Conformation of acylureas. Solvent polarity dependent specific rotation and the formation of molecular complexes with solvent molecules possessing a carbonyl or epoxy functionality

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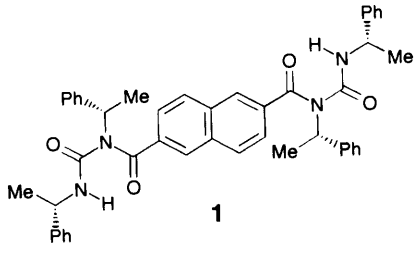
In order to elucidate the conformation of acylurea which possesses intramolecular hydrogen bonding between the carbonyl and NH groups, the relation between solvent polarity [$E_T(30)$] and specific rotation of 2,6-bis(ureidocarbonyl)naphthalene 1 was examined. A good linear relationship was observed, except for solvents with a carbonyl functionality. Some of these solvents formed molecular complexes with 1 (molar ratio of 1 : solvent, 1 : 2). Single crystal X-ray diffraction analysis of the molecular complex of 1 with ethyl acetate disclosed that the intramolecular hydrogen bonding was absent due to the intermolecular hydrogen bonding with ethyl acetate. In contrast, 2,4'-bis(ureidocarbonyl)benzophenone 2 formed 1 : 1 complexes with carbonyl compounds, and the bulkier 2,6-bis(ureidocarbonyl)naphthalene 3 could not form complexes with them.

Acylureas[1] which can be considered as diamides, possess intramolecular hydrogen bonding between the amide units. Their conformation can be regulated by this intramolecular hydrogen bonding, since such bonding is known to play an important role in conformational regulation, folding patterns, of di- and tri-amides.[2] As a part of our study of conformational control of chiral acylureas for asymmetric induction, in a previous paper[3] we reported the solvent polarity dependent conformation of cyclopropyl-carbonylureas and elucidated their conformation as a function of their ^1H NMR chemical shifts. In this paper, further study on the conformation of chiral acylureas, 2,6-bis(ureidocarbonyl)naphthalene **1** having two hydrogen bonding sites, was achieved using their specific rotation as an index of the strength of intramolecular hydrogen bonding. It is known that hydrogen bonding and the conformational change of a molecule affect its specific rotation,[4] such that disturbance of the intramolecular hydrogen bonding in **1** by solvation should affect its specific rotation.



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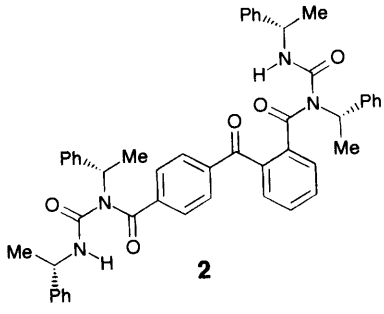

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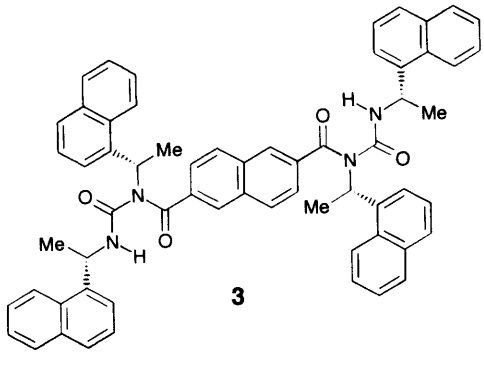

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Acylurea **1** was prepared according to the reported method,[1a] by the reaction of *N*,*N*'-bis[(*S*)-1-phenylethyl]carbodiimide with 2,6-naphthalene dicarboxylic acid. Fig. 1 shows the specific rotation of **1** in various solvents *vs.* solvent polarity parameter $E_T(30)$[5] which derived from the long-wavelength UV–VIS absorption band of the negative solvatochromic pyridinium-*N*-phenoxide betaine dye. The solvents examined can be classified into two categories: those with, and those without a carbonyl functionality. Solvents without a carbonyl functionality give a good linear relationship ($r = 0.96$) with $E_T(30)$. In this group, an increase of $[\alpha]_D$ of **1** was observed to be proportional to an increase in $E_T(30)$. It changed from $-72°$ in benzene to $+14°$ in methanol at $c = 1.00 \pm 0.01$ g, 100 cm^{-3}. However, solvents with a carbonyl functionality showed greater $[\alpha]_D$ than solvents of the first group with similar $E_T(30)$. The results can be interpreted in terms of the strong hydrogen bonding ability of the solvent carbonyl functionality to the amide hydrogen of **1**. In non-polar solvents, an intramolecularly hydrogen bonded conformation would be preferable. In this conformation, the hydrogen bonded ureidocarbonyl six membered ring plane would probably be perpendicular to the naphthalene ring due to steric repulsion. However, in polar solvents, especially those with a carbonyl functionality, intermolecular hydrogen bonding with solvent molecules becomes predominant resulting in a conformational change of **1**. As a result, the $[\alpha]_D$ of **1** is

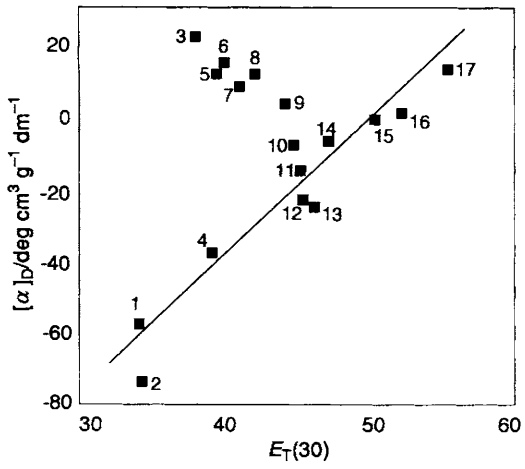

Fig. 1 $[\alpha]_D^{22.0\pm0.5}$ (c 1.00 ± 0.01 g, 100 cm^{-3}) of **1** *vs.* $E_T(30)$: solvent 1, toluene; 2, benzene; 3, ethyl acetate; 4, chloroform; 5, cyclopentanone; 6, hexan-2-one; 7, pentan-2-one; 8, acetone; 9, DMF; 10, methyl acrylate; 11, DMSO; 12, acetonitrile; 13, nitromethane; 14, cyclohexanol; 15, propan-1-ol; 16, ethanol; 17, methanol

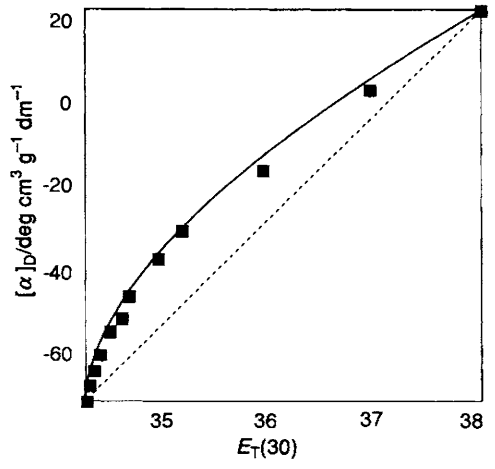

Fig. 2 $[\alpha]_D^{22\pm0.5}$ (c 1.00 ± 0.01 g, 100 cm^{-3}) of **1** in mixed benzene–ethyl acetate solvent system. $E_T(30)$ was deduced as a weighted average of their values.

dependent on the degree of solvation. Fig. 2 shows the $[\alpha]_D$ of **1** in a mixed benzene–ethyl acetate solvent system, with varying ratios. The parameter $E_T(30)$ in this figure was calculated from the ratio of the two solvents. The dotted line represents the estimated $[\alpha]_D$ as a linear combination of the solvent effect of benzene and ethyl acetate. The observed $[\alpha]_D$ was greater than the estimated one. The results indicated that an equilibrium is inclined to the formation of the solvation complex with ethyl acetate. Interestingly, **1** makes molecular complexes with solvents possessing carbonyl functionalities (the second solvent group).

The molecular complexes were prepared as follows. Acylurea **1** was dissolved in various solvents by heating and the resulting solution allowed to stand overnight or for several days. The molecular complexes appeared as crystals or solids and were collected and washed with hexane. The molar ratio of molecular complexes (**1**: solvent) was determined to be 1:2 by elemental analysis and from the integration of their ^{1}H NMR spectra. Solvents which give molecular complexes with **1** and the elemental analyses of the complexes are listed in Table 1. Thermogravimetric analysis was carried out for the complex with ethyl acetate, which also supported this ratio. Weight loss was observed during the temperature range of 69 to 82 °C (around the boiling point of ethyl acetate), which suggested that the binding of the complex was quite weak. Due to this weak binding ability, any induced shifts of the peaks associated with the binding were not observed in the ^{1}H NMR spectra of the complexes in $CDCl_3$. Table 2 shows a list of solvents which did not form isolable crystalline complexes with **1**. It is noteworthy to mention that the solvents possessing carbonyl functionality tend to form molecular complexes with **1**. Cyclohexene oxide also formed a complex with **1**. Single crystal X-ray diffraction analysis of the complex with ethyl acetate showed an interesting feature of hydrogen bonding (Fig. 3). Two molecules of ethyl acetate are bound to **1** *via* intermolecular hydrogen bonding with the amide hydrogen atoms. Intermolecular hydrogen bonding is known as the major binding force of molecular complexes.[6] Arylureas are known to form molecular complexes with carbonyl compounds.[7] The N···O and H···O distances, and the N–H···O angle of the C=O and N–H group are in the typical range for hydrogen bonding[8] (Fig. 3). Owing to this intermolecular hydrogen bonding, the orientation of the N–H and C=O group is not suitable for an intermolecular interaction. The complex has an interesting conformation in which the top face of naphthalene ring is covered with two phenethyl groups.

For comparison, acylureas **2** and **3** were prepared and their inclusion abilities with solvent molecules were examined. In contrast to **1** which possesses a symmetrical chemical structure, unsymmetrical acylurea **2** formed a 1:1 molecular complex with ethyl acetate, propyl acetate and hexan-2-one. Elemental analyses of the 1:1 molecular complexes of **2** with these carbonyl compounds are shown in Table 3. Due to the unsymmetrical arrangement of the ureidocarbonyl groups, only one of them can form intermolecular hydrogen bonds with carbonyl compounds. Naphthyl group substituted acylurea **3** did not show ability to form molecular complexes with these carbonyl compounds. The bulkiness of the ureidocarbonyl group may cause the decrease of the vacant space for the inclusion of carbonyl compounds.

Similar to the solvation controlled conformational regulation in solution, the conformation of acylureas in solid state can also be controlled by the carbonyl compounds.

Experimental

General details

Mps were determined on a Yanako MP-S3 melting point apparatus and are uncorrected. IR spectra were obtained on a JASCO A-202 spectrometer. ^{1}H NMR spectra were recorded on JOEL JNM FX 270 and GSX400 spectrometers. Coupling constants (J) are given in Hz. Mass spectra were obtained on a Hitachi RMU-7M mass spectrometer. Elemental analyses were performed on a Perkin-Elmer 240 analyser. Reaction solutions were concentrated on a rotary evaporator at 15–20 mmHg. Chromatographic separations were accomplished by flash column chromatography on silica gel (Fuji gel BW 200).

2,6-bis{*N*-[(*S*)-1-Phenylethyl]-*N*-[(*S*)-1-phenylethylcarbamoyl]}naphthalene 1

To the stirred acetonitrile solution (100 cm^3) of 2,6-naphthalenedicarboxylic acid (277 mg, 1.281 mmol) was added triethyl amine (285 mg, 2.818 mmol) at room temperature. Acetonitrile solution (20 cm^3) of *N*,*N*′-bis[(*S*)-1-phenylethyl]-carbodiimide (583 mg, 2.329 mmol) was added dropwise to the resulting mixture at 0 °C. After being stirred for one week, the solvent was evaporated and the residue was chromatographed on silica gel with hexane–ethyl acetate (3:2) as eluent to give 614 mg (67%) of **1**. Colourless plates from hexane–ethyl acetate; mp 150–151 °C (hexane–ethyl acetate); $[\alpha]_D^{23.3}$ −37.86 (c 1.01, $CHCl_3$); ν_{max}(KBr)/cm^{-1} 3340 (NH), 1700 (C–O) and 1646 (C–O); δ_H(270 MHz, $CDCl_3$, after ethyl acetate was eliminated in a vacuum oven) 1.12 (6 H, d, J 7.2), 1.82 (6 H, d, J 7.2), 4.72 (2 H, dq, J 7.2 and 7.2), 4.78 (2 H, q, J 7.2), 6.47 (2 H, br d, J 7.2), 6.67–6.87 (4 H, m), 6.94–7.15 (6 H, m), 7.20–7.40 (10 H, m),

Table 1 Elemental analyses of 1 : 2 molecular complexes of **1** with solvent

Solvent	Molecular formula of complex	Calc.			Found		
		C	H	N	C	H	N
$CH_3CO_2C_2H_5$	$C_{54}H_{60}N_4O_8$	72.62	6.77	6.27	72.61	6.74	6.29
$CH_2{=}C(CH_3)CO_2CH_3$	$C_{56}H_{60}N_4O_8$	73.34	6.59	6.10	73.32	6.59	6.13
$CH_2{=}CHCO_2CH_3$	$C_{54}H_{56}N_4O_8$	72.95	6.34	6.30	72.78	6.25	6.24
$(CH_3)_2C{=}O$	$C_{52}H_{56}N_4O_6$	74.97	6.77	6.72	74.74	6.65	6.61
$CH_2{=}C(CH_3)CO_2CH_3$	$C_{56}H_{60}N_4O_8$	73.34	6.59	6.10	73.32	6.59	6.13
$C_2H_5CO_2CH_3$	$C_{54}H_{60}N_4O_8$	72.62	6.77	6.27	72.49	6.74	6.37
$CH_3(C{=}O)C_3H_8$	$C_{56}H_{66}N_4O_6$	75.47	7.46	6.28	75.65	7.28	6.31
$(C_2H_5)_2C{=}O$	$C_{56}H_{64}N_4O_6$	75.64	7.25	6.30	75.74	7.28	6.30
$CH_3CO_2C_2H_5$	$C_{56}H_{60}N_4O_8$	73.34	6.59	6.10	73.42	6.53	6.10
cyclohexene oxide	$C_{58}H_{64}N_4O_6$	76.28	7.06	6.13	76.31	7.04	6.10

Table 2 Compounds which did not give isolable crystalline complexes with **1**

Hydrocarbons	Ketones and aldehyde	Alcohols	Esters and anhydride	Others
hexane	hexan-2-one	methanol	ethyl formate	1,4-dioxane
hexene	cyclopentanone	ethanol	methyl benzoate	triethylamine
benzene	cyclopent-2-en-1-one	butan-2-ol	ethyl benzoate	2-phenylethylamine
toluene	cyclohex-2-en-1-one	benzyl alcohol	ethyl cinnamate	diallylamine
	3-methylbutanal	4-pyridinemethanol	γ-butyrolactone	*N*,*N*-dimethylformamide
		2-methyl-3-buten-2-ol	cumarin	tetrachloromethane
		prop-2-yn-1-ol	adipic acid dimethylester	chloroform
		2-methylbut-3-yn-2-ol	acetic anhydride	acetonitrile

Table 3 Elemental analyses of 1 : 1 molecular complexes of **2** with solvent

Solvent	Molecular formula of complex	Calc.			Found		
		C	H	N	C	H	N
$CH_3CO_2C_2H_5$	$C_{53}H_{54}N_4O_7$	74.10	6.33	6.52	74.01	6.18	6.57
$CH_3CO_2C_3H_7$	$C_{54}H_{56}N_4O_7$	74.28	6.46	6.41	74.66	6.20	6.67
$CH_3(C{=}O)C_4H_9$	$C_{55}H_{58}N_4O_6$	75.83	6.71	6.43	75.51	6.31	6.65

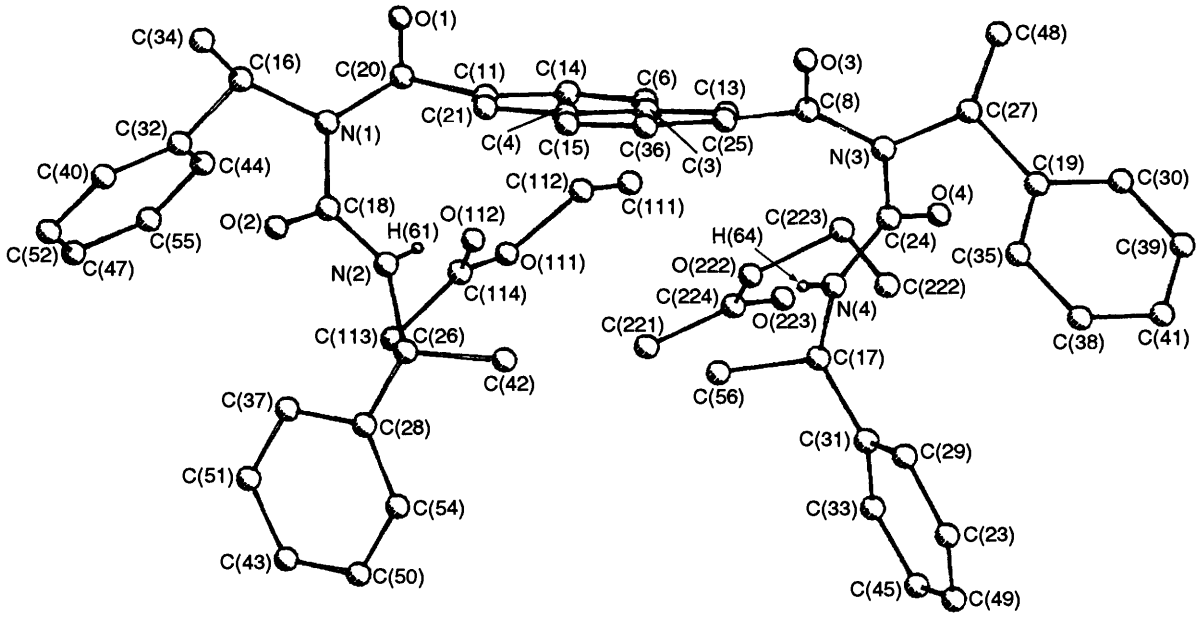

Fig. 3 X-Ray structure of the 1 : 2 complex of acylurea **1** with ethyl acetate. Hydrogen atoms are omitted for clarity except H(61) and H(64). N(2)···O(112) 2.962(8) Å, N(4)···O(223) 2.943(7) Å, H(61)···O(112) 2.02 Å, H(64)···O(223) 2.03 Å, N(2)–H(61)···O(112) 167°, N(4)–H(64)···O(223) 160°.

7.66 (2 H, dd, *J* 1.5 and 8.5), 7.82 (2 H, d, *J* 8.5) and 8.01 (2 H, d, *J* 1.5); MH^+ (FAB), 717.3441. $C_{46}H_{45}N_4O_4$ (MH^+), requires 717.3431.

Acylureas 2 and 3

These were prepared in a similar way. **2** [745 mg (0.966 mmol, 48%) from 540 mg (1.998 mmol) of benzophenone-2,4′-dicarboxylic acid]: colourless crystals; mp 120–121 °C (hexane–ethyl acetate); $[\alpha]_D^{26.2}$ −78.80 (*c* 1.00, $CHCl_3$); ν_{max}(KBr)/cm^{-1} 3324 (NH), 1708 (C=O) and 1650 (C=O); δ_H(270 MHz, $CDCl_3$, after ethyl acetate was eliminated in a vacuum oven) 0.85 (3 H, d, *J* 7.2), 1.28 (3 H, d, *J* 7.2), 1.78 (3 H, d, *J* 7.2), 1.87 (3 H, d, *J* 7.2), 5.81 (1 H, q, *J* 7.2), 6.63 (2 H, dd, *J* 1.9 and 7.7), 6.74 (1 H, d, *J* 7.7), 6.93–6.99 (2 H, m), 7.02–7.12 (3 H, m), 7.20–7.67

(20 H, m) and 7.89 (2 H, d, J 8.2); [MH^+ (FAB), 771.3544. $C_{49}H_{47}N_4O_5$ (MH^+), requires 771.3546. **3** [1584 mg (1.727 mmol, 69%) from 544 mg (2.52 mmol) of 2,6-naphthalenedicarboxylic acid]: colourless crystals; mp 107–108 °C (hexane–ethyl acetate); $[\alpha]_D^{26.1}$ +39.00 (c 1.00, $CHCl_3$); ν_{max}(KBr)/cm^{-1} 3412 (NH), 1704 (C=O) and 1646 (C=O); δ_H(400 MHz, $CDCl_3$) 0.80 (6 H, d, J 7.0), 1.94 (6 H, d, J 7.0), 4.80 (2 H, d, J 8.0), 5.21 (2 H, dq, J 7.0 and 7.0), 6.27 (2 H, d, J 7.2), 6.67 (2 H, q, J 7.0), 6.95 (2 H, t, J 7.8), 7.07 (2 H, t, J 7.8), 7.23 (2 H, d, J 7.2), 7.34–7.65 (10 H, m), 7.70 (4 H, d, J 8.5), 7.66–7.69 (4 H, m), 7.83 (2 H, d, J 8.5), 8.10 (1 H, s) and 8.15 (2 H, d, J 8.4); [MH^+ (FAB), 917.4067. $C_{62}H_{53}N_4O_4$ (MH^+), requires 917.4075].

Preparation of molecular complexes of 1 with solvent molecules

Acylurea **1** (*ca.* 10–20 mg) was dissolved in the solvent by heating and the solution allowed to stand overnight, or a few days, resulting in the slow evaporation of solvent. The crystals or solid which appeared were washed with hexane and dried on a filter paper under air. After brief drying under vacuum without heating, ^1H NMR and elemental analyses were performed.

X-Ray crystal structure determination of complex of 1 with ethyl acetate

A colourless rod crystal of the complex of **1** with ethyl acetate having approximate dimensions of 0.30 × 0.20 × 0.40 mm, mounted on a glass fibre was used for the X-ray study.

Crystal data. $C_{54}H_{60}N_4O_8$, M = 893.09, monoclinic, space group $P2_1$, a = 8.611(2), b = 32.347(2), c = 9.487(10) Å, β = 106.86(1)°, V = 2529(3) $Å^3$, Z = 2, D_c = 1.17 g cm^{-3}, $F(000)$ = 952, μ(Mo-Kα) 0.79 cm^{-1}.

Data collection, structure solution and refinement. The intensity data were collected on an Enraf-Nonius CAD4 diffractometer with graphite monochromated Mo-Kα radiation (λ 0.710 73 Å) using ω–2θ scan technique in the range of $2\theta < 46°$. Out of 3837 total reflections, 2860 reflections having intensities greater than $3\sigma(I)$ were used in the refinements. The data were corrected for Lorentz and polarisation factors but no absorption corrections were made. The structure was solved by direct methods using the SPD/VAX (Enraf-Nonius & B. A. Frenz and Associates). Least squares refinement including anisotropic thermal parameters for non-hydrogen atoms and isotropic refinement of hydrogen atoms located in a difference Fourier synthesis terminated at 0.052 (R_w 0.048).

Atomic coordinates, bond lengths and angles and thermal parameters have been deposited with the Cambridge Crystallographic Data Centre. For details of the CCDC deposition scheme see 'Instructions for Authors (1996)', *J. Chem. Soc., Perkin Trans. 2*, 1996, Issue 1.

References

1 (*a*) K. Kishikawa, M. Yamamoto, S. Kohmoto and K. Yamada, *J. Org. Chem.*, 1989, **54**, 2428; (*b*) K. Kishikawa, K. Horie, M. Yamamoto, S. Kohmoto and K. Yamada, *Chem. Lett.*, 1990, 1009; (*c*) K. Kishikawa, M. Yamamoto, S. Kohmoto and K. Yamada, *Chem. Lett.*, 1990, 1123; (*d*) H. Kasimura, K. Kishikawa, S. Kohmoto, M. Yamamoto and K. Yamada, *Anal. Chim. Acta*, 1990, **239**, 297; (*e*) W. Sankhavasi, M. Yamamoto, S. Kohmoto and K. Yamada, *Bull. Chem. Soc. Jpn.*, 1991, **64**, 1425; (*f*) W. Sankhavasi, S. Kohmoto, M. Yamamoto, T. Nishio, I. Iida and K. Yamada, *Bull. Chem. Soc. Jpn.*, 1992, **65**, 935; (*g*) S. Kohmoto, T. Kreher, Y. Miyaji, M. Yamamoto and K. Yamada, *J. Org. Chem.*, 1992, **57**, 3490; (*h*) K. Kishikawa, A. Furusawa, S. Kohmoto, M. Yamamoto and K. Yamada, *J. Org. Chem.*, 1993, **58**, 7296; (*i*) K. Kishikawa, W. Sankhavasi, K. Yoshizaki, S. Kohmoto, M. Yamamoto and K. Yamada, *J. Chem. Soc., Perkin Trans. 1*, 1994, 1205.

2 S. H. Gellman, G. P. Dado, G.-B. Liang and B. R. Adams, *J. Am. Chem. Soc.*, 1991, **113**, 1164; G.-B. Liang, G. P. Dado and S. H. Gellman, *J. Am. Chem. Soc.*, 1991, **113**, 3994; E. A. Gallo and S. H. Gellman, *J. Am. Chem. Soc.*, 1993, **115**, 9774; G. P. Dado and S. H. Gellman, *J. Am. Chem. Soc.*, 1994, **116**, 1054; R. R. Gardner, G.-B. Liang and S. H. Gellman, *J. Am. Chem. Soc.*, 1995, **117**, 3280.

3 S. Kohmoto, H. Kasimura, T. Nishio, I. Iida, K. Kishikawa, M. Yamamoto and K. Yamada, *J. Chem. Soc., Perkin Trans. 2*, 1994, 1565.

4 J. H. Brewster, *J. Am. Chem. Soc.*, 1959, **81**, 5353; K.-Y. Ko and E. L. Eliel, *J. Org. Chem.*, 1986, **51**, 5353; E. L. Eliel and E. Brunet, *J. Org. Chem.*, 1991, **56**, 1668.

5 K. Dimroth, C. Reichardt, T. Siepmann and F. Bohlmann, *Liebigs Ann. Chem.*, 1963, **661**, 1; C. Reichardt, *Liebigs Ann. Chem.*, 1971, **752**, 64; C. Reichardt, *Solvents and Solvent Effects in Organic Chemistry*, VCH, Weinheim, 1988, p. 365.

6 M. C. Etter, *Acc. Chem. Res.* 1990, **23**, 120; G. A. Jeffrey and W. Saenger, *Hydrogen Bonding in Biological Structures*, Springer, Berlin, 1991; Y.-L. Chang, M.-A. West, F. W. Foller and J. W. Lauher, *J. Am. Chem. Soc.*, 1993, **115**, 5991.

7 M. C. Etter, Z. Urbanczyk-Lipkowska, M. Zia-Ebrahimi and T. W. Panuto, *J. Am. Chem. Soc.*, 1990, **112**, 8415; M. C. Etter and S. M. Reutzel, *J. Am. Chem. Soc.*, 1991, **113**, 2586; B. C. Hamann, N. R. Branda and J. Rebek Jr., *Tetrahedron Lett.*, 1993, **43**, 6837; F. Erkang, S. A. Van Arman, S. Kincaid and A. D. Hamilton, *J. Am. Chem. Soc.*, 1993, **115**, 369; T. R. Kelly and M. H. Kim, *J. Am. Chem. Soc.*, 1994, **116**, 7072.

8 G. A. Jeffery, H. Maluszynska and H. Mitra, *Int. J. Biol. Macromol.*, 1985, **7**, 336; G. A. Jeffrey and H. Maluszynska, *J. Molec. Struct.*, 1986, **147**, 127.

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