Registry No. 1, 109-97-7; 2, 4031-15-6; 3, 141293-14-3; 4, 15186-48-8; 5, 141293-15-4; *ent*-5, 141393-87-5; 6, 141393-83-1; 7, 141293-16-5; 8, 141393-84-2; 9, 141293-17-6; 10, 141393-85-3; 11, 141293-18-7; *ent*-11, 141393-90-0; 12, 141393-86-4; 13, 95715-87-0; *ent*-13, 102308-32-7; 14, 81028-12-8; *ent*-14, 81801-09-4; 15, 141293-19-8; *ent*-15, 141393-88-6; 16, 141293-20-1; *ent*-16, 141393-89-7; 17, 141293-21-2; 18, 141293-22-3; 19, 141293-23-4; 20, 141293-24-5; 21, 141293-25-6; 22, 141293-26-7; 23, 141293-27-8; TBSOP, 141293-28-9.

Supplementary Material Available: Detailed synthetic procedures and physical data for all the described compounds and Scheme III illustrating the synthesis of 23 (10 pages). Ordering information is given on any current masthead page.

Molecular Scaffolds I: Intramolecular Hydrogen Bonding in a Family of Di- and Triureas

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Summary: Di- and triurea derivatives 1 can be prepared by an iterative procedure and are found to exist in intramolecularly hydrogen bonded 10-membered ring conformations, in which substituents R_1 and R_2 and hydrogen bonding control the direction of the urea carbonyl groups.

Hydrogen bonding is a central feature of intra- and intermolecular interactions in molecular recognition,[1] crystal packing,[2,3] and the folding of small di- and triamides in organic solvents.[4,5] In proteins, hydrogen bonding plays a fundamental role in the structure of β-sheets, α-helices, and some β-turns.[6,7] As part of a program of research aimed at developing small molecules as molecular receptors and peptide conformational templates,[8,9] we are studying intramolecular hydrogen bonding in families of oligoureas. In this paper, we report synthetic and spectroscopic studies of di- and triurea derivatives of 1,3-diaminopropane and *N*-(3-aminopropyl)-1,3-propanediamine. We find that intramolecular hydrogen bonding and substituents R_1 and R_2 provide extensive conformational control in di- and triureas of the general structure 1 (n = 2, 3).

Table I. Spectroscopic Properties of NH Groups in Compounds 1-3 at 295 K

compd	IR[a] (cm^{-1})	^1H NMR[b] (ppm)	% intramolec H bonding
1a	3306, 3463	6.88	50[c]
1b	3296, 3426 3455 (weak shoulder)	8.49, 6.17	85[d]
1c	3293, 3426, 3455 (weak shoulder)	8.67, 8.14, 6.17	95[c], 75[c]
1d	3284, 3429	5.61, 4.56	35[c]
1e	3294, 3428	5.40 (Val), 4.58 (Phe)	25[c]
2a	3464	6.24	
2b	3428	6.08	
2c	3427	6.16	
2d	3452	4.72	
2e	3424	4.62	
2f	3452	4.82	
3	3301, 3459 (weak)	8.37	85[d]

[a] IR spectra were recorded at 10 mM in $CHCl_3$ solution. [b] ^1H NMR spectra were recorded at 1.0 mM in $CDCl_3$ solution. [c] Approximate value based upon chemical shift of NH resonance. [d] Value determined by integration of infrared N-H stretch (see text).

Ureas **1b-1e** were prepared efficiently by an *iterative procedure* involving three steps: (1) conjugate addition of a primary amine to acrylonitrile;[10] (2) reaction of the resulting secondary amino group with an isocyanate; and (3) reduction of the nitrile group to generate a primary amine (eq 1).[10,11] This procedure permits the preparation

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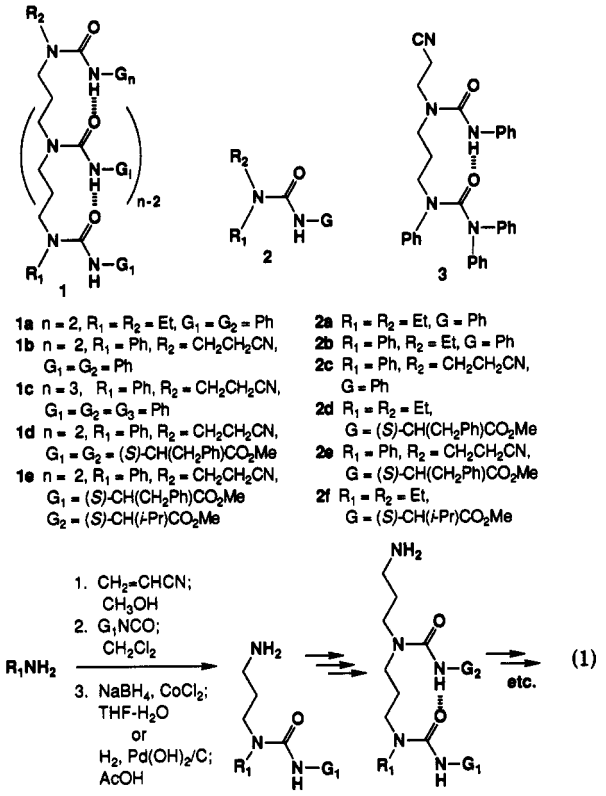


of oligoureas bearing a sequence of different groups G (e.g., **1e**). Ureas **2** and **3** were synthesized as reference compounds.[12] Monoureas **2a–2f** and diurea **1a** were prepared in a single step by the reaction of the corresponding amines and isocyanates. Peptide derivatives **1d**, **1e**, and **2d–2f** were prepared via the corresponding amino acid isocyanates.[13,14]

^{1}H NMR and infrared spectroscopy reveal significant *intra*molecular hydrogen bonding in ureas **1** in dilute (1–10 mM) chloroform solution (Table I). Diurea **1a** displays a single NH peak in the ^{1}H NMR spectrum, 0.64 ppm downfield of the corresponding monourea **2a**. The presence of a single NH peak indicates that all conformations interconvert rapidly at 295 K. The infrared spectrum exhibits free and intramolecularly hydrogen bonded NH stretching bands at 3463 and 3306 cm^{-1}, respectively. Under these conditions, no intermolecular hydrogen bonding is observed in ureas **1–3**.[15]

Amides and ureas bearing alkyl and aryl substituents on a single nitrogen atom are known to strongly favor a conformation in which the aryl group is trans to the carbonyl group.[16] This conformational preference controls

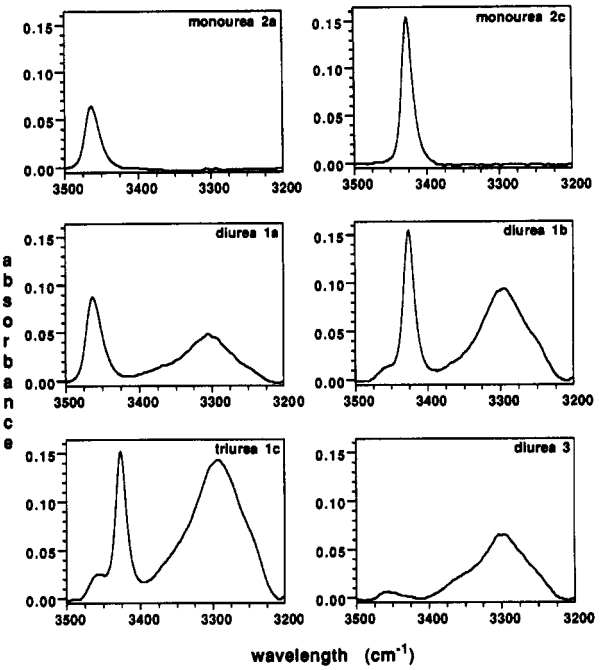
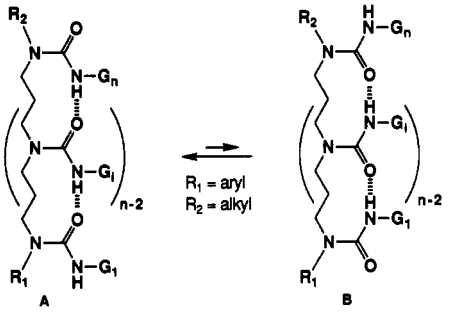


Figure 1. Infrared spectra (3200–3500 cm^{-1}) of compounds **1a**, **1b**, **1c**, **2a**, **2c**, and **3**. Spectra were recorded at 295 K as a 10 mM solution in $CHCl_3$ (1.0 mm path length) against a $CHCl_3$ reference, and are baseline corrected. Bands at 3426–3464 cm^{-1} result from non-hydrogen-bonded N–H stretching, and bands at 3293–3306 cm^{-1} result from hydrogen-bonded N–H stretching.

the orientation of the carbonyl groups in di- and triureas **1b–1e**. In these compounds, the phenyl group R_1 directs the adjacent carbonyl group, and intramolecular hydrogen bonding aligns all of the carbonyl groups in the same direction (eq 2). Thus, diurea **1b** exhibits a hydrogen-



bonded NH resonance in the ^{1}H NMR spectrum at δ 8.49 and a free NH resonance at δ 6.17. The large downfield shift of *one* hydrogen-bonded resonance (2.25 ppm relative to **2a**) and small downfield shift of the other (0.01–0.09 ppm relative to **2b** and **2c**) suggests that most of **1b** is in conformation **A** and little or none is in conformation **B**. Triurea **1c** displays *two* hydrogen-bonded NH resonances (δ 8.67 and 8.14) and one free NH resonance at 6.17, indicating alignment of all three carbonyl groups. The infrared spectra of di- and triureas **1b** and **1c** display hydrogen bonded N–H stretches at 3296 and 3293 cm^{-1}, respectively, and free N–H stretches at 3426 cm^{-1}.[17] Small shoulders at 3455 cm^{-1} in these compounds indicate that there is a small fraction of a non-hydrogen-bonded conformation. Figure 1 illustrates the N–H stretching region in the infrared spectra of these compounds and reference

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(14) Amino acid isocyanates were prepared in situ by reaction of the corresponding L-amino acid methyl ester hydrochlorides with phosgene and 4-(dimethylamino)pyridine in CH_2Cl_2. Control experiments showed no significant racemization during the generation and coupling of amino acid isocyanates, and the subsequent reactions of the peptide urea derivatives.

(15) ^{1}H NMR spectra of ureas 1–3 exhibit less than 0.02 ppm change in the position of the NH resonances between 1 and 10 mM in $CDCl_3$. IR spectroscopy on **2** shows no intermolecularly hydrogen bonded NH stretch in 10 mM chloroform solution.

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(17) The differences in free N–H stretching frequencies of *N,N*-dialkyl urea derivatives (e.g., 3464 cm^{-1}, **2a**) and *N*-alkyl-*N*-arylurea derivatives (e.g., 3428 cm^{-1}, **2b**) arise from weak intramolecular hydrogen bonding between the NH group and the aryl ring in *N*-alkyl-*N*-arylureas. For a related example, see: Schleyer, P. v. R.; Wintner, C.; Trifan, D. S.; Bacskai, R. *Tetrahedron Lett.* **1959**, *14*, 1.

compounds **2a**, **2c**, and **3**. Peptide ureas **1d** and **1e** also exhibit downfield shifting of only one NH group in the ^1H NMR and show both free and hydrogen-bonded N–H stretches in the IR.

The fraction of intramolecular hydrogen bonding in ureas **1** and **3** was determined by infrared and ^1H NMR spectroscopy. Comparison of the integrated absorbances of the free NH signals of **3** (3459 cm^{-1}) and **2a** (3464 cm^{-1}) indicates that 15 ± 5% of **3** is in a non-hydrogen-bonded conformation. Integration of the shoulder at 3455 cm^{-1} in **1b** (as the difference infrared absorption spectrum of **1b** and **2c**) reveals that 15 ± 5% of **1b** is in a non-hydrogen-bonded conformation. On the basis of these data and the ^1H NMR spectra of **1b**, **3**, and **2c**, we estimate the chemical shift of a fully hydrogen bonded NH group to be 2.5 ppm downfield of the free NH resonance in this family of urea derivatives. The percentages of intramolecular hydrogen bonding in ureas **1a**, **1c–1e** was estimated using this value. Table I summarizes these results.

These findings suggest that oligoureas of the general structure **1** may prove useful as *molecular scaffolding* to orient different groups in a parallel fashion off an oligoamine backbone. We are currently investigating this application and will report further results shortly.

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Supplementary Material Available: Experimental details for the preparation and spectroscopic characterization of all compounds described in the text (ureas 1–3) (17 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.

Rearrangements of 4-Alkynylcyclobutenones. Annelated Spiroepoxycyclohexadienones and Quinones from 4-(1,5-Dialkynyl)-4-methoxy(or hydroxy)cyclobutenones

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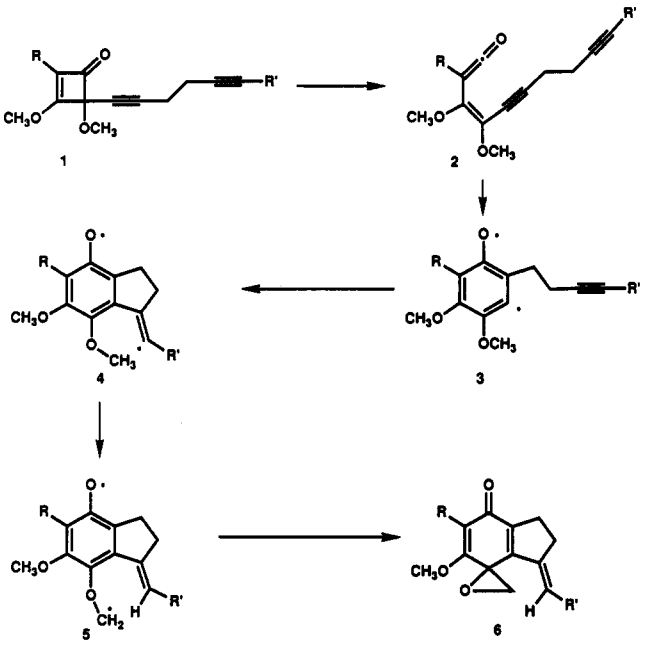
Summary: 4-(1,5-Dialkynyl)-4-methoxycyclobutenones **1** were shown to undergo a unique rearrangement to annelated spiroepoxides **6** upon thermolysis in toluene. The 4-hydroxy analogs also ring expand giving either quinones **13** or **14** as a function of the reaction solution concentration. This concentration dependence provides evidence for further mechanistic details of the general quinone synthesis stemming from 4-alkynyl-4-hydroxycyclobutenones.

Reported here are two unique ring expansions of 4-alkynylcyclobutenones; one leads to spiroepoxycyclohexadienones **6** and the other to annelated quinones **13**. *The spiroepoxides stem from 4-(1,5-dialkynyl)-4-methoxycyclobutenones* ***1a–f*** *which rearrange to* ***6a–f*** *in refluxing toluene (Scheme I).*[1] A reasonable mechanism involves initial formation of the enynylketenes **2** which lead to the diradicals **3**. The more reactive ring-based radical center undergoes exo addition to the proximal alkyne moiety to give **4**, and the resulting vinyl radical then abstracts a H-atom from the adjacent methoxy group to give **5** which leads directly to the spiroepoxides **6**.[2–4]

Scheme I



	R	R'	Yield
a)	OCH_3	H	54%
b)	OCH_3	C_6H_5	87%
c)	OCH_3	$C(CH_3)_2OBn$	62%
d)	C_6H_5	C_6H_5	71%
e)	OCH_3	C_6H_5	91%
f)	OCH_3	$(CH_2)_3CH{=}CH_2$	70%

The above annelation sequence is dependent upon the distance between the two alkynyl groups in the 4-substituent of the starting 4-methoxycyclobutenones. For example, the diradicals generated from **7a,b**, unlike those

(1) In a previous contribution the rearrangement of 4-alkynyl-4-(propargyloxy)cyclobutenones to methylenebenzofurans was described. See: Xu, S.; Moore, H. W. *J. Org. Chem.* **1991**, *56*, 6104.

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(3) For excellent reviews on radical cyclizations see: (a) Jasperse, C.; Curran, D. P.; Fevig, T. L. *Chem. Rev.* **1991**, *91*, 1237. (b) Curran, D. P. *Synthesis* **1988**, *6*, 417–39. (c) Curran, D. P. *Synthesis* **1988**, *7*, 489–513. (d) Giese, B. *Radicals in Organic Synthesis: Formation of Carbon–Carbon Bonds*; Pergamon Press: New York, 1986.

(4) Structure assignments are based on characteristic spectral properties. The *E*-stereochemistry of the alkylidene group in **6a–f** is based upon difference NOE studies. For **13c** a single-crystal X-ray structure was obtained.

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