl-3-(4'-nitrophenyl)urea (**2b**). In all four views the surfaces have been colored to indicate relative electrostatic potential. The most positive potentials are colored blue and most negative potentials are colored red. The color scale is the same for each of the four surface images, so comparisons are readily made.

As expected, the nitro containing molecule (AM1 geometry optimization) is more planar than the unsubstituted molecule. The optimum aryl-N dihedral angle is 41° for 1-methyl-3-phenylurea and 21° for 1-methyl-3-(4'-nitrophenyl)urea. The figure reveals that a nitro group has especially striking effects on surface electrostatic potentials. The nitro group substantially changes (makes more positive) the electric potential in the vicinity of the urea. For example, comparison of **i** with **iii** shows that the sulfur electron density surface becomes less negative and the surface of the methyl group becomes more positive. A different view is presented in **ii** and **iv**. Comparisons here shows that the maximum positive potential (at the N-H region of both molecules) is increased by the nitro group. On introduction of the nitro group, the electrostatic potential at the molecular surface changes from +73.8 kcal/mol to +87.6 kcal/mol. This increased positive potential in the vicinity of the N-H bonds will lead to increased affinity for the charged sulfonate region of the guest, a region that has a substantial negative electric potential. Calculated electrostatic surface potential in the region of intermolecular contact might therefore correlate well with the observed relative binding affinities.

To quantitatively test this idea, we used AM1 to optimize the geometry of thioureas **2a-2h**, and then calculated dipole moments by HF methods using a 631-G* basis set. Atomic charge distributions were calculated by a grid method.[15] This protocol (AM1/631-G*) was compared to several alternative approaches by calculating dipole moments for eight benzene derivatives. Calculated dipole moments for these benzene derivatives were compared with their known gas-phase dipole moments. Five methods of geometry optimization/charge calculation were compared: (a) AM1/AM1, (b) STO3G/STO3G, (c) 321-G*/321-G*, (d) AM1/631G*, (e) 321-G*/631-G**. (Figure 3) We chose for the present to pursue the AM1/631G* protocol rather than more advanced methods (which would include the effects of configuration interaction and geometry optimization with a larger basis set) because the AM1/631-G* method gave good values for dipole moments and can be extended economically to much larger molecules.[16]

This AM1/631G* method was applied to thioureas **2a-2h**. Calculated dipole moments for the urea receptors are included in Table 1. These dipole moments do not correlate well with the observed free energies of association (R^2 = 0.946, Figure 4a). A modified set of dipole moments, created by projecting the calculated moments onto a line defined by the C-S double bond, led to no better correlation. In contrast, calculated maximum electric potentials at the electron density

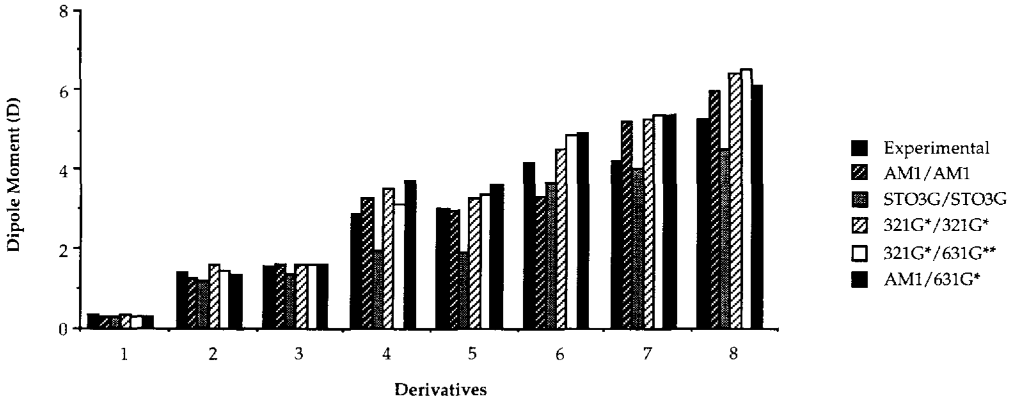


Figure 3. Experimental and calculated dipole moments of 8 benzene derivatives: 1, toluene; 2, anisole; 3, aniline; 4, trifluoromethylbenzene; 5, acetophenone; 6, benzonitrile; 7, nitrobenzene; 8, 4-nitroanisole. Results for five methods of calculation are shown.

surface give an excellent correlation with the observed energies of association ($r^2 = 0.980$, Figure 4b). The sole outlying point is that of the trifluoromethylated receptor. This point may be misplaced because AM1 does not well predict the geometry for the trifluoromethyl group. When this point is excluded, the correlation with dipole moment is only slightly improved ($r^2 = 0.955$), but the correlation with surface potential becomes outstanding ($r^2 = 0.997$). This greatly strengthens our proposal that it is the local electric field effects in the vicinity of the urea that most strongly influence the observed binding phenomena. The relatively poor correlation with net dipole moment should be unsurprising: many molecules with no dipole moment (i.e., terephthalic acid) are quite effective at hydrogen bond formation.

These studies of substituent effects on hydrogen bond enforced molecular recognition indicate that calculated local electric field strengths can be valuable indicators of molecular affinity. The studies confirm the expectation that inferences concerning relative binding affinity that are based on crystal engineering studies are not necessarily applicable to solution binding phenomena. We find that para and meta electron withdrawing substituents both have a strong effect on binding of ureas to this amphoteric salt. The effect of the para substituent is slightly greater than that of the meta substituent and the binding affinities correlate well with with σ^-. This empirical correlation is not of general use because substituent constants and knowledge of relative pK_a's are seldom available in cases where more complex hydrogen bonding surfaces are involved. In a search for an alternative predictor, it was found that the observed affinities are not well explained by the molecular dipole moments. Calculated (AM1/631-G*) surface electric potentials for these ureas, however, correlate well with the observed phenomena and such calculations may provide a generally applicable method for predicting relative association energies for other more complex receptor-substrate pairs.

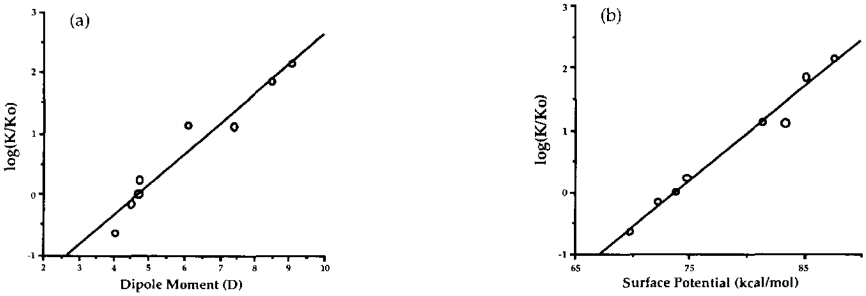


Figure 4. (a) Correlation of calculated dipole moments (AM1/631-G*) for ureas **2a-2h** with relative association free energies. (b) Calculated (AM1/631-G*) electron density surface electric potentials for ureas **2a-2h** better predict the observed relative association free energies.

Experimental.[19]

1-(*N*-Octylamino)-*N*-(3-nitrophenyl)methanthioamide (1): To a mixture of 3-nitroaniline (1.18 g, 8.55 mmol) and triethylamine (3.5 mL, 25.16 mmol) in THF (170 mL) was added dropwise thiophosgene (0.7 mL, 9.18 mmol) at 0 °C. After addition, the reaction mixture was allowed to stir at 25 °C for 12 h. Water (150 mL) was added and the mixture was extracted with diethyl ether (2 x 150 mL). The combined organic layers were washed with water (150 mL) and brine (150 mL), and dried over magnesium sulfate. Concentration and purification by flash column chromatography (hexanes/EtOAc = 20/1) yielded 3-nitrophenyl isothiocyanate as a pale brown solid (1.46 g; 95 %): mp 40-42 °C; ^{1}H NMR ($CDCl_3$) δ 8.14-8.10 (1 H, m), 8.05-8.04 (1 H, m), 7.60-7.52 (2 H, m); ^{13}C NMR ($CDCl_3$) δ 148.7, 139.5, 133.2, 131.5, 130.5, 121.8, 120.7; IR (thin film) 2118, 1533, 1473, 1350, 810 cm^{-1}; MS, *m/z* 180, 134, 90; HRMS, *m/z* calcd for $C_7H_4O_2N_2S$ 179.9959, found 179.9959.

To a stirred solution of 3-nitrophenyl isothiocyanate (0.62 g, 3.44 mmol) in THF (8 mL) was added *n*-octylamine (0.44 g, 3.44 mmol) in THF (8 mL) at 25 °C. After addition, the reaction mixture was allowed to stir at 25 °C for 12 h. Concentration and purification by flash column chromatography (hexanes/EtOAc = 3/1) yielded thiourea **1** as a yellow solid (1.05 g; 99 %); mp 97-99 °C; ^{1}H NMR ($CDCl_3$) δ 8.47-8.03 (3 H, m), 7.76-7.58 (2 H, m), 6.49-5.97 (1 H, broad), 3.62 (2 H, m), 1.63 (2 H, m), 1.26 (10 H, m), 0.87 (3 H, m); ^{13}C NMR ($CDCl_3$) δ 180.2, 148.6, 138.4, 130.5, 130.2, 120.7, 118.8, 45.4, 31.7, 29.1 (2 carbons), 28.7, 26.9, 22.6, 14.1; IR (thin film) 3341, 2926, 1527, 1352, 1255 cm^{-1}.

1-(*N*-Octylamino)-*N*-phenylmethanthioamide (2a): To a stirred solution of phenyl isothiocyanate (0.59 g, 4.37 mmol) in THF (11 mL) was added *n*-octylamine (0.56 g, 4.37 mmol) in THF (11 mL) at 25 °C. After addition, the reaction mixture was allowed to stir at 25 °C for 12 h. Concentration and purification by flash column chromatography (hexanes/EtOAc = 5/1) yielded thiourea **2a** as a pale yellow solid (1.14 g; 99 %): mp 37-39 °C; ^{1}H NMR ($CDCl_3$) δ 8.02-7.84 (1 H, broad), 7.46-7.40 (2 H, m), 7.33-7.27 (1 H, m), 7.22-7.19 (2 H, m), 6.14-5.92 (1 H, broad), 3.61 (2 H, m), 1.56 (2 H, m), 1.25 (10 H, m), 0.87 (3 H, t, *J* = 6.7 Hz); ^{13}C NMR ($CDCl_3$) δ 179.9, 136.3, 129.8, 126.7, 124.8, 45.2, 31.5, 28.9 (2 carbons), 28.7, 26.6, 22.4, 13.9; IR (thin film) 3237, 2922, 1558, 1506, 1352 cm^{-1}; MS, *m/z* 264, 231, 135, 118, 93, 77; HRMS, *m/z* calcd for $C_{15}H_{24}N_2S$ 264.1660, found 264.1637.

1-(*N*-Octylamino)-*N*-(4-nitrophenyl)methanthioamide (2b): To a stirred solution of 4-nitrophenyl isothiocyanate (0.49 g, 2.72 mmol) in THF (7 mL) was added *n*-octylamine (0.35 g, 2.72 mmol) in THF (7 mL) at 25 °C. After addition, the reaction mixture was allowed to stir at 25 °C for 12 h. Concentration and purification by flash column chromatography (hexanes/EtOAc = 3/1) yielded thiourea **2b** as a yellow solid (0.80 g; 95 %): mp 99-101 °C; ^{1}H NMR ($CDCl_3$) δ 9.12-8.65 (1 H, broad), 8.15 (2 H, d, *J* = 8.9 Hz), 7.46 (2 H, d, *J* = 8.6 Hz), 6.79-6.41 (1 H, broad), 3.59 (2 H, m), 1.61 (2 H, m), 1.24 (10 H, m), 0.85 (3 H, t, *J* = 6.5 Hz); ^{13}C NMR ($CDCl_3$) δ 179.8, 144.0, 143.6, 125.3, 122.3, 45.6, 31.7, 29.1 (2 carbons), 28.6, 26.9, 22.6, 14.0; IR (thin film) 3331, 2920, 1545, 1496, 1327, 1111 cm^{-1}; MS, *m/z* 309, 218, 180, 134, 90; HRMS, *m/z* calcd for $C_{15}H_{23}O_2N_3S$ 309.1472, found 309.1472.

1-(*N*-Octylamino)-*N*-(4-cyanophenyl)methanthioamide (2c): To a stirred solution of 4-cyanophenyl isothiocyanate (0.57 g, 3.56 mmol) in THF (9 mL) was added *n*-octylamine (0.46 g, 3.56 mmol) in THF (9 mL) at 25 °C. After addition, the reaction mixture was allowed to stir at 25 °C for 12 h. Concentration and purification by flash column chromatography (hexanes/EtOAc = 3/1) yielded thiourea **2c** as a pale yellow solid (0.47 g; 46 %): mp 88-90 °C; ^{1}H NMR ($CDCl_3$) δ 8.40-8.02 (1 H, broad), 7.69 (2 H, d, *J* = 8.4 Hz), 7.36 (2 H, d, *J* = 7.3 Hz), 6.51-5.79 (1 H, broad), 3.63 (2 H, m), 1.62 (2 H, m), 1.27 (10 H, m), 0.88 (3 H, t, *J* = 6.5 Hz); ^{13}C NMR ($CDCl_3$) δ 179.8, 141.6, 133.7, 123.1, 118.4, 108.2, 45.4, 31.7, 29.1 (2 carbons), 28.6, 26.9, 22.5, 14.0; IR (film) 3262, 2922, 2849, 1554, 1342, 1275 cm^{-1}. Anal. Calcd for $C_{16}H_{23}N_3S$: C, 66.39; H, 8.01; N, 14.52. Found: C, 66.18; H, 8.00; N, 14.47.

1-(*N*-Octylamino)-*N*-(4-trifluoromethylphenyl)methanthioamide (2d): To a mixture of 4-aminobenzotrifluoride (1.14 g, 7.08 mmol) and triethylamine (3 mL, 21.56 mmol) in THF (140 mL) was added dropwise thiophosgene (0.6 mL, 7.87 mmol) at 0 °C. After addition, the reaction mixture was allowed to stir at 25 °C for 12 h. Water (150 mL) was added and the mixture was extracted with diethyl ether (2 x 150 mL). The combined organic layers were washed with water (150 mL) and brine (150 mL), and dried over magnesium sulfate. Concentration and purification by flash column chromatography (hexanes/EtOAc = 100/1) yielded 4-trifluoromethylphenyl isothiocyanate as a yellow solid (1.33 g; 93 %): mp 29-31 °C; ^{1}H NMR ($CDCl_3$) δ 7.63 (2 H, d, *J* = 8.4 Hz), 7.33 (2 H, d, *J* = 8.3 Hz); ^{13}C NMR ($CDCl_3$) δ 138.4, 135.0, 129.1 (q, J_{CF} = 33.0 Hz), 126.8, 126.0, 123.6 (q, J_{CF} = 270.7 Hz); IR (thin film) 2123, 1327, 1126, 1105, 1064 cm^{-1}; MS, *m/z* 203, 184, 145, 132, 44; HRMS, *m/z* calcd for $C_8H_4NSF_3$ 203.0016, found 202.9999.

To a stirred solution of 4-trifluoromethylphenyl isothiocyanate (0.54 g, 2.66 mmol) in THF (7 mL) was added *n*-octylamine (0.34 g, 2.66 mmol) in THF (7 mL) at 25 °C. After addition, the reaction mixture was allowed to stir at 25 °C for 12 h. Concentration and purification by flash column chromatography (hexanes/EtOAc = 5/1) yielded thiourea **2d** as a pale yellow solid (0.87 g; 99 %): mp 69-71 °C; ^{1}H NMR (CDCl$_3$) δ 8.79-7.99 (1 H, broad), 7.68 (2 H, d, *J* = 8.3 Hz), 7.34 (2 H, d, *J* = 8.0 Hz), 6.27-5.98 (1 H, broad), 3.62 (2 H, m), 1.60 (2 H, m), 1.28 (10 H, m), 0.87 (3 H, t, *J* = 6.5 Hz); ^{13}C NMR (CDCl$_3$) δ 180.0, 139.9, 128.3 (q, J_{CF} = 33.0 Hz), 127.3, 124.0, 123.7 (q, J_{CF} = 270.7 Hz), 45.6, 31.7, 29.1 (2 carbons), 28.6, 26.9, 22.6, 14.1; IR (thin film) 3272, 2920, 1556, 1334, 1124 cm^{-1}; MS, *m/z* 332, 255, 203, 161, 145; HRMS, *m/z* calcd for $C_{16}H_{23}N_2SF_3$ 332.1534, found 332.1512.

Ethyl 4-(*N*-Octylamino)methanthioamidobenzoate (2e): To a mixture of ethyl 4-aminobenzoate (1.14 g, 6.91 mmol) and triethylamine (3 mL, 21.56 mmol) in THF (140 mL) was added dropwise thiophosgene (0.6 mL, 7.87 mmol) at 0 °C. After addition, the reaction mixture was allowed to stir at 25 °C for 12 h. Water (150 mL) was added and the mixture was extracted with diethyl ether (2 x 150 mL). The combined organic layers were washed with water (150 mL) and brine (150 mL), and dried over magnesium sulfate. Concentration and purification by flash column chromatography (hexanes/EtOAc = 30/1) yielded ethyl 4-isothiocyanatobenzoate as a yellow solid (1.41 g; 99 %): mp 38-40 °C; ^{1}H NMR (CDCl$_3$) δ 8.03 (2 H, d, *J* = 8.5 Hz), 7,26 (2 H, d, *J* = 8.5 Hz), 4.37 (2 H, q, *J* = 7.1 Hz), 1.39 (3 H, t, *J* = 7.1 Hz); ^{13}C NMR (CDCl$_3$) δ 165.3, 137.6, 135.4, 130.9, 128.9, 125.5, 61.2, 14.2; IR (thin film) 2118, 1709, 1601, 1282, 852 cm^{-1}; MS, *m/z* 207, 179, 162, 134, 90; HRMS, *m/z* calcd for $C_{10}H_9O_2NS$ 207.0354, found 207.0354.

To a stirred solution of ethyl 4-isothiocyanatobenzoate (0.58 g, 2.80 mmol) in THF (7 mL) was added *n*-octylamine (0.36 g, 2.80 mmol) in THF (7 mL) at 25 °C. After addition, the reaction mixture was allowed to stir at 25 °C for 12 h. Purification by flash column chromatography (hexanes/EtOAc = 3/1) yielded thiourea **2e** as a pale yellow solid (0.90 g; 96 %): mp 70-72 °C; ^{1}H NMR (CDCl$_3$) δ 8.21-8.13 (1 H, broad), 8.08 (2 H, d, *J* = 8.5 Hz), 7.26 (2 H, d, *J* = 8.0 Hz), 6.31-6.13 (1 H, broad), 4.37 (2 H, q, *J* = 7.1 Hz), 3.63 (2 H, m), 1.59 (2 H, m), 1.39 (3 H, t, *J* = 7.1 Hz), 1.26 (10 H, m), 0.87 (3 H, t, *J* = 6.6 Hz); ^{13}C NMR (CDCl$_3$) δ 179.7, 165.6, 141.1, 131.1, 127.3, 122.6, 61.0, 45.3, 31.6, 29.0 (2 carbons), 28.6, 26.6, 22.4, 14.1, 13.9; IR (thin film) 3240, 2924, 1714, 1280, 1113 cm^{-1}; MS, *m/z* 207 (M^+-$C_8H_{19}N$), 179, 162, 134, 120; HRMS, *m/z* calcd for M – $C_8H_{19}N$ 207.0354, found 207.0368. Anal. Calcd for $C_{18}H_{28}N_2O_2S$: C, 64.25; H, 8.38; N, 8.32. Found: C, 64.25; H, 8.36; N, 8.31.

1-(*N*-Octylamino)-*N*-(4'-biphenyl)methanthioamide (2f): To a solution of biphenylamine (0.25 g, 1.5 mmol), Et$_3$N (0.63 mL,4.5 mmol) in THF (40 mL) was added 0.12 mL (1.57 mmol) of thiophosgene. The reaction mixture was stirred for 12 h at room temperature. Water (50 mL) was added to the reaction mixture and extracted with diethyl ether (3 x 50 mL), washed with water (50 mL), with brine (50 mL), dried over magnesium sulfate, and filtered. The volatile components of the filtrate were removed under reduced pressure to afford a dark brown solid, the crude isothiocyanate (0.306 g, 97 %): mp 62-64 °C; R_f 0.81 (SiO$_2$, 50% EtOAc/hexanes); ^{1}H NMR (300 MHz, CDCl$_3$) δ 7.59-7.55 (m, 4 H), 7.45 (t, 2 H, *J* = 7.1 Hz), 7.37 (t, 1 H, *J* = 7.2 Hz), 7.29 (t, 2

H, *J* = 7.8 Hz); ^{13}C NMR (300 MHz, $CDCl_3$) δ 140.2, 139.6, 135.5, 130.2, 128.9, 128.1, 127.8, 126.9, 126.1; IR (KBr) 2182, 2110, 1669, 1651, 1507, 1408, 1105, 1076, 1007, 928, 839, 766, 750, 702 cm^{-1}; HRMS, *m/z* calcd for $C_{13}H_9NS$ 211.0456, found 211.0442.

A solution of the crude 4-biphenyl isothiocyanate (0.169 g, 0.8 mmol), *n*-octylamine (0.103 g, 0.8 mmol) in CH_2Cl_2 (5 mL) was stirred for 12 h at room temperature. The volatile components of the reaction mixture were removed under reduced pressure to afford a brown solid. The crude compound was purified by chromatography (CH_2Cl_2, then 25% EtOAc/hexanes) to afford **2f** as a pale-yellow solid (0.234 g, 86.0 %): R_f 0.3 (SiO_2, 25% EtOAc/hexanes); mp 148-149 °C ; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.65 (d, 2 H, *J* = 8.5 Hz), 7.57 (d, 2 H, *J* = 2.0 Hz), 7.46 (t, 2 H, *J* = 7.7 Hz), 7.38 (t, 1 H, *J* = 7.2 Hz), 7.27 (d, 2 H, *J* = 8.3 Hz), 6.05 (s, 1 H), 3.65 (dd, 2 H, *J* = 5.9 Hz, *J′* = 6.8 Hz), 1.61-1.55 (m, 2H), 1.30-1.26 (m, 10 H), 0.89-0.85 (m, 3 H); ^{13}C NMR (300 MHz, $CDCl_3$) δ 180.3, 139.99, 139.69, 135.2, 128.9, 128.7, 127.7, 126.9, 125.3, 45.6, 31.7, 29.1, 28.9, 26.8, 22.6, 14.0; IR (KBr) 3247, 3060, 2957, 2923, 2851, 1617, 1578, 1553, 1509, 1489, 1466, 1458, 1451, 1345, 1242, 835, 760. 725, 693 cm^{-1}; Anal. Calcd for $C_{21}H_{28}N_2S$: C, 74.07; H, 8.29; N, 8.23. Found: C, 73.79; H, 8.31; N, 8.20.

1-(*N*-Octylamino)-*N*-(4-ethoxyphenyl)methanthioamide (2g): To a solution of p-phenetidine (0.34 g,2.5 mmol), Et_3N (1 mL, 7.5 mmol) in THF (40 mL) was added 0.19 mL (2.5 mmol) of thiophosgene. The reaction mixture was stirred for 12 h at room temperature. Water (50 mL) was added to the reaction mixture and extracted extracted with diethyl ether (3 x 50 mL), washed with water (50 mL), with brine (50 mL), dried over magnesium sulfate, and filtered. The volatile components of the filtrate were removed under reduced pressure to afford a dark brown solid, the crude isothiocyanate (0.46 g, 99 %): R_f 0.77 (SiO_2, 50% EtOAc/hexanes); mp 58-60 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.15 (d, 2 H, *J* = 8.8 Hz), 6.83 (d, 2 H, *J* = 8.9 Hz), 4.01 (q, 2 H, *J* = 7.0, *J′* = 6.9 Hz), 1.41 (t, 3 H, *J* = 7.0 Hz); ^{13}C NMR (300 MHz, $CDCl_3$) δ 157.9, 133.6, 126.9, 123.2, 115.2, 63.8, 14.6; IR (KBr) 2982, 2174, 2128, 1580, 1501, 1478, 1387, 1298, 1252, 1169, 1115, 1046, 918, 835, 822, 799, 646 cm^{-1}; HRMS, *m/z* calcd for C_9H_9NOS 179.0405, found 179.0397.

A solution of crude 4-ethoxyphenyl isothiocyanate (0.129 g, 1.0 mmol), *n*-octylamine (0.179 g, 1.0 mmol) in CH_2Cl_2 (5 mL) was stirred for 12 h at room temperature. The volatile components of the reaction mixture were removed under reduced pressure to afford a brown solid. The crude compound was purified by chromatography (CH_2Cl_2, then 25% EtOAc/hexanes) to afford **2g** as a pale-yellow solid (0.23 g, 75.0 %). R_f 0.25 (SiO_2, 25% EtOAc/hexanes); mp 79-80 °C ; IR (KBr) 3237, 3069, 2924, 2853, 1554, 1511, 1478, 1466, 1350, 1248, 1173, 1115, 1049, 824, 723 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.38 (s, 1 H), 7.15 (d, 2 H, *J* = 6.8 Hz), 6.93 (d, 2 H, *J* = 8.9 Hz), 5.75 (s, 1 H), 4.22 (dd, 2 H, *J* = 6.9 Hz, *J′* =7.0 Hz), 3.59 (dd, 2 H, *J* = 7.3 Hz, *J′* = 5.7 Hz), 1.55-1.50 (m, 2 H), 1.35-1.20 (m, 10 H), 0.89-0.85 (m, 3 H); ^{13}C NMR (300 MHz, $CDCl_3$) δ 180.9, 158.3, 128.2, 127.7, 115.7, 63.7, 45.4, 31.7, 29.1, 28.9, 26.7, 22.6, 14.7, 14.0; HRMS, *m/z* calcd for $C_{17}H_{28}N_2OS$ 308.1922, found 308.1901. Anal. Calcd for $C_{17}H_{28}N_2SO$: C, 66.19; H, 9.15; N, 9.08; S, 10.39. Found: C, 66.28; H, 9.19; N, 9.10; S,10.48.

***N*-(4-(*N*,*N*-Dimethylamino)phenyl)-1-(*N*-octylamino)methanthioamide (2h):** To a mixture of *N*,*N*-dimethyl-1,4-phenylenediamine (0.76 g, 5.59 mmol) and triethylamine (2.5 mL, 17.97 mmol) in THF (110 mL) was added dropwise thiophosgene (0.5 mL, 6.56 mmol) at 0 °C. After addition, the reaction mixture was allowed to stir at 25 °C for 12 h. Water (100 mL) was added and the mixture was extracted with diethyl ether (2 x 100 mL). The combined organic layers were washed with water (100 mL) and brine (100 mL), and dried over magnesium sulfate. Concentration and purification by flash column chromatography (hexanes/EtOAc = 50/1) yielded 4-(*N*,*N*-dimethylamino)phenyl isothiocyanate as a yellow solid (0.98 g; 99 %): mp 49-51 °C; ^{1}H NMR ($CDCl_3$) δ 7.12 (2 H, d, *J* = 9.1 Hz), 6.62 (2 H, d, *J* = 8.9 Hz), 2.97 (6 H, s); ^{13}C NMR ($CDCl_3$) δ 149.3, 131.9, 126.7, 118.6, 112.3, 40.4; IR (thin film) 2818, 2137, 1556, 1379, 1074 cm^{-1}; MS, *m/z* 178, 162, 134, 89, 77; HRMS, *m/z* calcd for $C_9H_{10}N_2S$ 178.0564, found 178.0575.

To a stirred solution of 4-(*N*,*N*-dimethylamino)phenyl isothiocyanate (0.41 g, 2.30 mmol) in THF (6 mL) was added *n*-octylamine (0.30 g, 2.30 mmol) in THF (6 mL) at 25 °C. After addition, the reaction mixture was allowed to stir at 25 °C for 12 h. Concentration and purification by flash column chromatography (hexanes/EtOAc = 3/1) yielded thiourea **2h** as a pale yellow solid (0.70 g; 99 %); mp 47-49 °C; ^{1}H NMR ($CDCl_3$) δ 7.41 (1 H, broad), 7.06 (2 H, d, *J* = 8.6 Hz), 6.71 (2 H, d, *J* = 8.5 Hz), 5.78 (1 H, broad), 3.58 (2 H, m), 2.98 (6 H, s), 1.52 (2 H, m), 1.25 (10 H, m), 0.87 (3 H, t, *J* = 6.5 Hz); ^{13}C NMR ($CDCl_3$) δ 181.2, 149.9, 127.6, 123.9, 113.0, 45.4, 40.4, 31.7, 29.2 (2 carbons), 29.0, 26.8, 22.6, 14.1; IR (thin film) 3283, 2853, 1504, 1165, 823 cm^{-1}; MS, *m/z* 307, 273, 178, 136, 89; HRMS, *m/z* calcd for $C_{17}H_{29}N_3S$ 307.2082, found 307.2082.

4-(Tri-1-butylammonium) butane-1-sulfonate (3): 1,4-Butane sultone (2.0 mL, 19.5 mmol), tri-n-butylamine (5.0 mL, 21.0 mmol) and 4.0 mL of absolute ethanol were heated on a steam bath for 20 h. The ethanol was removed under reduced pressure and the resulting viscous liquid was dissolved in 50 mL of water and washed with 2 x 25 mL of ether. The water was removed from the resulting aqueous solution by lyophillization and the white solid obtained was passed through a bed of type-2 quaternary ammonium ion exchange resin (hydroxide form) to provide, after lyophillization, several grams of **3**. This crystallized as white wedge-shaped prisms from acetonitrile/ ether; mp 217-218 °C ; ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.44 (bm, 2H), 3.21 (m, 6H), 2.88 (m, 2H), 1.92 (bm, 4H), 1.63 (m, 6H), 1.42 (m, 6H), 1.00 (t, 9H, *J* = 7.2 Hz); HRMS, *m/z* calcd for $C_{16}H_{35}NO_3S$: 321.2338, measured: 321.2338. Anal. Calcd for $C_{16}H_{35}NO_3S$: C, 59.77; H, 10.97; N, 4.36; S, 9.97. Found: C, 59.84; H, 11.03; N, 4.41; S,10.05.

1-(*N*-(3-Nitrophenyl)amino)-*N*-(3-nitrophenyl)methanamide (4): To a stirred solution of 3-nitrophenyl isocyanate (164.1 mg, 1.00 mmol) in THF (5 mL) was added 3-nitroaniline (138.1 mg, 1.00 mmol) in THF (5 mL) at 25 °C. The reaction mixture was allowed to stir at 25 °C for 24 h. Concentration and purification by flash column chromatography (hexanes/EtOAc = 1/1) yielded thiourea **4** as a yellow solid (77.5 mg; 26 %): mp 234-236°C; ^{1}H NMR ($CDCl_3$) δ 8.85 (2 H, s), 8.40 (2 H, s), 7.85 (4 H, m), 7.50 (2 H, m); ^{13}C NMR ($CDCl_3$) δ 152.1, 148.2, 140.2, 129.2, 124.0, 116.5, 112.8; IR (thin film) 3449, 2924, 2853, 2253, 2127, 1655, 1438 cm^{-1}; MS, *m/z* 302, 202, 164, 138, 92, 65; HRMS, *m/z* calcd for $C_{13}H_{10}N_4O_5$, 302.0651, found, 302.0651.

1-(*N*-Octylamino)-*N*-(3-nitrophenyl)methanamide (6): To a stirred solution of 3-nitrophenyl isocyanate (0.60 g, 3.66 mmol) in THF (9 mL) was added *n*-octylamine (0.47 g, 3.66 mmol) in THF (9 mL) at 25 °C. After addition, the reaction mixture was allowed to stir at 25 °C for 12 h. Concentration and purification by flash column chromatography (hexanes/EtOAc = 2/1) yielded urea **6** as a pale yellow solid (0.80 g; 75 %): mp 97-99 °C; ^{1}H NMR ($CDCl_3$) δ 8.15 (1 H, t, *J* = 2.1 Hz), 7.86-7.78 (2 H, m), 7.42 (1 H, t, *J* = 8.1 Hz), 6.90 (1 H, broad), 4.96 (1 H, broad), 3.28 (2 H, t, J = 6.8 Hz), 1.54 (2 H, m), 1.26 (10 H, m), 0.87 (3 H, t, *J* = 6.6 Hz); ^{13}C NMR ($CDCl_3$) δ 155.6, 148.4, 141.4, 129.4, 123.8, 115.9, 112.5, 39.8, 31.7, 30.0, 29.2 (2 carbons), 26.8, 22.5, 14.0; IR (thin film) 3343, 2918, 1641, 1344, 1248 cm^{-1}; MS, *m/z* 293, 164 (M^+-$C_8H_{19}N$), 138, 90, 57; HRMS, *m/z* calcd for (M – $C_8H_{19}N$) 164.0221, found 164.0233. Anal. Calcd for $C_{15}H_{23}N_3O_2S$: C, 58.22; H, 7.49; N, 13.58. Found: C, 57.97; H, 7.41; N, 13.41.

1-(*N*-Octylamino)-*N*-(4-nitrophenyl)methanamide (7): To a stirred solution of 4-nitrophenyl isocyanate (0.76 g, 4.63 mmol) in THF (12 mL) was added *n*-octylamine (0.60 g, 4.63 mmol) in THF (12 mL) at 25 °C. After addition, the reaction mixture was allowed to stir at 25 °C for 12 h. Concentration and purification by recrystallization (EtOAc/hexanes) yielded urea **7** as a pale yellow solid (0.98 g; 72 %): mp 96-98 °C; ^{1}H NMR ($CDCl_3$) δ 8.57 (1 H, broad), 8.04 (2 H, d, *J* = 9.1 Hz), 7.48 (2 H, d, *J* = 9.1 Hz), 5.86 (1 H, m), 3.15 (2 H, m), 1.44 (2 H, m), 1.20 (10 H, m), 0.80 (3 H, t, *J* = 6.4 Hz); ^{13}C NMR ($CDCl_3$) δ 155.3, 146.5, 141.3, 125.1, 117.1, 39.9, 31.7, 29.9, 29.2 (2 carbons), 26.8, 22.5, 14.0; IR (thin film) 3362, 2928, 1703, 1504, 1028 cm^{-1}; MS, *m/z* 293, 164 (M^+-$C_8H_{19}N$), 138, 90, 55; HRMS, *m/z* calcd for (M – $C_8H_{19}N$) 164.0221, found 164.0219.

Salt Induced Changes in UV Spectra: Stock solutions of ureas **2a-2e**, with and without zwitterion **3**, were prepared using chloroform filtered through dry basic alumina. UV data are summarized in Table 2.

Table 2. The effects of zwitterion **3** on UV absorption.

Urea	[Urea], M^{-1}	[3], M^{-1}	λ_{max}, nm
2a	2.0x10^{-4}	0	266.6
2a	2.0x10^{-4}	1.3x10^{-3}	266.4
2b	5.0x10^{-4}	0	332.6
2b	5.0x10^{-4}	3.9x10^{-4}	350.5
2c	8.0x10^{-5}	0	297.8
2c	8.0x10^{-5}	4.0x10^{-4}	300.6
2d	2.0x10^{-4}	0	279.8
2d	2.0x10^{-4}	1.0x10^{-3}	280.2
2e	8.0x10^{-5}	0	295.7
2e	8.0x10^{-5}	4.0x10^{-4}	296.9

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