Molecular Scaffolds. 2. Intramolecular Hydrogen Bonding in 1,2-Diaminoethane Diureas

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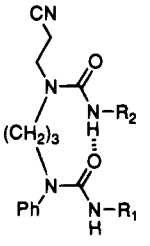
Abstract: Intramolecular hydrogen bonding creates remarkably stable folded structures in diurea derivatives of substituted 1,2-diaminoethanes. 1,2-Diaminoethane diureas **2** [PhN(CONHR$_1$)CH$_2$CH$_2$N(CONHR$_2$)CH$_2$CH$_2$CN; **2a**, R$_1$ = R$_2$ = Ph; **2b**, R$_1$ = (*S*)-CH(CH$_2$Ph)CO$_2$CH$_3$, R$_2$ = (*S*)-CH(*i*-Pr)CO$_2$CH$_3$; **2c**, R$_1$ = R$_2$ = (*S*)-CH(CH$_2$Ph)CO$_2$CH$_3$; **2d**, R$_1$ = R$_2$ = CH$_3$] are prepared in high yield by reaction of diamine **4** (PhNHCH$_2$CH$_2$NHCH$_2$CH$_2$CN) with isocyanates. The differing reactivities of the two amino groups in **4** permit the preparation of diureas bearing different substituents R$_1$ and R$_2$ (e.g., **2b**) with ≥95% regioselectivity. The *N*-phenyl substituent on the 1,2-diamine backbone of diureas **2** helps maintain conformational homogeneity by controlling the direction of the urea group that bears this substituent (NCONHR$_1$). Intramolecular hydrogen bonding aligns the other urea group (NCONHR$_2$). Infrared and ^{1}H NMR spectroscopic studies indicate ureas **2** are largely or wholly hydrogen bonded (ca. 75−100%) in chloroform solution, whereas the homologous 1,3-diaminopropane diureas **1** [PhN(CONHR$_1$)CH$_2$CH$_2$CH$_2$N(CONHR$_2$)CH$_2$CH$_2$CN] exhibit a lesser degree of intramolecular hydrogen bonding (25−80%). These findings indicate that the 9-membered hydrogen-bonded ring structures of 1,2-diaminoethane diureas **2** are more stable than the 10-membered hydrogen-bonded ring structures of 1,3-diaminopropane diureas **1**. ^{1}H NMR and X-ray crystallographic studies establish that the 1,2-diaminoethane backbone of diureas **2** adopts an anti conformation, both in solution and in the solid state.

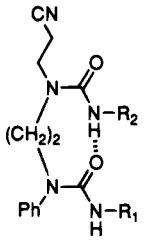
U-turns are important architectural elements of both natural and unnatural molecules. In proteins, β-turns[1] allow the polypeptide backbones to fold back upon themselves, thus contributing to the proteins' globular structures. In peptides, β-turns provide arrays of side chains that are frequently responsible for biological activity. Considerable effort has been devoted to the development of U-turns as β-turn mimics, which are potentially useful for the creation of synthetic peptide analogs with physiological activities similar to those of biologically active peptides.[2,3] In the field of molecular recognition, U-turns have been used for the creation of molecular receptors.[4]

Most of the molecular U-turns that have been developed rely upon cyclic or polycyclic molecules to provide rigid frameworks for the attachment of substitutents. Although these molecules are conformationally well-defined, they are generally more difficult to synthesize than acyclic compounds. The development of conformationally well-defined acyclic U-turns would provide simpler building blocks for the creation of molecular receptors and peptide structural mimics.

As part of a program of research aimed at the development of molecular receptors and conformationally constrained peptides, we have become interested in developing acyclic molecules in which intramolecular hydrogen bonding creates conformationally well-defined structures. We recently discovered that diurea derivatives of 1,3-propanediamine (e.g., **1**) adopt



1a R$_1$ = R$_2$ = Ph
1b R$_1$ = (*S*)-CH(CH$_2$Ph)CO$_2$Me
R$_2$ = (*S*)-CH(*i*-Pr)CO$_2$Me
1c R$_1$ = (*S*)-CH(CH$_2$Ph)CO$_2$Me
R$_2$ = (*S*)-CH(CH$_2$Ph)CO$_2$Me
1d R$_1$ = R$_2$ = CH$_3$



2a R$_1$ = R$_2$ = Ph
2b R$_1$ = (*S*)-CH(CH$_2$Ph)CO$_2$Me
R$_2$ = (*S*)-CH(*i*-Pr)CO$_2$Me
2c R$_1$ = (*S*)-CH(CH$_2$Ph)CO$_2$Me
R$_2$ = (*S*)-CH(CH$_2$Ph)CO$_2$Me
2d R$_1$ = R$_2$ = CH$_3$

intramolecularly hydrogen bonded conformations.[5] Because of their intramolecularly hydrogen bonded U-turn structures, we have termed these diureas, and related oligoureas, *molecular scaffolds*. We now report that diurea derivatives of 1,2-ethanediamine (e.g., **2**) adopt folded structures of well-defined geometry and exhibit a substantially higher degree of intramolecular hydrogen bonding than the homologous derivatives of 1,3-propanediamine.

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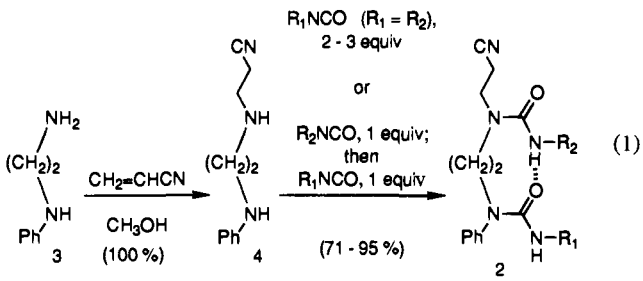
Results and Discussion

Synthesis of Urea Derivatives of 1,2-Diamines. Ureas are generated cleanly, and in high yield, by reaction of amines with the appropriate isocyanates. This reaction allowed the efficient preparation of all ureas described in this paper (except the tetrasubsituted urea groups of diureas **8** and **9**, which were prepared by reaction of amines with dimethylcarbamyl chloride). Ureas **2** were prepared as shown in eq 1. Michael addition of

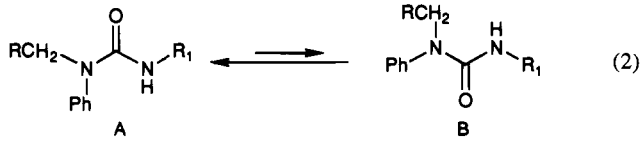


(1)

N-phenylethylenediamine (**3**) to acrylonitrile occurs exclusively at the aliphatic amino group, and with high selectivity for monoaddition, generating diamine **4** in quantitative yield.[6] Reaction of diamine **4** with slight excesses of the appropriate isocyanates generated diureas **2a**, **2c**, and **2d**.

The substantial difference in reactivity between aliphatic and aromatic amino groups permits the preparation of diureas in which different groups R_1 and R_2 are attached to the diamine backbone (e.g., **2b**) in a highly regioselective fashion. Thus, sequential reaction of diamine **4** with valine methyl ester isocyanate[7] and phenylalanine methyl ester isocyanate[7] afforded **2b** in 73% yield. The regioselectivity of this procedure was determined to be ≥20:1 by ^{1}H NMR analysis of the crude reaction mixtures.

Directional Control in Diurea Derivatives. The *N*-phenyl substituent on the 1,2-diamine backbone of ureas **1** and **2** helps maintain conformational homogeneity by controlling the direction of the urea group that bears this substituent. In amides and ureas bearing both an aryl and an alkyl substituent on one nitrogen atom, there is a strong bias for the aryl substituent to be s-trans to the carbonyl group (eq 2).[8] In ureas **1** and **2**, this



(2)

bias makes the "lower" carbonyl group point "upwards" (as illustrated in the drawings of the structures). Intramolecular hydrogen bonding aligns the "upper" carbonyl group in the same direction.

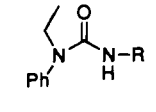
Table 1. Spectroscopic Properties of NH Groups in Ureas at 295 K

compd	IR (cm^{-1})[a]	^{1}H NMR (ppm)[b]
1a[c]	3455,[d] 3426, 3296	8.49, 6.17
1b[c]	3428, 3294	5.40 (Val), 4.58 (Phe)
1c[c]	3429, 3284	5.61, 4.56
1d	3483, 3460, 3325	5.62, 4.17
2a	3425, 3309	9.02, 6.25
2b	3425, 3305	6.72 (Val), 4.70 (Phe)
2c	3427, 3294	7.09, 4.73
2d	3456, 3338	6.81, 4.25
5a[c]	3428	6.08
5c	3428	4.49
5d	3460	4.06
6a[c]	3464	6.24
6b[c]	3452	4.82
6c[c]	3452	4.72
6d	3487	4.32
7a	3462	6.34
7d	3487	4.39
8	3483, 3465, 3340	5.39
9	3340	6.85
11a	3423, 3314	8.38, 6.01
11d	3486[d], 3457, 3354	6.28, 4.03

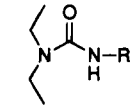
[a] IR spectra were recorded at 10 mM in $CHCl_3$ solution at 295 K. [b] ^{1}H NMR spectra were recorded at 1.0 mM in $CDCl_3$ solution at 295 K. [c] Reference 5. [d] Weak shoulder.

Molecular mechanics calculations performed on *N,N'*-dimethyl-*N*-phenylurea and *N,N'*-diphenyl-*N*-methylurea using the versions of MM2, MM3, AMBER, and OPLS available in MacroModel V3.5a show conformer A to be favored by 2–7 kcal/mol. On the basis of these calculations, well over 95% of the molecules are expected to adopt conformation A. This conclusion is supported by the observed differences in the infrared spectra of ureas **5** and **6**, which are discussed in the next section.

Infrared Spectroscopic Studies of Diureas. Infrared spectroscopy indicates that diureas **1** and **2** adopt hydrogen-bonded conformations in chloroform solution. Hydrogen bonding can be seen by comparison of the infrared spectra of these compounds to the spectra of appropriately substituted monoureas: Monoureas **5**, derivatives of *N*-ethylaniline, serve



5a R = Ph
5c R = (*S*)-CH(CH$_2$Ph)CO$_2$Me
5d R = CH$_3$



6a R = Ph
6b R = (*S*)-CH(*i*-Pr)CO$_2$Me
6c R = (*S*)-CH(CH$_2$Ph)CO$_2$Me
6d R = CH$_3$

as references for the "bottom half" of diureas **1** and **2**. Monoureas **6**, derivatives of diethylamine, serve as references for the "top half" of diureas **1** and **2**.

Ureas **5** and **6** exhibit NH stretches at significantly different frequencies (Table 1). Urea **6a** (R = Ph) exhibits an NH stretch at 3464 cm^{-1} in dilute $CHCl_3$ solution, whereas urea **5a** (R = Ph) exhibits an NH stretch at 3428 cm^{-1}. Similar differences are observed between ureas **6d** and **5d** (R = CH_3; 3487 and 3460 cm^{-1}, respectively) and ureas **6c** and **5c** (R = (*S*)-CH(CH$_2$Ph)CO$_2$CH$_3$; 3452 and 3428 cm^{-1}, respectively). The 24–36 cm^{-1} lower frequency of the NH stretch of *N*-phenyl-*N*-ethyl derivatives **5** can be attributed to weak hydrogen bonding

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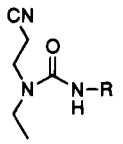
between the NH group and the phenyl group on the adjacent nitrogen atom.[9]

To test the validity of *N,N*-diethylureas **6** as models for the upper half of diureas **1** and **2**, we prepared *N*-(cyanoethyl)-*N*-ethylureas **7a** and **7d**. IR and ^{1}H NMR studies of these



7a R = Ph
7d R = CH_3

cyanoethyl derivatives show that the cyano group has little interaction with the urea group. In their IR spectra, diureas **7a** and **7d** exhibit NH stretches at comparable positions to those of **6a** and **6d** (Table 1). Only minor effects of the cyano group are seen in the ^{1}H NMR spectra of ureas **7**; the NH resonances of **7a** and **7d** appear 0.07–0.10 ppm downfield of those of **6a** and **6d** (Table 1). The inductive effect of the cyano group may account for this slight downfield shift.

The differences in frequencies between the infrared NH stretching bands of **5** and **6** permit detailed interpretation of the infrared spectra of diureas **1** and **2** in the 3200–3500 cm^{-1} region. Analysis of the spectra of 1,3-diaminopropane diureas **1** illustrates this point. Dimethyl derivative **1d** exhibits peaks at 3483, 3460, and 3325 cm^{-1} (Figure 1). The peak at 3460 cm^{-1} corresponds to the NH stretch of the bottom half of the molecule. (Further analysis of this band is described later in this section.) This assignment is evident from the position and shape of the peak, which are similar to those of monourea **5d** (Figure 1). The peaks at 3483 and 3325 cm^{-1} arise from the NH stretch of the top half of the molecule; the peak at 3483 cm^{-1} comes from non-hydrogen-bonded conformers, whereas the broad peak at 3325 cm^{-1} comes from hydrogen-bonded conformers. The diureas bearing phenyl substituents also exhibit well-resolved IR spectra. Thus, diurea **1a** has major absorption bands at 3426 and 3296 cm^{-1} and a weak shoulder at 3455 cm^{-1}.[5] The band at 3426 cm^{-1} arises from the lower NH group; the band at 3296 cm^{-1} comes from the hydrogen-bonded upper NH group; and the shoulder at 3455 cm^{-1} is produced by the upper NH group of the molecules that are in a non-hydrogen-bonded conformation. Diurea **1a** also exhibits weak bands at 3249 (a shoulder on the hydrogen-bonded absorption), 3194, and 3133 cm^{-1}. At present, the origin of these minor bands is not wholly clear.[10] In diureas bearing peptide substituents, the non-hydrogen-bonded NH bands corresponding to the "upper" and "lower" halves of the molecules are not as well resolved. For example, phenylalanine valine diurea **1b** shows a single free NH band at 3428 cm^{-1} and a hydrogen-bonded NH band at 3294 cm^{-1} (Figure 1). The band at 3428 cm^{-1} is broader and more intense than those of monoureas **5c** and **6b**, and the band at 3294 cm^{-1} is relatively weak. These observations indicate that **1b** is partially in a non-hydrogen-bonded

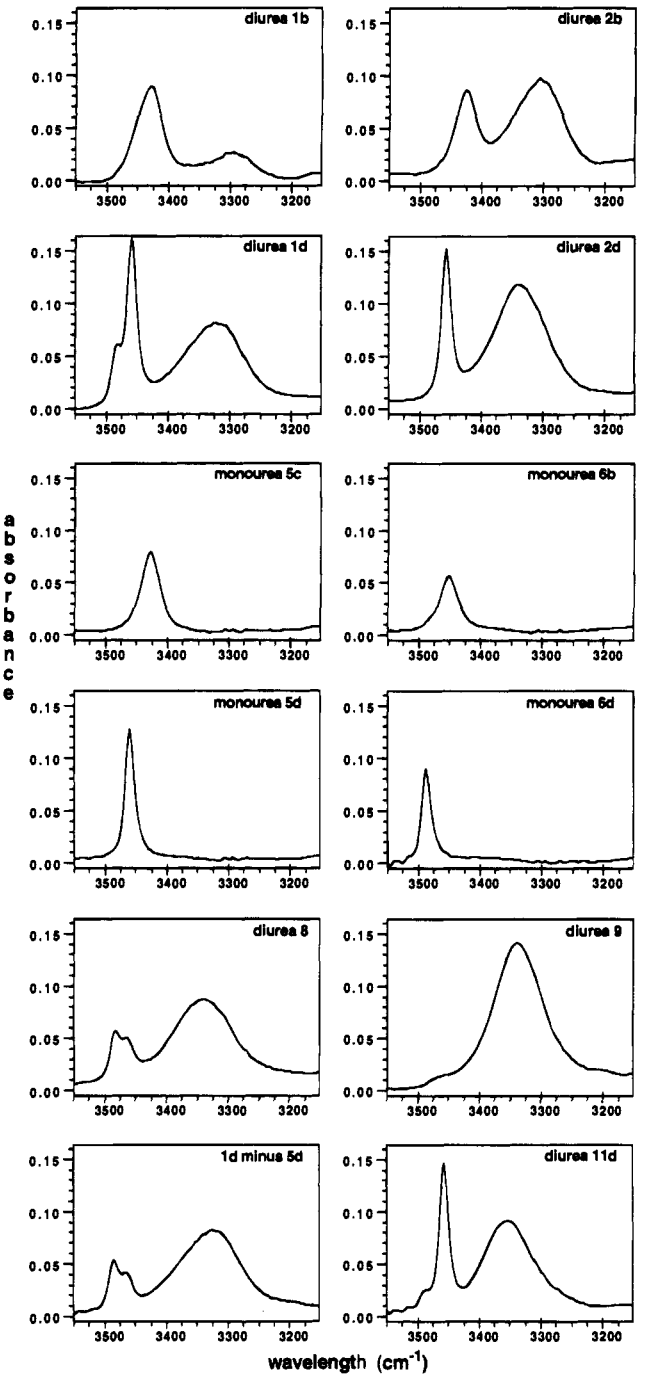


Figure 1. Infrared spectra (3150–3550 cm^{-1}) of ureas **1b**, **1d**, **2b**, **2d**, **5c**, **5d**, **6b**, **6d**, **8**, **9**, **11d**, and **1d** minus **5d** (difference spectrum). Spectra were recorded at 295 K using a 10 mM solution in $CHCl_3$ (1.0 mm path length) against a $CHCl_3$ reference. Spectra are not baseline corrected.

conformation and that the free NH bands of the upper and lower halves of the molecule overlap.[11]

Whereas diureas **1** are mixtures of hydrogen-bonded and non-hydrogen-bonded conformers, diureas **2** are largely or wholly hydrogen bonded. Thus, diurea **2d** has peaks at 3456 and 3338 cm^{-1} in the infrared spectrum, corresponding to the free NH

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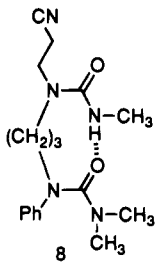
(10) Similar bands are present in the spectra of the other phenyl-subsituted diureas (e.g., **2a** and **11a**), however these bands are lacking in the spectra of monoureas **5a** and **6a**.

(11) The free NH bands are unresolved in the peptide diurea derivatives, because the free NH stretching bands are relatively broad in ureas bearing peptide substituents; the NH stretching bands of peptide monoureas **5c**, **6b**, and **6c** are 32 cm^{-1} wide at half-height, whereas those of aryl and alkyl monoureas **5a**, **5d**, **6a**, and **6d** are 15–22 cm^{-1} wide. For this reason, ureas **1a** and **1d** each exhibit two free NH peaks, whereas ureas **1b** and **1c** each exhibit only one free NH peak.

stretch of the lower urea group and the hydrogen-bonded NH stretch of the upper urea group, repectively (Figure 1). The absence of a peak at ca. 3487 cm^{-1} indicates the absence of a significant population of non-hydrogen-bonded conformers. Similarly, diurea **2a** has peaks at 3425 (lower NH) and 3309 cm^{-1} (hydrogen-bonded upper NH) but lacks a peak at ca. 3464 cm^{-1} (non-hydrogen-bonded upper NH). Because the NH bands of the peptide ureas are not as well resolved, it is not possible to determine whether non-hydrogen-bonded conformers of diureas **2b** and **2c** contribute to their IR spectra. However, the hydrogen-bonded NH band of urea **2b** (3305 cm^{-1}) is far more intense than that of **1b** (3294 cm^{-1}), and the non-hydrogen-bonded NH band of **2b** (3425 cm^{-1}) is significantly weaker than that of **1b** (3428 cm^{-1}) (Figure 1). These differences indicate that there is a substantially greater degree of intramolecular hydrogen bonding in 1,2-diaminoethane diurea **2b**. The IR spectra of diureas **1c** and **2c** exhibit similar differences, indicating that **2c** is hydrogen bonded to a greater degree than **1c**.

To gain additional insight into the structures of diurea derivatives of 1,3-diaminopropane and 1,2-diaminoethane, we have prepared diureas **8** and **9**. These compounds may be thought of as analogs of **1d** and **2d** in which the lower urea hydrogen has been replaced with a methyl group. Because the lower NH group is lacking, the IR spectrum of each of these compounds is unobstructed by additional peaks in the 3400–3500 cm^{-1} region, and peaks in that region come exclusively from the upper NH group. The most notable feature of the spectrum of 1,2-diaminoethane diurea **9** is a hydrogen-bonded NH band at 3340 cm^{-1} (Figure 1). This band is similar in shape, intensity, and position to the hydrogen-bonded NH band of diurea **2d**, reflecting the similar structures of these compounds. The spectrum of **9** also exhibits an extremely weak, irregularly



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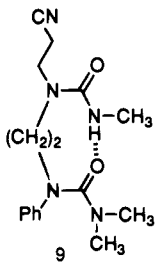


9

shaped band from ca. 3450–3485 cm^{-1}. Because of the weak intensity of this band, it is not possible to be certain of its origin (or even its existence). We postulate that this band arises from the small population of non-hydrogen-bonded conformers. The small area of this band (about 2% of the NH band of **6d**) indicates that this population is extremely small. For this reason, we estimate that 98% or more of the molecules are in a hydrogen-bonded conformation in chloroform solution at 295 K.

Whereas 1,2-diaminoethane diurea **9** is fully (≥98%) hydrogen bonded, 1,3-diaminopropane diurea **8** is only partially hydrogen bonded. The IR spectrum of this compound exhibits three bands in the NH region at 3483, 3465, and 3340 cm^{-1}. The band at 3340 cm^{-1} results from a conformation in which the upper NH group is hydrogen bonded to the lower carbonyl group (a hydrogen-bonded conformer), and the band at 3483 cm^{-1} results from a conformation in which the upper NH group is not hydrogen bonded to the lower carbonyl group (a non-hydrogen-bonded conformer). The band at 3465 cm^{-1} apparently comes from a conformation in which the upper NH group is not hydrogen bonded to the lower carbonyl group, but is weakly hydrogen bonded to the phenyl ring. (For the purposes of this discussion, we will call this a non-hydrogen-bonded conformer, because it lacks an N–H···O hydrogen bond.) The similarity in position of this peak to that of monourea **5d** (3460 cm^{-1}) supports this explanation.

This analysis of the IR spectrum of **8** prompts further analysis of the spectrum of **1d** (vide supra). In **1d** the NH band at 3460 cm^{-1} is substantially greater in intensity than that of **5d** (3460 cm^{-1}), suggesting that this band may encompass another band (Figure 1). Spectral subtraction supports this notion. When the spectrum of monourea **5d** is subtracted from that of diurea **1d**, the resulting difference spectrum is virtually identical to the spectrum of diurea **8**, exhibiting bands at 3485, 3466, and 3327 cm^{-1} (Figure 1). This subtraction experiment indicates that diurea **1d** also adopts three types of conformations, in which the upper NH group is respectively not hydrogen bonded, hydrogen bonded to the phenyl ring, and hydrogen bonded to the lower carbonyl group.

These infrared studies establish that 1,2-diaminoethane diureas exhibit a substantially greater degree of intramolecular hydrogen bonding than 1,3-diaminopropane diureas in chloroform solution. We attribute the greater tendency of the 1,2-diaminoethane diureas to adopt intramolecularly hydrogen bonded conformations to entropic differences between the 9- and 10-membered hydrogen-bonded rings that form. This observation parallels the findings of Gellman et al., that 9-membered hydrogen-bonded ring structures are more thermodynamically favorable than 10-membered ring structures in simple diamide derivatives.[12]

The urea derivatives show a greater degree of intramolecular hydrogen bonding than similar amides. Thus, diurea **2d** is largely or wholly hydrogen bonded in $CHCl_3$ solution at ambient temperature, whereas *N,N,N'*-trimethylhexanediamide [$Me_2NCO(CH_2)_4CONHMe$] is largely not hydrogen bonded in CH_2Cl_2.[12a,b] We ascribe the greater degree of hydrogen bonding in the ureas to the presence of fewer bonds that can rotate and to limited rotational freedom of the 1,2-diaminoethane backbone. Studies by Gellman and co-workers lend support to this explanation: Hex-3-enediamide derivatives that are rigidified by substituents that introduce allylic strain show substantially greater intramolecular hydrogen bonding than *N,N,N'*-trimethylhexanediamide or hex-3-enediamide derivatives lacking substituents.[12c,d]

Quantitation of Intramolecular Hydrogen Bonding in Diureas. ^1H NMR spectroscopy provides a means to approximate the relative populations of hydrogen-bonded and non-hydrogen-bonded conformers in diurea derivatives. All conformers of diureas **1** and **2** interconvert rapidly on the ^1H NMR time scale at ambient temperature. For this reason, the measured chemical shifts of the NH groups are the weighted averages of the shifts of the various conformers. On the basis of the observed shifts in diureas **2d** and **9** and monourea **6d**, we estimate the hydrogen-bonded NH group of a fully-hydrogen-bonded diurea to appear 2.5 ppm downfield of the NH group of an analogous monourea. The slightly greater downfield shifting of diurea **2a** relative to monourea **6a** suggests the ureas bearing aryl substituents R_1 and R_2 may exhibit slightly greater downfield shifting (ca. 2.8 ppm). We have previously estimated

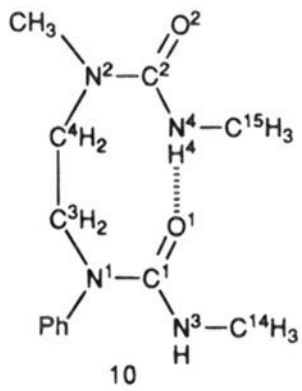
(12) (a) Gellman, S. H.; Adams, B. R. *Tetrahedron Lett.* **1989**, *30*, 3381. (b) Gellman, S. H.; Dado, G. P.; Liang, G.-B.; Adams, B. R. *J. Am. Chem. Soc.* **1991**, *113*, 1164. (c) Liang, G.-B.; Dado, G. P.; Gellman, S. H. *J. Am. Chem. Soc.* **1991**, *113*, 3994. (d) Liang, G.-B.; Desper, J. M.; Gellman, S. H. *J. Am. Chem. Soc.* **1993**, *115*, 925. For related examples, see: (e) Dado, G. P.; Desper, J. M.; Gellman, S. H. *J. Am. Chem. Soc.* **1990**, *112*, 8630. (f) Dado, G. P.; Desper, J. M.; Holmgren, S. K.; Rito, C. J.; Gellman, S. H. *J. Am. Chem. Soc.* **1992**, *114*, 4834. (g) Dado, G. P.; Gellman, S. H. *J. Am. Chem. Soc.* **1993**, *115*, 4228.

comparable downfield shifts in diurea derivatives of 1,3-propanediamine.[5]

These values allow the estimation of the relative populations of hydrogen-bonded conformers and non-hydrogen-bonded conformers. For example, the upper NH group of diurea **1d** (δ 5.62) is shifted 1.30 ppm downfield of the NH group of monourea **6d** (δ 4.32). This downfield shift corresponds to 52% intramolecular hydrogen bonding [(1.3/2.5) × 100%]. This calculation assumes that there are no significant effects upon the chemical shift, other than hydrogen bonding to the lower urea carbonyl group. Since anisotropic groups (e.g., aromatic rings) at remote positions generally introduce effects of a few tenths of a ppm or less in ^{1}H NMR spectra, we estimate this value to be accurate to within about 10%. By measuring the chemical shifts of **1d** at varying concentrations (1 and 10 mM) and observing no significant differences in chemical shift of the NH resonances (≤0.01 ppm), we conclude that there are no significant effects of intermolecular hydrogen bonding upon chemical shift at these concentrations.[13] Through similar calculations, we estimate the following degrees of intramolecular hydrogen bonding in diureas **1**, **2**, **8**, and **9** (to the nearest 5%): **1a**, 80%; **1b**, 25%; **1c**, 35%; **1d**, 50%; **2a**, 100%; **2b**, 75%; **2c**, 95%; **2d**, 100%; **8**, 45%; **9**, 100%.

Conformational Analysis and Molecular Modeling of Diureas 2. In the preceding two sections of this paper, IR and ^{1}H NMR spectroscopy have established that diurea derivatives of 1,2-diaminoethane (e.g., **2**) adopt hydrogen-bonded conformations in chloroform solution. In this section and the following two sections, molecular modeling, X-ray crystallography, and ^{1}H NMR spectroscopy provide insight into the structures of the hydrogen-bonded conformations.

Five torsion angles ($N^4-C^2-N^2-C^4$, $C^2-N^2-C^4-C^3$, $N^2-C^4-C^3-N^1$, $C^4-C^3-N^1-C^1$, and $C^3-N^1-C^1-N^3$ in structure **10**) largely determine the conformation of the 1,2-diaminoethane



10

diurea group. Of these, the $C^3-N^1-C^1-N^3$ torsion angle is expected to be fixed (ca. 180°) by the conformational bias of the *N*-phenyl substituent (vide supra) and the planarity of the urea group. For the ureas to adopt hydrogen-bonded conformations, as is seen experimentally, the $N^4-C^2-N^2-C^4$ torsion angle must also be fixed (ca. 0°). Thus, the $C^2-N^2-C^4-C^3$, $N^2-C^4-C^3-N^1$, and $C^4-C^3-N^1-C^1$ torsion angles define the geometries of the hydrogen-bonded conformers of diureas **2**. Examination of molecular models reveals that the $C^2-N^2-C^4-C^3$ and $C^4-C^3-N^1-C^1$ torsion angles should be roughly ±90°, whereas the $N^2-C^4-C^3-N^1$ torsion angle can be either ca. ±60° or ca. 180°.

(13) For this compound to form a hydrogen-bonded dimer (or oligomer) with so great an association constant that no changes in chemical shift are observed, the dimerization constant would have to be extremely high (≥1 000 000 M^{-1}). Since the IR spectra of monoureas **5** and **6** show no evidence of dimerization at 10 mM, and the dimerization constants of typical di- and triamides are on the order of 10^2-10^3 M^{-1} (Raj, P. A.; Balaram, P. *Biopolymers* **1985**, *24*, 1131), it is highly unlikely that diureas **1** and **2** are dimerized at these concentrations.

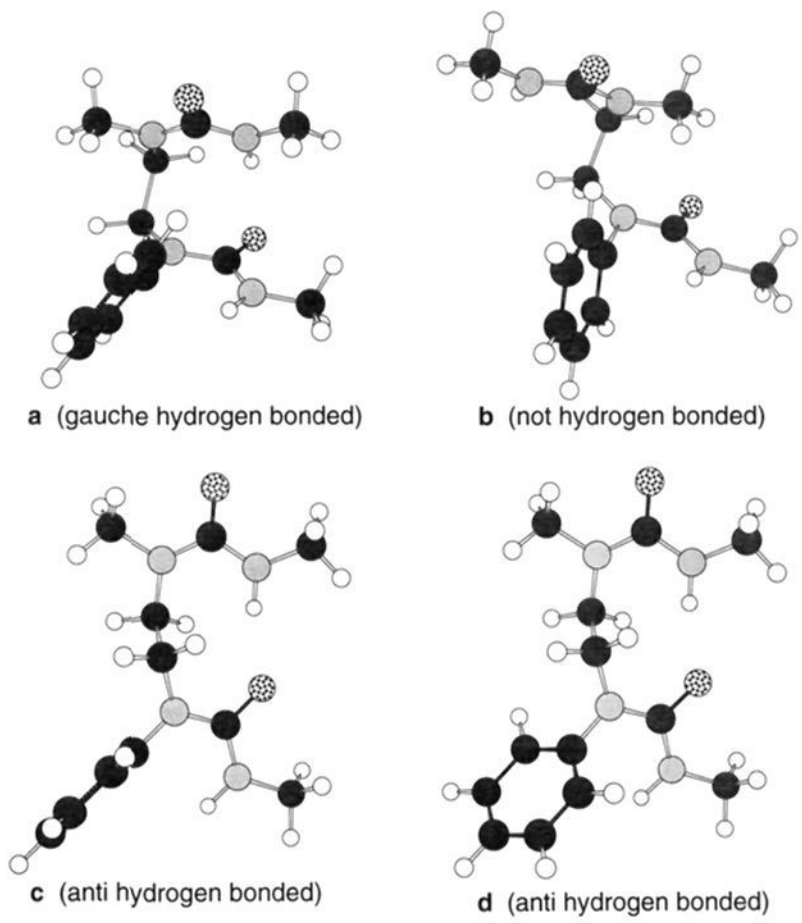


Figure 2. Low-energy conformations of **10** as calculated by molecular mechanics: (a) gauche hydrogen bonded, 0.0 kJ/mol; (b) not hydrogen bonded, 6.2 kJ/mol; (c) anti hydrogen bonded, 8.9 kJ/mol; (d) anti hydrogen bonded, 9.7 kJ/mol. (See text for details.)

On the basis of the $N^2-C^4-C^3-N^1$ torsion angle, the intramolecularly hydrogen bonded conformations of diureas **2** may be grouped into two families, *gauche* and *anti*. Molecular modeling studies provide insight into the structures and relative stabilities of the conformers that make up these families. Molecular mechanics calculations on **10** using MacroModel V3.5a with the AMBER*[14] force field, the GB/SA chloroform model,[15] and Monte Carlo multiple-minimum (MCMM) conformational searching[16] identified four conformers within the lowest 10 kJ/mol.[17] Figure 2 shows these conformers. A gauche conformer (a) was found to be lowest in enthalpy (0 kJ/mol). At substantially higher energies a non-hydrogen-bonded conformer (b, 6.2 kJ/mol) and two anti conformers (c, 8.9 kJ/mol; d, 9.7 kJ/mol) were identified. The two anti conformers are essentially identical, differing mainly in rotation about the N−Ph bond.

Table 2 summarizes the torsion angles and other key structural parameters of these conformers. The anti and gauche conformers have 160° and 50° $N^2-C^4-C^3-N^1$ torsion angles, respectively. The conformers also differ substantially in the orientations of the CH_3 subsitutents on the urea groups ($C^{14}H_3$ and $C^{15}H_3$). These substituents are closer in the gauche conformation than in the anti conformations (4.4 vs 6.2 Å), and the N^3-C^{14} and N^4-C^{15} bonds are more divergent in the anti conformers than in the gauche conformer.

(14) (a) McDonald, D. Q.; Still, W. C. *Tetrahedron Lett.* **1992**, *33*, 7743. (b) McDonald, D. Q.; Still, W. C. *Tetrahedron Lett.* **1992**, *33*, 7747.

(15) Still, W. C.; Tempczyk, A.; Hawley, R. C.; Hendrickson, T. *J. Am. Chem. Soc.* **1990**, *112*, 6127.

(16) (a) Chang, G.; Guida, W. C.; Still, W. C. *J. Am. Chem. Soc.* **1989**, *111*, 4379. (b) Saunders, M.; Houk, K. N.; Wu, Y-D.; Still, W. C.; Lipton, M.; Chang, G.; Guida, W. C. *J. Am. Chem. Soc.* **1990**, *112*, 1419.

(17) In this search, only conformations in which the carbonyl groups pointed "upwards" were considered. Enantiomeric conformations were considered to be identical. A number of additional conformers were identified in this energy range that differed only slightly from the four main conformers (by rotation about the N−Ph bond). For the purposes of this discussion, these were not considered to differ from the four main conformers.

Table 2. Selected Structural Parameters of Diurea Derivatives of 1,2-Diaminoethane.

structure	$C^2-N^2-C^4-C^3$ torsion (deg)	$N^2-C^4-C^3-N^1$ torsion (deg)	$C^4-C^3-N^1-C^1$ torsion (deg)	$C^{15}-C^{14}$ dist (Å)	O^1-H^4 dist (Å)	O^1-N^4 dist (Å)	$N^4-H^4-O^1$ angle (deg)	ϕ_H[a] (deg)	θ_H[a] (deg)
10, conf a (calcd)	102.0	−50.0	−69.9	4.37	2.05	2.96	148	14	16
10, conf c (calcd)	79.8	−160.7	77.3	6.21	1.98	2.97	167	39	82
10, conf d (calcd)	80.0	−159.9	73.0	6.19	1.96	2.96	168	39	76
2a conf a (exptl)[b]	82.5	−164.8	72.5	6.19	2.02	3.01	161	42	67
2a conf b (exptl)[b]	−88.0	159.0	−72.4	5.97	1.89	2.87	157	45	60
2c (exptl)[b]	78.6	−168.0	73.9	6.37	2.13	3.09	155	41	83
9 (exptl)[b]	70.4	−168.7	75.0	6.36	2.06	3.04	159	42	84

[a]Reference 18. [b]The length of the N^4-H^4 bond was normalized to 1.03 Å in calculating parameters for these crystallographically determined structures. See ref 18 for details.

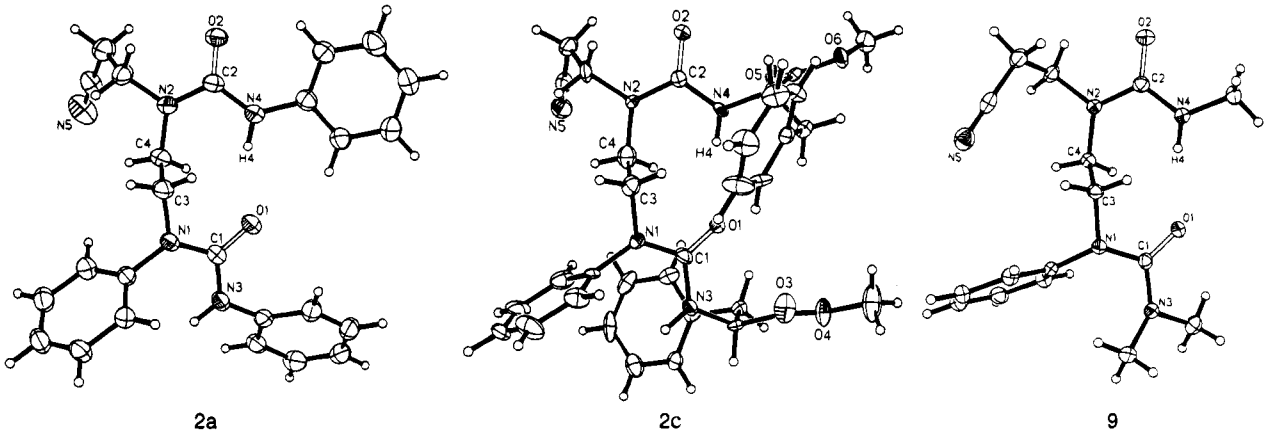


Figure 3. X-ray crystallographic structures of diureas **2a**, **2c**, and **9**.

The geometry of the hydrogen bond in the gauche conformer (Figure 2a) is unusual, because the NH group of the upper urea is hydrogen bonded to the π face of the lower carbonyl group. In contrast, the upper NH group is directed toward one of the sp^2 lone pairs of electrons of the lower carbonyl group in each of the anti conformers (Figure 2, conformers c and d). Taylor et al. have quantified these geometrical relationships by the angles ϕ_H and θ_H.[18] The angle θ_H describes the relationship of the NH group with respect to the plane of the carbonyl group: A value of $\theta_H = 0°$ corresponds to a hydrogen bond in which the NH group is directed at the π-orbital of the carbonyl oxygen atom, whereas a value of $\theta_H = 90°$ corresponds to a hydrogen bond in which the NH group lies in the plane of the carbonyl group. The angle ϕ_H describes the orientation of the NH group within the plane of the carbonyl group: If $\phi_H = 30°$ and $\theta_H = 90°$, the NH group is directed at the sp^2 lone pair of electrons of the carbonyl group. In the gauche conformer, $\theta_H = 16°$ and $\phi_H = 30°$, whereas in the anti conformers, $\theta_H = 82°$ and 76° and $\phi_H = 39°$. In surveying the Cambridge Structural Database, Taylor et al. find hydrogen bonds with the former geometry to be among the most uncommon and hydrogen bonds with the latter geometry to be among the most common.[18] Additional parameters used to describe hydrogen bonds between NH and carbonyl groups include the O−H and O−N distances and the NHO angle. In both the gauche and the anti conformers, these values fall well within the normal ranges (Table 2).[18b]

In light of the unusual hydrogen-bond geometry predicted for the gauche conformer, it is surprising that molecular mechanics calculations predict this conformer to be substantially lower in enthalpy. These calculations must be regarded with caution, however, because the AMBER* force field does not explicitly address the angular dependence of hydrogen bonding[14,19] and is poorly parametrized for the $N^2-C^4-C^3-N^1$ torsion and other features of 1,2-diaminoethane diureas **2**. In the next two sections, we describe experiments indicating that the anti conformation is actually the favored conformation in both the solid and solution states.

X-ray Crystallographic Structures of Diurea Derivatives of 1,2-Diaminoethane. Whereas diurea derivatives of 1,3-diaminopropane tend to be glassy solids, diurea derivatives of 1,2-diaminoethane are crystalline, and diureas **2a**, **2c**, and **9** afforded X-ray crystallographic quality crystals.[20] X-ray crystallography reveals that these compounds adopt hydrogen-bonded anti conformations in the solid state (Figure 3).[21] The conformations of the hydrogen-bonded nine-membered rings in each of these compounds are similar to each other and to the anti conformations predicted by molecular mechanics calculations. Table 2 summarizes key structural parameters. In keeping with the method of Taylor et al., the length of the N^4-H^4 bond has been normalized to 1.03 Å in calculating these parameters.[18] The O−H and O−N distances and the NHO, ϕ_H, and θ_H angles of these compounds all fall within the ranges normally found for N−H···O=C hydrogen bonds.

Solution-Phase Conformation of Diurea Derivatives of 1,2-Diaminoethane. The ^1H NMR spectra of diureas **2a**, **2d**, and **9** exhibit non-first-order multiplets associated with the AA′BB′ spin system of the 1,2-diaminoethane backbone.[22,23] To elucidate the conformations of these compounds in the solution state, we have analyzed these multiplets. By simulating AA′BB′

(18) (a) Taylor, R.; Kennard, O.; Versichel, W. *J. Am. Chem. Soc.* **1983**, *105*, 5761. (b) Taylor, R.; Kennard, O.; Versichel, W. *Acta Crystallogr., Sect. B* **1984**, *40*, 280.

(19) Ferguson, D. M.; Kollman, P. A. *J. Comp. Chem.* **1991**, *12*, 620.

(20) We attribute the greater crystallinity of the 1,2-diaminoethane diureas to the more well-ordered structures of these compounds.

(21) Diurea **2a** was found to have two crystallographically-independent molecules of **2a** per asymmetric unit cell. The conformations of these two molecules are almost enantiomeric, differing mainly in the rotational orientations of the *N*-phenyl substituents. The two molecules are referred to as conformer a and conformer b in Table 2; only conformer a is shown in Figure 3. The crystal of **9** contained a chiral conformer as a single enantiomer. The absolute stereochemistry of this conformer was arbitrarily chosen to be the same as that of **2c**.

(22) (a) Pople, J. A.; Schneider, W. G.; Bernstein, H. J. *High-Resolution Nuclear Magnetic Resonance*; McGraw-Hill: New York, 1959; pp 138–151, 377–385. (b) Roberts, J. D. *An Introduction to the Analysis of Spin–Spin Splitting in High-Resolution Nuclear Magnetic Resonance Spectra*; W. A. Benjamin: New York, 1962; Chapter 4.

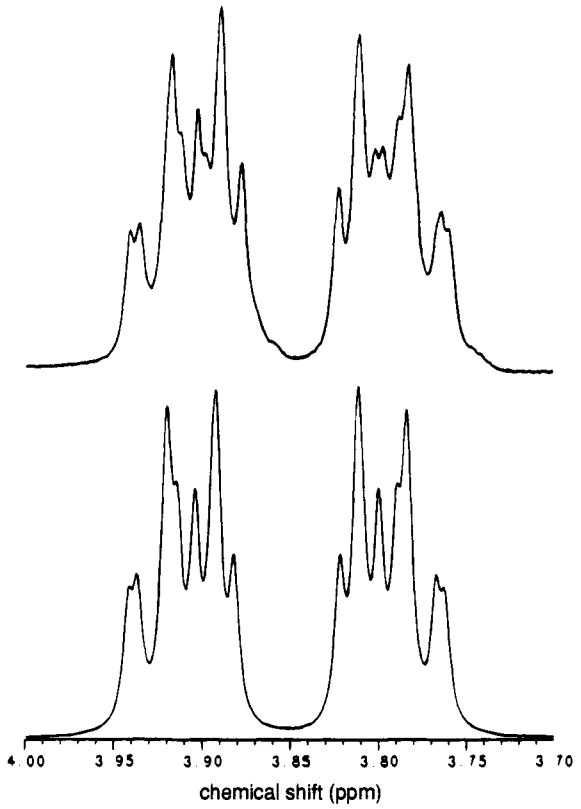
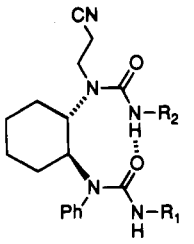


Figure 4. Experimental (upper) and simulated (lower) 300.13 MHz ^{1}H NMR spectra of the diaminoethane group of diurea **2a** in $CDCl_3$. The following values were used in the simulation: $\nu_A = \nu_{A'} = 1174$ Hz, $\nu_B = \nu_{B'} = 1138$ Hz, $J_{AB} = J_{A'B'} = 5$ Hz, $J_{AB'} = J_{A'B} = 10$ Hz, $J_{AA'} = J_{BB'} = -15$ Hz, Lorenzian line width = 2 Hz. The shoulders at δ 3.74 and 3.86 in the experimental spectrum are artifacts associated with the shimming of the spectrometer.

spin systems with various coupling constants and comparing the experimental and simulated spectra, we determined coupling constants of 5 Hz for J_{AB} and $J_{A'B'}$ and 10 Hz for $J_{AB'}$ and $J_{A'B}$. Spectra were simulated using the GEMSIM program of a General Electric GN-500 NMR spectrometer. Figure 4 shows the experimental and simulated spectra of **2a** at 300 MHz. These coupling constants were compared to those calculated for the gauche and anti conformers using the NMR feature of Macro-Model V3.5a. The gauche conformer was considered to be a racemic mixture of two rapidly equilibrating enantiomeric conformers with $N^2-C^4-C^3-N^1$ torsion angles of $\pm 50°$. Similarly, the anti conformer was considered to be a racemic mixture of two rapidly equilibrating enantiomeric conformers with $N^2-C^4-C^3-N^1$ torsion angles of $\pm 160°$. Coupling constants of 5 and 6 Hz were calculated for the gauche conformer, and 4 and 11 Hz were calculated for the anti conformer. The experimentally determined coupling constants (5 and 10 Hz) are in reasonable agreement with those calculated for the anti conformation. These studies suggest that ureas **2** are largely or wholly in anti conformations in chloroform solution and confirm that the solution state conformations of the compounds are similar to those observed in the crystal structures. The findings provide further evidence that the molecular modeling studies described above do not accurately predict the relative stabilities of the gauche and anti conformers.

Conformational Studies of Diurea Derivatives of *trans*-1,2-Diaminocyclohexane. To determine the effect of a gauche conformation on diurea derivatives of 1,2-ethanediamine, we have prepared and studied diureas **11a** and **11d**. These compounds were readily synthesized by conjugate addition of *N*-phenyl-*trans*-1,2-diaminocyclohexane[24] to acrylonitrile, followed by reaction of the adduct with phenyl or methyl isocyanate.



11a $R_1 = R_2 = Ph$
11d $R_1 = R_2 = CH_3$

^{1}H NMR spectroscopy (500 MHz) reveals dimethyl derivative **11d** to be a 9:1 mixture of two slowly-interconverting conformational isomers in chloroform solution at ambient temperature. At this temperature the peaks of the major conformer are broad, and the minor conformer exhibits only one distinct peak, a methyl resonance. As the temperature is lowered, the peaks of the major conformer sharpen, and some of the other peaks of the minor conformer appear. At -10 °C, the major isomer shows two triplets of doublets associated with the cyclohexyl methine groups (δ 4.41, J = 10.9, 3.2 Hz; δ 2.97, J = 11.3, 3.6 Hz). The large (11 Hz) coupling between these protons indicates that the urea subsitutuents are both equatorial on the cyclohexane ring.[25] One of the NH resonances is shifted substantially downfield with respect to the other (δ 6.35 vs δ 4.08), indicating that this conformer is intramolecularly hydrogen bonded. The peaks of the minor conformer are broad between -60 and -10 °C, and the coupling constants cannot be determined accurately. However, the shape of the downfield cyclohexyl methine resonance (δ 4.75 at -30 °C) is consistent with a broadened triplet with a coupling constant of 11 Hz, indicating that the minor conformer is also diequatorial. In light of the IR spectrum of this compound (described below), this conformer appears to not be intramolecularly hydrogen bonded.[26] The involvement of additional dynamic processes at lower temperatures (e.g., reduced rate of rotation about the N–Ph bond and changes in the equilibrium population of conformers) complicates the interpretation of the low-temperature ^{1}H NMR spectra of this compound.

In the infrared spectrum, diurea **11d** exhibits peaks at 3457 and 3354 cm^{-1} corresponding to the non-hydrogen-bonded stretching band of the lower NH group and the hydrogen-bonded stretching band of the upper NH group (Figure 1). The spectrum also exhibits a shoulder at 3486 cm^{-1}, which arises from the upper NH group in a non-hydrogen-bonded conformation. Comparison of the integrated absorbance of this shoulder to the integrated absorbance of monourea **6d** (3487 cm^{-1}) indicates that about 10% of **11d** is in a non-hydrogen-bonded conforma-

(23) Pople, J. A.; Schneider, W. G.; Bernstein, H. J. *Can. J. Chem.* **1957**, *35*, 1060.

(24) Egli, M.; Hoesch, L.; Dreiding, A. S. *Helv. Chim. Acta* **1985**, *68*, 220.

(25) The protons of the cyanoethyl group appear as four distinct doublets of doublets in the 500 MHz ^{1}H NMR at -10 °C (δ 3.57, J = 13.7, 10.4, 4.9 Hz; δ 3.04, J = 16.6, 9.9, 5.0 Hz; δ 2.72, J = 13.9, 10.1, 5.0 Hz; δ 2.39, J = 16.5, 10.2, 5.0 Hz). These coupling constants suggest that the cyanoethyl group adopts an anti conformation. Molecular modeling studies indicate that the large differences in chemical shift between diastereotopic hydrogens arise from a conformation in which the cyanoethyl group is near the phenyl group and the "upper" carbonyl group.

(26) Because only one NH resonance of the minor conformer is observed by ^{1}H NMR spectroscopy (δ 3.89, q, J = 4.6 Hz, at -30 °C in $CDCl_3$ solution), it is not possible to establish with certainty whether this conformer is hydrogen bonded.

tion. These observations are consistent with the ^{1}H NMR results described above.

Molecular modeling studies (CPK and molecular mechanics) establish that the hydrogen-bonded diequatorial conformation of **11d** is essentially superimposable with the gauche conformer shown in Figure 2a. Because of the proximity of the two urea groups in this conformation, the upper NH group is hydrogen bonded to the π orbital of the lower carbonyl group, rather than to the sp^2 lone pair. This unusual hydrogen-bonding geometry is expected to result in measurable spectroscopic differences between **11d** and **2d**. Such differences are seen experimentally. In the ^{1}H NMR spectrum, the hydrogen-bonded NH resonance of **11d** appears at 6.28 ppm, whereas that of **2d** appears at 6.81 ppm (Table 1). In the IR spectrum, the hydrogen-bonded NH stretch of **11d** occurs at 3354 cm^{-1}, whereas that of **2d** appears at 3338 cm^{-1} (Table 1).

Diurea **11a** also adopts a diequatorial (gauche) conformation. Although the peaks in the ^{1}H NMR spectrum of **11a** are broad at room temperature, they sharpen as the temperature is lowered, and the coupling constants of the methine resonances indicate that the urea substituents are in the equatorial positions of the cyclohexane ring. In contrast to **11d**, only a single set of peaks is observed for **11a** (−55 to 40 °C), suggesting that the compound is exclusively hydrogen bonded. Infrared spectroscopy supports this conclusion, since NH stretching bands appear at 3423 and 3314 cm^{-1}, but no peak or shoulder is present at 3460 cm^{-1}. The hydrogen-bonded NH groups of **11a** and **2a** differ substantially in their ^{1}H NMR peak positions (8.38 vs 9.02 ppm) and modestly in their infrared stretching frequencies (3314 vs 3309 cm^{-1}).

The spectroscopic differences between diureas **11** and **2** reflect the differing conformations of these compounds. The differing ^{1}H NMR chemical shifts of the hydrogen-bonded NH groups of these compounds may arise from magnetic anisotropy of the carbonyl groups to which the NH groups are hydrogen bonded; the upfield positions of the hydrogen-bonded NH resonances in diureas **11** are consistent with a model in which these NH groups are above the π-electron clouds of the carbonyl groups.[27] The slightly higher infrared stretching frequencies of the hydrogen-bonded NH groups of diureas **11** suggest that the intramolecular hydrogen bonds in ureas **2** are stronger than those in ureas **11** and the sp^2 lone pairs of electrons are stronger hydrogen-bond bases than the π electrons.

Conclusion

The studies described above establish that diurea derivatives of 1,2-diaminoethane **4** adopt conformationally well-defined U-turn structures in chloroform solution and in the solid state. Two features help provide these compounds with orderly structures: intramolecular hydrogen bonding and the directional control provided by the phenyl substituent on the diamine backbone. An important question, which these studies have not answered, is whether these compounds adopt the same structures in highly polar solvents, such as water and dimethyl sulfoxide. Preliminary studies in our laboratories suggest that this is indeed the case, and we will report these findings in a subsequent paper.

The ease of synthesis of diurea derivatives of **4** (2−3 steps from inexpensive starting materials) and the ability to prepare derivatives bearing two different substitutents in a highly regioselective fashion render these diureas attractive as scaffolding for the creation of complex molecular architectures. We are particularly interested in using these compounds to create conformationally constrained polypeptide derivatives (e.g., homologs of **2b** and **2c** containing polypeptide chains) in which the 1,2-diaminoethane diurea U-turn permits the juxtaposition of two polypeptide strands. The 1,2-diaminoethane diurea U-turn may be thought of as analogous to a β-turn, with the notable difference that the pendant peptide strands are oriented in a parallel fashion, rather than an antiparallel fashion. We are currently determining whether the diurea scaffold can be used to induce parallel β-sheet formation in polypeptide derivatives.

(27) Silverstein, R. M.; Bassler, G. C.; Morill, T. C. *Spectrometric Identification of Organic Compounds*; Wiley: New York, 1991; pp 174−175.

Experimental Section

Materials and Methods. Commercial grade reagents and solvents were used without further purification, except as indicated below. Dichloromethane was distilled from calcium hydride. IR studies were performed using either hydrocarbon-stabilized chloroform or EtOH-stabilized chloroform that had been purified to remove EtOH: hydrocarbon-stabilized chloroform was used without further purification; EtOH-stabilized chloroform was extracted repeatedly with water, dried over $MgSO_4$, and distilled from P_2O_5 prior to use. All reactions were performed in oven-dried glassware under a positive pressure of nitrogen gas with magnetic stirring. We have previously reported the preparation and characterization of ureas **1a−c**, **5a**, and **6a−c** (ref 5, supplementary material). Spectroscopic data and representative procedures for the preparation of the remaining compounds are provided below. IR spectra were obtained on a Mattson Galaxy Series 5000 FTIR spectrometer. High-resolution mass spectra (HRMS) were obtained using chemical ionization with isobutane.

PhNHCH$_2$CH$_2$NHCH$_2$CH$_2$CN (4). A 100-mL, two-necked, round-bottomed flask, equipped with a nitrogen inlet adapter, a rubber septum, and a magnetic stirring bar, was charged with 50 mL of methanol, *N*-phenylethylenediamine (1.3 mL, 10 mmol), and acrylonitrile (1.0 mL, 15 mmol). After 20 h, the reaction mixture was concentrated by rotary evaporation to yield 1.92 g of a yellow-brown oil. Kugelrohr distillation (220 °C oven, 0.1 mmHg) afforded 1.89 g (100%) of **4** as a pale yellow oil: IR ($CHCl_3$) 3394, 3055, 3030, 2952, 2906, 2848, 2251, 1603, 1462, 1431, 1321, 1134, 694, 663 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.19 (appar t, J = 8.0 Hz, 2 H), 6.72 (t, J = 7.3 Hz, 1 H), 6.65 (d, J = 8.4 Hz, 2 H), 4.11 (br s, 1 H), 3.22 (appar q, J = 5.6 Hz, 2 H), 2.95 (t, J= 6.5 Hz, 2 H), 2.92 (t, J = 5.7 Hz, 2 H), 2.52 (t, J = 6.5 Hz, 2 H), 1.29 (br s, 1 H).

PhNHCH$_2$CH$_2$CH$_2$NHCH$_2$CH$_2$CN. A 25-mL, one-necked, round-bottomed flask, equipped with a nitrogen inlet adapter and a magnetic stirring bar, was charged with 8 mL of methanol, *N*-phenyl-1,3-propanediamine[28,29] (0.464 g, 3.09 mmol), and acrylonitrile (0.220 mL, 3.34 mmol). After 20 h, the reaction mixture was concentrated by rotary evaporation to yield 0.634 g (101%) of PhNHCH$_2$CH$_2$CH$_2$-NHCH$_2$CH$_2$CN as a yellow oil: IR (film) 3394, 3320, 3051, 3022, 2931, 2845, 2247, 1603, 1510, 1475, 1432, 1321, 1261, 1180, 1126, 870, 752, 694 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.18 (t, J = 7.7 Hz, 2 H), 6.70 (t, J = 7.3 Hz, 1 H), 6.62 (d, J = 7.7 Hz, 2 H), 4.06 (br s, 1 H), 3.22 (t, J = 6.5 Hz, 2 H), 2.93 (t, J = 6.5 Hz, 2 H), 2.78 (t, J = 6.6 Hz, 2 H), 2.52 (t, J = 6.5 Hz, 2 H), 1.81 (quint, J = 6.6 Hz, 2 H), 1.21 (br s, 1 H).

Diurea 2b. A 50-mL, one-necked round-bottomed flask, equipped with a nitrogen inlet adapter and a magnetic stirring bar, was charged with diamine **4** (0.878 g, 4.64 mmol), 15 mL of CH_2Cl_2, and valine methyl ester isocyanate[7] (0.729 g, 4.64 mmol). After 24 h, the reaction mixture was concentrated by rotary evaporation to generate 1.65 g of a brown oil. Column chromatography on silica gel (CH_3OH−EtOAc, 1:9) afforded 1.41 g (88%) of PhNHCH$_2$CH$_2$N[CONHCH(*i*-Pr)CO$_2$-CH$_3$]CH$_2$CH$_2$CN as a yellow oil: IR ($CHCl_3$) 3435, 3305, 3026, 3010, 2968, 2875, 2251, 1736, 1657, 1605, 1512, 1468, 1437, 1371, 1325, 1254, 1161, 1038, 1024, 999, 694, 665 cm^{-1}; ^{1}H NMR (300 MHz,

(28) (a) Gall, A. A.; Kurbatov, V. A.; Mustaev, A. A.; Shishkin, G. V. *Izv. Sib. Otd. Akad. Nauk SSSR, Ser. Khim. Nauk.* **1979**, 99; *Chem. Abstr.* **1979**, 91:20048d. (b) Assef, G.; Kister, J.; Metzger, J. *Bull. Soc. Chim. Fr.* **1979**, II-165.

(29) This compound was prepared by catalytic hydrogenation of 3-(phenylamino)propanenitrile. For a procedure, see: Bergeron, R. J.; Garlich, J. R. *Synthesis* **1984**, 782.

$CDCl_3$) δ 7.20 (appar. t, J = 7.6 Hz, 2 H), 6.76 (t, J = 7.3 Hz, 1 H), 6.68 (d, J = 7.7 Hz, 2 H), 5.73 (d, J = 8.6 Hz, 1 H), 4.25 (br s, 1 H), 4.24 (dd, J = 8.7, 5.2 Hz, 1 H), 3.72 (s, 3 H), 3.69−3.58 (m, 2 H), 3.55−3.41 (m, 4 H), 2.79−2.61 (m, 2 H), 2.01−1.86 (m, 1 H), 0.85 (d, J = 6.8 Hz, 3 H), 0.69 (d, J = 6.9 Hz, 3 H).

A 50-mL, one-necked, recovery flask, equipped with a magnetic stirring bar and a cold-finger condenser fitted with a nitrogen inlet adapter, was charged with $PhNHCH_2CH_2N[CONHCH(i\text{-}Pr)CO_2CH_3]CH_2CH_2CN$ (1.322 g, 3.82 mmol), 10 mL of 1,2-dichloroethane, and phenylalanine methyl ester isocyanate[7] (0.789 g, 3.84 mmol). The reaction mixture was heated at reflux for 28 h, allowed to cool, and concentrated by rotary evaporation to afford 2.19 g of a yellow oil. The oil was dissolved in 30 mL of CH_2Cl_2, and the solution was extracted sequentially with two 20-mL portions of 1 M aqueous HCl and 20 mL of saturated aqueous NaCl, dried over $MgSO_4$, filtered, and concentrated by rotary evaporation to afford 1.98 g of yellow oil. Column chromatography on silica gel (EtOAc−hexanes, 2:1) afforded 1.757 g (83%) of **2b** as a yellow oil, which solidified upon standing: mp 95−97 °C; IR ($CHCl_3$) 3425, 3305, 3066, 3018, 2954, 2877, 2251, 1740, 1649, 1597, 1514, 1497, 1439, 1406, 1373, 1335, 1283, 1095, 1024, 787, 700, 669 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.38 (t, J = 6.9 Hz, 2 H), 7.32 (t, J = 6.8 Hz, 1 H), 7.23−7.22 (m, 3 H), 7.07 (d, J = 6.7 Hz, 2 H), 6.97−6.96 (m, 2 H), 6.74 (d, J = 7.1 Hz, 1 H), 4.72−4.66 (m, 2 H), 4.23 (t, J = 6.8 Hz, 1 H), 3.85−3.79 (m, 1 H), 3.72 (s, 3 H), 3.69 (s, 3 H), 3.66−3.53 (m, 3 H), 3.51−3.43 (m, 1 H), 3.35−3.30 (m, 1 H), 3.07 (dd, ABX pattern, J_{AB} = 13.7 Hz, J_{AX} = 4.8 Hz, 1 H), 2.91 (dd, ABX pattern, J_{AB} = 13.7 Hz, J_{BX} = 5.8 Hz, 1 H), 2.67 (dt, J = 16.9, 6.7 Hz, 1 H), 2.52 (dt, J = 16.8, 5.8 Hz, 1 H), 2.27−2.20 (m, 1 H), 1.04 (d, J = 7.0 Hz, 3 H), 1.01 (d, J = 6.7 Hz, 3 H); HRMS *m/e* for $C_{29}H_{38}N_5O_6$ $(M + H)^+$, calcd 552.2822, found 552.2826. Anal. Calcd for $C_{29}H_{37}N_5O_6$: C, 63.14; H, 6.76; N, 12.70. Found: C, 62.83; H, 6.92; N, 12.40.

Representative Procedure for the Preparation of Diureas 1d, 2a, and 2d. Preparation of Diurea 2c. A 25-mL, one-necked, recovery flask, equipped with a magnetic stirring bar and a cold-finger condenser fitted with a nitrogen inlet adapter, was charged with diamine **4** (0.124 g, 0.655 mmol), 5 mL of 1,2-dichloroethane, and phenylalanine methyl ester isocyanate[7] (0.250 mL, 0.289 g, 1.41 mmol). The reaction mixture was heated at reflux for 24 h, allowed to cool, and partitioned between 3 mL of CH_2Cl_2 and 10 mL of 1 M aqueous HCl. The aqueous phase was extracted with two 1-mL portions of CH_2Cl_2, and the combined organic phases were dried over $MgSO_4$, filtered, and concentrated by rotary evaporation to afford 0.356 g of yellow oil. Column chromatography on silica gel (EtOAc−CH_2Cl_2, 1:1) afforded 0.276 g (71%) of **2c** as a colorless oil, which solidified upon standing: mp 115−117 °C; IR ($CHCl_3$) 3425, 3292, 3088, 3066, 3014, 2954, 2860, 2251, 1741, 1649, 1597, 1514, 1497, 1439, 1373, 1336, 787, 702, 669 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.39−7.21 (m, 11 H), 7.08 (d, J = 7.7 Hz, 1 H), 7.05 (appar d, J = 7.4 Hz, 2 H), 6.98−6.96 (m, 2 H), 4.74−4.70 (m, 2 H), 4.61−4.57 (m, 1 H), 3.86 (appar t, J = 8.3 Hz, 1 H), 3.70 (s, 6 H), 3.55−3.49 (m, 3 H), 3.42−3.35 (m, 1 H), 3.29−3.24 (m, 1 H), 3.21 (dd, J = 13.9 Hz, 5.3 Hz, 1 H), 3.13−3.08 (m, 2 H), 2.94 (dd, J = 13.8, 6.5 Hz, 1 H), 2.55 (dt, J = 16.9, 6.8 Hz, 1 H), 2.46 (dt, J = 16.9, 5.9 Hz, 1 H); HRMS *m/e* for $C_{33}H_{38}N_5O_6$ $(M + H)^+$, calcd 600.2822, found 600.2811. Anal. Calcd for $C_{33}H_{37}N_5O_6$: C, 66.10; H, 6.22; N, 11.68. Found: C, 65.91; H, 6.41; N, 11.60.

Diurea 1d. Reaction of $PhNHCH_2CH_2CH_2NHCH_2CH_2CN$ (0.631 g, 3.05 mmol) and methyl isocyanate (0.400 mL, 6.78 mmol) in 10 mL of CH_2Cl_2 (22 °C), followed by repeated column chromatography of the crude product on silica gel (CH_3OH−CH_2Cl_2, 1:9), afforded **1d** (0.351 g, 37%) as a yellow oil, which solidified upon standing: mp 92−94 °C; IR ($CHCl_3$) 3481 (sh), 3458, 3338, 3005, 2951, 2251, 1645, 1597, 1529, 1495, 1417, 1371, 1296, 1275, 1153, 702, 665 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.46 (t, J = 7.5 Hz, 2 H), 7.37 (t, J = 7.5 Hz, 1 H), 7.21 (d, J = 7.7 Hz, 2 H), 5.65 (appar d, J = 3.8 Hz, 1 H), 4.18 (appar d, J = 4.3 Hz, 1 H), 3.74 (t, J = 6.3 Hz, 2 H), 3.48 (t, J = 6.5 Hz, 2 H), 3.34 (t, J = 7.0 Hz, 2 H), 2.80 (d, J = 4.4 Hz, 3 H), 2.73 (d, J = 4.7 Hz, 3 H), 2.66 (t, J = 6.4 Hz, 2 H), 1.77 (quint, J = 6.7 Hz, 2 H); HRMS *m/e* for $C_{16}H_{24}N_5O_2$ $(M + H)^+$, calcd 318.1930, found 318.1919. Anal. Calcd for $C_{16}H_{23}N_5O_2$: C, 60.55; H, 7.30; N, 22.07. Found: C, 59.62; H, 7.18; N, 21.54.

Diurea 2a. Reaction of diamine **4** (0.172 g, 0.908 mmol) and phenyl isocyanate (0.210 mL, 1.93 mmol) in 4 mL of 1,2-dichloroethane (16 h at reflux), followed by column chromatography of the crude product on silica gel (EtOAc−hexanes, 1:1), afforded 0.370 g (95%) of **2a** as white crystals: mp 148−149 °C; IR ($CHCl_3$) 3425, 3307, 3142, 3062, 3010, 2947, 2251, 1662, 1597, 1549, 1529, 1498, 1483, 1446, 1400, 1362, 1327, 1313, 1242, 1182, 1074, 1030, 901, 700, 665 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 9.02 (s, 1 H), 7.71 (d, J = 8.2 Hz, 2 H), 7.54 (t, J = 7.7 Hz, 2 H), 7.46 (t, J = 7.6 Hz, 1 H), 7.34−7.28 (m, 8 H), 7.07−7.02 (m, 2 H), 6.24 (s, 1 H), 3.92−3.89 (m, 2 H), 3.80−3.77 (m, 2 H), 3.56 (t, J = 6.3 Hz, 2 H), 2.71 (t, J = 6.2 Hz, 2 H); HRMS *m/e* for $C_{25}H_{26}N_5O_2$ $(M + H)^+$, calcd 428.2086, found 428.2072. Anal. Calcd for $C_{25}H_{25}N_5O_2$: C, 70.24; H, 5.89; N, 16.38. Found: C, 69.97; H, 5.92; N, 16.25.

Diurea 2d. Reaction of diamine **4** (0.333 g, 1.76 mmol) and methyl isocyanate (0.210 mL, 3.56 mmol) followed by recrystallization of the crude product from CH_2Cl_2−pentane afforded **2d** (0.390 g, 73%) as white crystals: mp 124−126 °C; IR ($CHCl_3$) 3456, 3338, 3003, 2951, 2812, 2251, 1641, 1597, 1556, 1497, 1417, 1369, 1359, 1333, 1325, 1296, 1240, 701, 665 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.45 (t, J = 7.6 Hz, 2 H), 7.37 (t, J = 7.4 Hz, 1 H), 7.19 (d, J = 7.8 Hz, 2 H), 6.82 (br s, 1 H), 4.26 (appar d, J = 4.0 Hz, 1 H), 3.70−3.67 (m, 2 H), 3.55−3.52 (m, 2 H), 3.47 (t, J = 6.2 Hz, 2 H), 2.89 (d, J = 4.2 Hz, 3 H), 2.75 (d, J = 4.6 Hz, 3 H), 2.62 (t, J = 6.2 Hz, 2 H); HRMS *m/e* for $C_{15}H_{22}N_5O_2$ $(M + H)^+$, calcd 304.1773, found 304.1769. Anal. Calcd for $C_{15}H_{21}N_5O_2$: C, 59.39; H, 6.98; N, 23.09. Found: C, 59.11; H, 7.13; N, 23.01.

Representative Procedure for the Preparation of Monoureas 5c, 5d, 6d, 7a, and 7d. Preparation of Monourea 5c. A 50-mL, two-necked, round-bottomed flask, equipped with a nitrogen inlet adapter, a rubber septum, and a magnetic stirring bar, was charged with *N*-ethylaniline (0.280 mL, 2.23 mmol), 20 mL of CH_2Cl_2, and (*S*)-phenylalanine methyl ester isocyanate[7] (0.460 g, 2.24 mmol). After 28 h, the reaction mixture was concentrated by rotary evaporation to generate 0.742 g of a viscous yellow oil. Column chromatography on silica gel (EtOAc−CH_2Cl_2, 1:9) afforded 0.634 g (87%) of urea **5c** as a viscous yellow oil: IR ($CHCl_3$) 3427, 3066, 3030, 3008, 2954, 2935, 2875, 1741, 1651, 1597, 1510, 1444, 1381, 1350, 1292, 1178, 1095, 700, 665 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.36 (t, J = 7.5 Hz, 2 H), 7.31 (d, J = 7.2 Hz, 1 H), 7.19−7.18 (m, 3 H), 7.10 (d, J = 7.4 Hz, 2 H), 6.94−6.92 (m, 2 H), 4.72 (q, J = 6.7 Hz, 1 H), 4.49 (d, J = 7.8 Hz, 1 H), 3.73−3.65 (m, 2 H), 3.68 (s, 3 H), 3.03 (dd, ABX pattern, J_{AB} = 13.8 Hz, J_{AX} = 5.5 Hz, 1 H), 2.92 (dd, ABX pattern, J_{AB} = 13.7 Hz, J_{BX} = 6.5 Hz, 1 H), 1.06 (t, J = 7.1 Hz, 3 H); HRMS *m/e* for $C_{19}H_{22}N_2O_3$, calcd 326.1630, found 326.1621. Anal. Calcd for $C_{19}H_{22}N_2O_3$: C, 69.92; H, 6.79; N, 8.58. Found: C, 69.85; H, 6.81; N, 8.51.

Monourea 5d. Reaction of *N*-ethylaniline (0.200 mL, 1.59 mmol) and methyl isocyanate (0.100 mL, 1.70 mmol) in 10 mL of CH_2Cl_2 (22 °C, 15 h), followed by extraction of the reaction mixture with 1 M aqueous HCl, drying of the organic phase over $MgSO_4$, filtration, and concentration of the solution by rotary evaporation, afforded **5d** (0.212 g, 75%) as white crystals: mp 68−69 °C; IR ($CHCl_3$) 3460, 3066, 2999, 2935, 2875, 2812, 1647, 1597, 1518, 1497, 1452, 1369, 1292, 1259, 1126, 702, 663 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.44 (t, J = 7.5 Hz, 2 H), 7.34 (t, J = 6.8 Hz, 1 H), 7.22 (d, J = 7.3 Hz, 1 H), 4.10 (br s, 1 H), 3.73 (q, J = 7.1 Hz, 2 H), 2.72 (s, 3 H), 1.10 (t, J = 7.1 Hz, 3 H); HRMS *m/e* for $C_{10}H_{15}N_2O$ $(M + H)^+$, calcd 179.1184, found 179.1186. Anal. Calcd for $C_{10}H_{14}N_2O$: C, 67.39; H, 7.92; N, 15.72. Found: C, 67.44; H, 8.14; N, 15.75.

Monourea 6d. Reaction of diethylamine (1.03 mL, 10.0 mmol) and methyl isocyanate (0.88 mL, 15.0 mmol) in 20 mL of CH_2Cl_2 (22 °C, 1 h), followed by kugelrohr distillation of the crude product, afforded **6d** (1.29 g, 99%) as oily colorless crystals: mp 34−35 °C; IR ($CHCl_3$) 3487, 3383, 2989, 2935, 2875, 1635, 1529, 1416, 1381, 1273, 1196, 1097, 663 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 4.29 (br s, 1 H), 3.25 (q, J = 7.1 Hz, 4 H), 2.81 (d, J = 4.6 Hz, 3 H), 1.13 (t, J = 7.1 Hz, 6 H); HRMS *m/e* for $C_6H_{15}N_2O$ $(M + H)^+$, calcd 131.1184, found 131.1187. Anal. Calcd for $C_6H_{14}N_2O$: C, 55.35; H, 10.84; N, 21.52. Found: C, 55.27; H, 11.15; N, 21.54.

Monourea 7a. Reaction of 3-(ethylamino)propanenitrile[30] (0.509 g, 5.19 mmol) and phenyl isocyanate (0.700 mL, 6.44 mmol) in 6 mL of CH_2Cl_2 (22 °C, 4.5 h), followed by column chromatography of the crude product on silica gel (EtOAc–hexanes, 2:3), afforded **7a** in 84% yield as white crystals: mp 61–62 °C; IR ($CHCl_3$) 3461, 3392, 3008, 2980, 2937, 2251, 1666, 1597, 1525, 1500, 1446, 1371, 1311, 1263, 1243, 1182, 1145 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.37 (d, J = 8.1 Hz, 2 H), 7.31 (appar t, J = 7.9 Hz, 2 H), 7.07 (t, J = 7.1 Hz, 1 H), 6.39 (br s, 1 H), 3.62 (t, J = 6.4 Hz, 2 H), 3.47 (q, J = 7.2 Hz, 2 H), 2.72 (t, J = 6.4 Hz, 2 H), 1.32 (t, J = 7.2 Hz, 3 H); HRMS *m/e* for $C_{12}H_{16}N_3O$ $(M + H)^+$, calcd 218.1293, found 218.1286. Anal. Calcd for $C_{12}H_{15}N_3O$: C, 66.34; H, 6.96; N, 19.34. Found: C, 66.31; H, 7.06; N, 19.27.

Monourea 7d. Reaction of 3-(ethylamino)propanenitrile[30] (0.528 g, 5.38 mmol) and methyl isocyanate (0.400 mL, 6.78 mmol) in 6 mL of CH_2Cl_2 (22 °C, 4.5 h), followed by column chromatography of the crude product on silica gel (EtOAc), afforded **7d** in 91% yield as white crystals: mp 45–47 °C; IR ($CHCl_3$) 3487, 3398, 3004, 2981, 2950, 2914, 2879, 2811, 2251, 1645, 1531, 1417, 1371, 1275, 1157, 665 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 4.47 (br s, 1 H), 3.54 (t, J = 6.5 Hz, 2 H), 3.30 (q, J = 7.2 Hz, 2 H), 2.82 (d, J = 4.6 Hz, 3 H), 2.67 (t, J = 6.4 Hz, 2 H), 1.20 (t, J = 7.1 Hz, 3 H); HRMS *m/e* for $C_7H_{14}N_3O$ $(M + H)^+$, calcd 156.1137, found 156.1143. Anal. Calcd for $C_7H_{13}N_3O$: C, 54.17; H, 8.44; N, 27.07. Found: C, 54.10; H, 8.68; N, 27.16.

Diurea 8. A 50-mL, one-necked, round-bottomed flask, equipped with a nitrogen inlet adapter and a magnetic stirring bar, was charged with $PhNHCH_2CH_2CH_2NHCH_2CH_2CN$ (0.660 g, 3.25 mmol), 10 mL of CH_2Cl_2, and methyl isocyanate (0.200 mL, 3.39 mmol). After 21 h, the reaction mixture was concentrated by rotary evaporation to generate 0.920 g of a yellow oil. Column chromatography on silica gel (EtOAc) afforded 0.779 g (92%) of $PhNHCH_2CH_2CH_2N(CONHMe)CH_2CH_2CN$ as a white solid: ^1H NMR (500 MHz, $CDCl_3$) δ 7.22 (t, J = 7.8 Hz, 2 H), 6.82 (t, J = 7.3 Hz, 1 H), 6.71 (d, J = 8.2 Hz, 2 H), 5.65 (appar d, J = 3.8 Hz, 1 H), 3.57 (br s, 1 H), 3.53 (t, J = 6.4 Hz, 2 H), 3.44 (t, J = 6.3 Hz, 2 H), 3.17 (t, J = 5.8 Hz, 2 H), 2.72 (t, J = 6.3 Hz, 2 H), 2.50 (d, J = 4.5 Hz, 3 H), 1.89 (quint, J = 6.1 Hz, 2 H).

A 50-mL, one-necked, round-bottomed flask, equipped with a nitrogen inlet adapter and a magnetic stirring bar, was charged with $PhNHCH_2CH_2CH_2N(CONHMe)CH_2CH_2CN$ (0.770 g, 2.96 mmol), 10 mL of 1,2-dichloroethane, 4-(dimethylamino)pyridine (0.376 g, 3.08 mmol), and dimethylcarbamyl chloride (0.327 g, 3.04 mmol). The reaction mixture was heated at reflux for 1 day, allowed to cool, and extracted with two 20-mL portions of 1 M aqueous HCl. Each aqueous extract was reextracted with two 3-mL portions of CH_2Cl_2, and the combined organic phases were dried over $MgSO_4$, filtered, and concentrated by rotary evaporation to generate 0.654 g of a brown oil. Column chromatography on silica gel (CH_3OH–EtOAc, 8:92) afforded 0.560 g (57%) of **8** as a colorless oil: IR ($CHCl_3$) 3483, 3464, 3340, 3001, 2947, 2251, 1637, 1597, 1535, 1497, 1396, 1375, 702 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.36 (t, J = 7.8 Hz, 2 H), 7.14 (t, J = 7.4 Hz, 1 H), 7.03 (d, J = 8.3 Hz, 2 H), 5.43 (appar d, J = 4.0 Hz, 1 H), 3.68 (t, J = 6.4 Hz, 2 H), 3.45 (t, J = 6.5 Hz, 2 H), 3.30 (t, J = 7.5 Hz, 2 H), 2.75 (d, J = 4.5 Hz, 3 H), 2.67 (s, 6 H), 2.62 (t, J = 6.6 Hz, 2 H), 1.78 (quint, J = 7.0 Hz, 2 H); HRMS *m/e* for $C_{17}H_{26}N_5O_2$ $(M + H)^+$, calcd 332.2086, found 332.2078. Anal. Calcd for $C_{17}H_{25}N_5O_2$: C, 61.61; H, 7.60; N, 21.13. Found: C, 61.33; H, 7.55; N, 20.98.

Diurea 9. A 50-mL, one-necked, round-bottomed flask, equipped with a nitrogen inlet adapter and a magnetic stirring bar, was charged with diamine **4** (0.202 g, 1.03 mmol), 10 mL of CH_2Cl_2, and methyl isocyanate (0.070 mL, 1.19 mmol). After 22 h, the reaction mixture was concentrated by rotary evaporation to generate 0.314 g of a yellow viscous oil. Column chromatography on silica gel (CH_3OH–CH_2Cl_2–concentrated aqueous NH_3, 5:95:1) afforded 0.215 g (82%) of $PhNHCH_2CH_2N(CONHMe)CH_2CH_2CN$ as a yellow film: IR ($CHCl_3$) 3438, 3055, 3008, 2949, 2916, 2881, 2251, 1647, 1603, 1531, 1506, 1240, 694, 665 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.22 (appar t, J = 7.9 Hz, 2 H), 6.78 (t, J = 7.3 Hz, 1 H), 6.64 (d, J = 7.8 Hz, 2 H), 4.88 (appar d, J = 3.9 Hz, 1 H), 4.09 (br s, 1 H), 3.54 (t, J = 6.4 Hz, 2 H), 3.49 (appar t, J = 5.5 Hz, 2 H), 3.39–3.37 (m, 2 H), 2.71 (t, J = 6.4 Hz, 2 H), 2.66 (d, J = 4.6 Hz, 3 H).

A 100-mL, one-necked, round-bottomed flask, equipped with a magnetic stirring bar and a condenser fitted with a nitrogen inlet adapter, was charged with $PhNHCH_2CH_2N(CONHMe)CH_2CH_2CN$ (0.390 g, 1.58 mmol), 13 mL of 1,2-dichloroethane, 4-(dimethylamino)pyridine (0.442 g, 3.61 mmol), and dimethylcarbamyl chloride (0.291 mL, 3.16 mmol). The reaction mixture was heated at reflux for 4 days, allowed to cool, extracted with 100 mL of 1 M aqueous HCl, dried over $MgSO_4$, filtered, and concentrated by rotary evaporation to afford a light brown solid. Column chromatography on silica gel (EtOAc–tetrahydrofuran) followed by recrystallization ($CHCl_3$–EtOAc) afforded 0.165 g (33%) of **9** as white crystals: mp 100–101.5 °C; IR ($CHCl_3$) 3338, 3018, 3003, 2949, 2251, 1630, 1595, 1583, 1564, 1495, 1398, 1377, 1335, 1182, 787, 698, 665 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.36 (t, J = 7.8 Hz, 2 H), 7.17 (t, J = 7.4 Hz, 1 H), 7.05 (d, J = 7.9 Hz, 2 H), 6.85 (appar d, J = 3.7 Hz, 1 H), 3.74–3.71 (m, 2 H), 3.43 (t, J = 6.4 Hz, 2 H), 3.41–3.38 (m, 2 H), 2.87 (d, J = 4.4 Hz, 3 H), 2.66 (s, 6 H), 2.59 (t, J = 6.3 Hz, 2 H); HRMS *m/e* for $C_{16}H_{24}N_5O_2$ $(M + H)^+$, calcd 318.1930, found 318.1920. Anal. Calcd for $C_{16}H_{23}N_5O_2$: C, 60.55; H, 7.30; N, 22.07. Found: C, 60.29; H, 7.39; N, 21.94.

***trans*-*N*-Phenyl-*N'*-(2-cyanoethyl)-1,2-cyclohexanediamine.** A 25-mL, one-necked, recovery flask, equipped with a magnetic stirring bar and a cold-finger condenser fitted with a nitrogen inlet adapter, was charged with 1-nitrocyclohexene (0.564 mL, 5.00 mmol), 5 mL of CH_3OH, and aniline (0.456 mL, 5.00 mmol). The reaction mixture was heated at reflux for 4 days and then concentrated by rotary evaporation to afford 1.079 g of a brown oil. ^1H NMR analysis revealed the crude product to be a 4:1 mixture of the *trans* and *cis* isomers of 2-(aminophenyl)nitrocyclohexane. Column chromatography on silica gel (EtOAc–hexanes, 1:5) afforded 0.447g (43%) of *trans*-2-(aminophenyl)nitrocyclohexane as a yellow solid: ^1H NMR (300 MHz, $CDCl_3$) δ 7.16 (t, J = 7.9 Hz, 2 H), 6.74 (appar t, J = 7.4 Hz, 1 H), 6.64 (appar d, J = 8.1 Hz, 2 H), 4.37 (appar td, J = 10.7, 4.1 Hz, 1 H), 3.90 (appar qd, J = 10.3, 4.2 Hz, 1 H), 3.41 (d, J = 9.4 Hz, 1 H), 2.34–2.23 (m, 2 H), 2.02 (appar qd, J = 12.3, 3.9 Hz, 1 H), 1.92–1.77 (m, 2 H), 1.50–1.28 (m, 2 H), 1.23–1.09 (m, 1 H).

A 25-mL, two-necked, round-bottomed flask, equipped with a magnetic stirring bar, a nitrogen inlet adapter, and a rubber septum, was charged with *trans*-2-(aminophenyl)nitrocyclohexane (0.301 g, 1.37 mmol), 0.305 g of 10% Pd/C, 15 mL of CH_3OH, and ammonium formate (0.862 g, 13.7 mmol).[31] After 2 h, the reaction mixture was filtered through Celite with 10 mL of CH_3OH, and the filtrate was concentrated by rotary evaporation to afford a white solid. The solid was partitioned between 10 mL of 1 M aqueous NaOH and 10 mL of CH_2Cl_2, and the aqueous phase was extracted with an additional 10-mL portion of CH_2Cl_2. The combined organic phases were dried over K_2CO_3, filtered, and concentrated by rotary evaporation to afford 0.237 g (91%) of *trans*-*N*-phenyl-1,2-cyclohexanediamine[24] as a pale yellow oil: IR (film) 3354, 3286, 3051, 3024, 2926, 2854, 1601, 1498, 1448, 1319, 1259, 748, 692 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.16 (appar t, J = 7.9 Hz, 2 H), 6.71–6.65 (m, 3 H), 3.44 (br s, 1 H), 2.97 (br s, 1 H), 2.52 (appar td, J = 9.8, 3.9 Hz, 1 H), 2.16–2.11 (m, 1 H), 2.01-1.97 (m, 1 H), 1.76-1.72 (m, 2 H), 1.58 (br s, 2 H), 1.36–1.21 (m, 3 H), 1.10–1.02 (m, 1 H).

A 25-mL, one-necked, round-bottomed flask, equipped with a magnetic stirring bar and a nitrogen inlet adapter, was charged with *trans*-*N*-phenyl-1,2-cyclohexanediamine (0.237 g, 1.24 mmol), 3 mL of CH_3OH, and acrylonitrile (0.246 mL, 3.74 mmol). After 19 h, the reaction mixture was concentrated by rotary evaporation to afford 0.300 g (99%) of *trans*-*N*-phenyl-*N'*-(2-cyanoethyl)-1,2-cyclohexanediamine as a pale yellow solid: IR (film) 3348, 3051, 3022, 2929, 2856, 2247, 1601, 1498, 1460, 1315, 1257, 1132, 750, 694 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.17 (appar t, J = 7.9 Hz, 2 H), 6.72 (t, J = 7.4 Hz, 1 H), 6.68 (d, J = 8.6 Hz, 2 H), 3.59 (br s, 1 H), 3.07 (td, J = 10.1, 3.2 Hz, 1 H), 3.03–2.98 (m, 1 H), 2.91–2.86 (m, 1 H), 2.52–2.36 (m, 3 H), 2.22–2.17 (m, 1 H), 2.12–2.07 (m, 1 H), 1.88 (br s, 1 H), 1.80–1.72 (m, 2 H), 1.38–1.05 (m, 4 H).

Diurea 11a. A 25-mL, one-necked, recovery flask, equipped with a magnetic stirring bar and a nitrogen inlet adapter, was charged with

(30) 3-(Ethylamino)propanenitrile was prepared by reaction of 70% aqueous ethylamine (6.5 mL, 0.080 mol) and acrylonitrile (5.2 mL, 0.080 mol) in 10 mL of methanol for 16 h at 25 °C followed by distillation of the reaction mixture under reduced pressure.

(31) Ehrenkaufer, R. E.; Ram, S. *Tetrahedron Lett.* **1984**, *25*, 3415.

trans-*N*-phenyl-*N'*-(2-cyanoethyl)-1,2-cyclohexanediamine (0.082 g, 0.34 mmol), 3 mL of CH_2Cl_2, and phenyl isocyanate (0.110 mL, 1.02 mmol). After 7 days, the reaction mixture was concentrated by rotary evaporation to afford a white solid. Column chromatography on silica gel (EtOAc–hexanes, 2:3) afforded 0.121 g (74%) of diurea **11a** as a pale yellow glassy solid: mp 156–158 °C; IR ($CHCl_3$) 3423, 3315, 3062, 3010, 2941, 2863, 2251, 1653, 1597, 1527, 1502, 1444, 1363, 1317, 787, 702, 692, 665 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$, −55 °C) δ 8.53 (s, 1 H), 7.59–6.93 (m, ~15 H), 6.08 (s, 1 H), 4.67 (appar t, J = 10.1 Hz, 1 H), 3.65 (appar td, J = 12.2, 4.4 Hz, 1 H), 3.29-3.22 (m, 2 H), 2.83 (appar td, J = 11.9, 3.8 Hz, 1 H), 2.71 (appar q, J = 12.1 Hz, 1 H), 2.45 (ddd, J = 16.1, 11.0, 4.2 Hz, 1 H), 2.31 (br d, J = 12.0 Hz, 1 H), 2.09 (br d, J = 10.2 Hz, 1 H), 1.97–1.87 (m, 2 H), 1.50–1.39 (m, 2 H), 1.35–1.27 (m, 1 H); HRMS *m/e* for $C_{29}H_{32}N_5O_2$ $(M + H)^+$, calcd 482.2556, found 482.2557. Anal. Calcd for $C_{29}H_{31}N_5O_2$: C, 72.33; H, 6.49; N, 14.54. Found: C, 70.41; H, 6.50; N, 13.96.

Diurea 11d. A 100-mL, one-necked, recovery flask, equipped with a magnetic stirring bar and a cold-finger condenser fitted with a nitrogen inlet adapter, was charged with *trans*-*N*-phenyl-*N'*-(2-cyanoethyl)-1,2-cyclohexanediamine (0.182 g, 0.75 mmol), 8 mL of 1,2-dichloroethane, and methyl isocyanate (1.0 mL, 17 mmol). The reaction mixture was heated at reflux for 2 days, allowed to cool, and stirred with 20 mL of 1 M aqueous HCl for 10 min. The aqueous phase was separated and extracted with 5 mL of CH_2Cl_2, and the combined organic phases were extracted with 10 mL of 1 M aqueous HCl, dried over $MgSO_4$, filtered, and concentrated by rotary evaporation to generate 0.337 g of a yellow-brown oil. Column chromatography on silica gel (EtOAc) afforded 0.191 g (71%) of **11d** as a tan solid: mp 179–181 °C; IR ($CHCl_3$) 3458, 3352, 3005, 2941, 2864, 2251, 1643, 1595, 1549, 1524, 1493, 1365, 1315, 1296, 1277, 704, 664 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$, −10 °C) 92:8 mixture of conformers: major conformer δ 7.45 (t, J = 7.5 Hz, 2 H), 7.37 (t, J = 7.4 Hz, 1 H), 7.07 (br s, 2 H), 6.35 (appar d, J = 4.2 Hz, 1 H), 4.41 (td, J = 10.9, 3.2 Hz, 1 H), 4.08 (appar d, J = 4.6 Hz, 1 H), 3.57 (ddd, J = 13.7, 10.4, 4.9 Hz, 1 H), 3.04 (ddd, J = 16.6, 9.9, 5.0 Hz, 1 H), 2.97 (td, J = 11.3, 3.6 Hz, 1 H), 2.78 (d, J = 4.3 Hz, 3 H), 2.72 (ddd, J = 13.9, 10.1, 5.0 Hz, 1 H), 2.66 (d, J = 4.6 Hz, 3 H), 2.70–2.57 (m, 1 H), 2.39 (ddd, J = 16.5, 10.2, 5.0, 1 H), 2.13 (br d, J = 12.7 Hz, 1 H), 1.98 (br d, J = 12.2 Hz, 1 H), 1.85–1.75 (m, 2 H), 1.45–1.26 (m, 2 H), 1.24–1.15 (m, 1 H); minor conformer (partial data) δ 4.77 (br s, 1 H), 4.18 (br s, 1 H), 3.89 (br s, 1 H), 3.67 (br s, 1 H), 2.86 (d, J = 4.6 Hz, 3 H); HRMS *m/e* for $C_{19}H_{28}N_5O_2$ $(M + H)^+$, calcd 358.2243, found 358.2245. Anal. Calcd for $C_{19}H_{27}N_5O_2$: C, 63.84; H, 7.61; N, 19.59. Found: C, 63.48; H, 7.73; N, 19.45.

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Supplementary Material Available: Infrared spectra of ureas **1a–d**, **2a–d**, **5a**, **5c**, **5d**, **6a–d**, **7a**, **7d**, **8**, **9**, **11a**, and **11d** (10 mM solution in $CHCl_3$, 1.0 mm pathlength, 3600–3100 cm^{-1}) and experimental details of the X-ray crystallographic structure determination, tables of distances, angles, fractional coordinates, thermal parameters, and thermal ellipsoid plots for diureas **2a**, **2c**, and **9** (61 pages). This material is contained in many libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

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