ORGANIC LETTERS

2011
Vol. 13, No. 19
5160–5163

Alkoxyamine-derived Formamidines: Configurational Control and Molecular Folding

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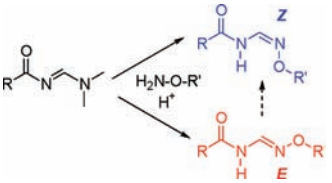
Received July 27, 2011

ABSTRACT



***N,N′*-Disubstituted formamidines, and amidines in general, have very rich configurational, conformational, and tautomeric diversities. As part of an effort to incorporate alkoxyamine-derived formamidine units into foldamers, the first evidence for the isolation of the up-to-now unknown E isomer, the conditions for its exclusive formation, its stability and self-assembly properties, and its configurational isomerization to its much more common Z counterpart are reported. Considering the distinctly different H-bonding patterns displayed by both E and Z isomers, such configurational control may find applications in self-assembly, molecular recognition, and biomimetic systems.**

Amidines have been important units in coordination chemistry,[1] catalysis,[1d,f,2] biological recognition,[3] separation[4] and supramolecular self-assemby.[5] In all these applications, shape and H-bonding patterns are critical features determining the resulting properties. If *N*,*N*′-disubstituted formamidines derived from aryl and alkylamines have been well-characterized as E (trans) isomers (with one exception[6a]), formamidines derived from alkoxyamines[6b] (or formamidoximes) have received much less attention. The Cambridge Crystallographic Database reports only Z (cis) isomers rationalized by a stabilizing 5-membered H-bonded ring which compensates for the cost of maintaining a cis (Z) C=N double bond. With its controlled curved structure, this motif may be valuable in the preorganization of folded structures (foldamers).[7] In our recent synthetic work incorporating the Z-formamidine configurational codon with the well-known pyridyl-carboxamide conformational codon,[8] we observed the anticipated ZZ isomer of **1Bn$_2$** (Figure 1a) as the only product when trifluoroacetic acid was used in the reaction, but the unexpected ZE isomer (~25%) was observed with acetic acid in the reaction medium. The configuration of the unusual ZE isomer was confirmed in solution (see the Supporting Information) and in the crystal (Figure 1a).[9]

(1) (a) Barker, J.; Kilner, M. *Coord. Chem. Rev.* **1994**, *133*, 219–300. (b) Cotton, F. A.; Lin, C.; Murillo, C. A. *Acc. Chem. Res.* **2001**, *34*, 759–771. (c) Chisholm, M. H.; Macintosh, A. M. *Chem. Rev.* **2005**, *105*, 2949–2976. (d) Coles, M. P. *Dalton Trans.* **2006**, *8*, 985–1001. (e) Díaz, D. D.; Gupta, S. S.; Kuzelka, J.; Cymborowski, M.; Sabat, M.; Finn, M. G. *Eur. J. Inorg. Chem.* **2006**, 4489–4493. (f) Junk, P. C.; Cole, M. L. *Chem. Commun.* **2007**, *16*, 1579–1590. (g) Edelmann, F. T. *Adv. Organomet. Chem.* **2008**, *57*, 183–352. (h) Arquier, D.; Vendier, L.; Miqueu, K.; Sotiropoulos, J.-M.; Bastin, S.; Igau, A. *Organometallics* **2009**, *28*, 4945–4957. (i) Edelmann, F. T. *Chem. Soc. Rev.* **2009**, *38*, 2253–2268.

(2) Hirano, K.; Urban, S.; Wang, C.; Glorius, F. *Org. Lett.* **2009**, *11*, 1019–1022.

(3) (a) Bailly, C.; Donkor, I. O.; Gentle, D.; Thornalley, M.; Waring, M. J. *Mol. Pharmacol.* **1994**, *46*, 313–322. (b) Jenkins, T. C.; Lane, A. N. *Biochim. Biophys. Acta, Gene Struct. Expression* **1997**, *1350*, 189–204. (c) Lane, A. N.; Jenkins, T. C.; Frenkiel, T. A. *Biochim. Biophys. Acta, Gene Struct. Expression* **1997**, *1350*, 205–220. (d) Wei, L.; Carrasco, C.; Kumar, A.; Stephens, C. E.; Bailly, C.; Boykin, D. W.; Wilson, W. D. *Biochemistry* **2001**, *40*, 2511–2521. (e) Bielawski, K.; Wolczynski, S.; Bielawska, A. *Biol. Pharm. Bull.* **2001**, *24*, 704–706. (f) Nguyen, B.; Lee, M. P. H.; Hamelberg, D.; Joubert, A.; Bailly, C.; Brun, R.; Neidle, S.; Wilson, W. D. *J. Am. Chem. Soc.* **2002**, *124*, 13680–13681. (g) Rahimian, M.; Kumar, A.; Say, M.; Bakunov, S. A.; Boykin, D. W.; Tidwell, R. R.; Wilson, W. D. *Biochemistry* **2009**, *48*, 1573–1583. (h) Mathews, T. P.; Kennedy, A. J.; Kharel, Y.; Kennedy, P. C.; Nicoara, O.; Sunkara, M.; Morris, A. J.; Wamhoff, B. R.; Lynch, K. R.; MacDonald, T. L. *J. Med. Chem.* **2010**, *53*, 2766–2778. (i) Marzano, C.; Mazzega Sbovata, S.; Gandin, V.; Colavito, D.; Del Giudice, E.; Michelin, R. A.; Venzo, A.; Seraglia, R.; Benetollo, F.; Schiavon, M.; Bertani, R. *J. Med. Chem.* **2010**, *53*, 6210–6227. (j) Athri, P.; Wenzler, T.; Tidwell, R.; Bakunova, S. M.; Wilson, W. D. *Eur. J. Med. Chem.* **2010**, *45*, 6147–6151. (k) Jarak, I.; Marjanovic, M.; Piantanida, I.; Kralj, M.; Karminski-Zamola, G. *Eur. J. Med. Chem.* **2011**, *46*, 2807–2815.

10.1021/ol202032k
Published on Web 08/26/2011

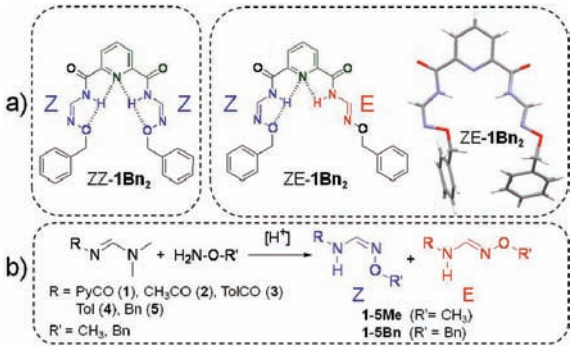


Figure 1. (a) Chemical structure of the ZZ isomer, crystal structure of the ZE species; (b) reaction studied.

To understand the conditions of the formation of the never-before observed E configurational isomer, as well as to explore its properties, a model reaction was studied (Figure 1b). The present manuscript reports the systematic study of this reaction, and the first isolation of E isomers of formamidoximes and their properties.

E isomer: First Evidence and Properties. As indicated above, reactions of *N*,*N*-dimethylformamidine electrophiles such as **1** (see Figure 1 for numbering) with alkoxyamine nucleophiles promoted by certain acids led to mixtures.[9] In those, two sets of ^{1}H NMR signals in $CDCl_3$ pointed to two different isomeric structures (Figure 2): on the one hand, the expected Z isomer is characterized by a down-shielded H-bonded NH and an up-shielded formamidine Hf. On the other hand, another species is characterized by a down-shielded formamidine Hf (~8.5 ppm) and an up-shielded NH proton (~7.5 ppm), which suggests that Hf experiences an electron-rich environment while NH is not involved in any strong H-bond. These observations are consistent with the co-existence of the E isomer which, up to now, has never been clearly identified (one report[10a] suggests that this species may exist based on minute amounts of a side product in a 1D ^{1}H NMR spectrum). To test this hypothesis, 2D NOESY experiments were conducted on a 0.9:1.0 mixture of Z/suspected E species (**2Bn**) and confirm the spacial proximity of the OCH_2 and Hf protons in the new species (Figure 2), while no such effect is present in the Z isomer.[11]

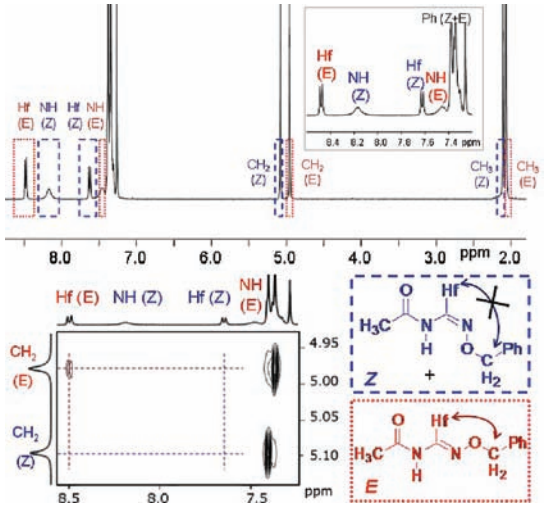


Figure 2. ^{1}H NMR of 1.0:0.9 mixture of (*E*)-**2Bn** and (*Z*)-**2Bn**; 1D (top) and 2D NOESY (bottom) spectra ($CDCl_3$*, 500 MHz).

The pure E isomers of alkoxylamine-derived formamidines (**1Me**, **2Me**, **2Bn**, **3Bn**) were then isolated after reaction under specific conditions leading to high proportions or exclusive formation of the E species (as described below). Crystallization of such species and X-ray diffraction confirmed their stereochemical identity (E), as highlighted below with **2Bn** (Figure 3).[12]

In the solid state, bond lengths in the E and the Z isomers are very similar (see the Supporting Information), indicating that, despite the absence of an intramolecular H-bond in the

(4) (a) Endo, T.; Nagai, D.; Monma, T.; Yamaguchi, H.; Ochiai, B. *Macromolecules* **2004**, *37*, 2007–2009. (b) Perez, E. R.; Santos, R. H. A.; Gambardella, M. T. P.; De Macedo, L. G. M.; Rodrigues-Filho, U. P.; Launay, J.-C.; Douglas, D. W. *J. Org. Chem.* **2004**, *69*, 8005–8011. (c) Liu, Y.; Jessop, P. G.; Cunningham, M.; Eckert, C. A.; Liotta, C. L. *Science* **2006**, *313*, 958–960. (d) Yamada, T.; Lukac, P. J.; George, M.; Weiss, R. G. *Chem. Mater.* **2007**, *19*, 967–969. (e) Yamada, T.; Lukac, P. J.; Yu, T.; Weiss, R. G. *Chem. Mater.* **2007**, *19*, 4761–4768. (f) Nagai, D.; Endo, T. *J. Polym. Sci., Part A Polym. Chem.* **2009**, *47*, 653–657. (g) Desset, S. L.; Hamilton, D. J. *Angew. Chem., Int. Ed.* **2009**, *48*, 1472–1474.

(5) (a) Hosseini, M. W.; Ruppert, R.; Schaeffer, P.; De Cian, A.; Kyritsakas, N.; Fischer, J. *J. Chem. Soc., Chem. Commun.* **1994**, 2135–2136. (b) Auer, F.; Nelles, G.; Sellergen, B. *Chem.–Eur. J.* **2004**, *10*, 3232–3240. (c) Ikeda, M.; Tanaka, Y.; Hasegawa, T.; Furusho, Y.; Yashima, E. *J. Am. Chem. Soc.* **2006**, *128*, 6806–6807. (d) Hasegawa, T.; Morino, K.; Tanaka, Y.; Katagiri, H.; Furusho, Y.; Yashima, E. *Macromolecules* **2006**, *39*, 482–488. (e) Katagiri, H.; Tanaka, Y.; Furusho, Y.; Yashima, E. *Angew. Chem., Int. Ed.* **2007**, *46*, 2435–2439. (f) Maeda, T.; Furusho, Y.; Sakurai, S.-I.; Kumaki, J.; Okoshi, K.; Yashima, E. *J. Am. Chem. Soc.* **2008**, *130*, 7938–7945. (g) Yashima, E.; Maeda, K.; Furusho, Y. *Acc. Chem. Res.* **2008**, *41*, 1166–1180. (h) Iida, H.; Shimoyama, M.; Furusho, Y.; Yashima, E. *J. Org. Chem.* **2010**, *75*, 417–423. (i) Ito, H.; Ikeda, M.; Hasegawa, T.; Furusho, Y.; Yashima, E. *J. Am. Chem. Soc.* **2011**, *133*, 3419–3432.

(6) (a) Xing, L.; Wiegert, C.; Petitjean, A. *J. Org. Chem.* **2009**, *74*, 9513–9516. (b) Capela, M. dF.; Mosey, N. J.; Xing, L.; Wang, R.; Petitjean, A. *Chem.—Eur. J.* **2011**, *17*, 4598–4612. (c) Petitjean, A.; Xing, L.; Wang, R. *CrystEngComm.* **2010**, *12*, 1397–1400.

(7) (a) Gellman, S. H. *Acc. Chem. Res.* **1998**, *31*, 173–180. (b) Hill, D. J.; Mio, M. J.; Prince, R. B.; Hughes, T. S.; Moore, J. S. *Chem. Rev.* **2001**, *101*, 3893–4011. (c) *Foldamers: Structure, Properties and Applications*; Hecht, S., Huc, I., Ed.; Wiley-VCH: Weinheim, 2007. (d) Gong, B. *Acc. Chem. Res.* **2008**, *41*, 1376–1386. (e) Saraogi, I.; Hamilton, A. D. *Chem. Soc. Rev.* **2009**, *38*, 1726–1743. (f) Juwarker, H.; Suk, J; Jeong, K.-S. *Chem. Soc. Rev.* **2009**, *38*, 3316–3325. (g) Tew, G. N.; Scott, R. W.; Klein, M. L.; De Grado, W. F. *Acc. Chem. Res.* **2010**, *43*, 30–39.

(8) (a) Hamuro, Y.; Geib, S. J.; Hamilton, A. D. *Angew. Chem., Int. Ed.* **1994**, *33*, 446–448. (b) Hunter, C. A.; Low, C. M. R.; Packer, M. J.; Spey, S. E.; Vinter, J. G.; Vysotsky, M. O.; Zonta, C. *Angew. Chem., Int. Ed.* **2001**, *40*, 2678–2682. (c) Huc, I. *Eur. J. Org. Chem.* **2004**, 17–29. (d) Ballester, P.; Costa, A.; Deyà, P. M.; Frontera, A.; Gomila, R. M; Oliva, A. I.; Sanders, J. K. M.; Hunter, C. A. *J. Org. Chem.* **2005**, *70*, 6616–6622.

(9) Zhao, W. MSc thesis, Queen's University, Canada, 2011.

(10) (a) Hayakawa, K.; Eguchi, Y.; Nakayama, A. *J. Pesticide Sci.* **1993**, *18*, 191–196. (b) Hayakawa, K.; Nakayama, A.; Nishikawa, H.; Nakata, A.; Sano, S.; Yokota, C. *J. Pesticide Sci.* **1991**, *16*, 481–490. (c) Hayakawa, K.; Nakayama, A.; Nishikawa, H.; Nakata, A.; Sano, S.; Yokota, C. *J. Pesticide Sci.* **1992**, *17*, 17–25.

(11) The ^{1}H NMR signature of the Z isomer is known based on reactions leading to the exclusive Z species, which were characterized by 2D NMR as well as X-ray crystallography (Supporting Information).

(12) for X-ray structure of (*E*)-**1Me**, see Supporting Information.

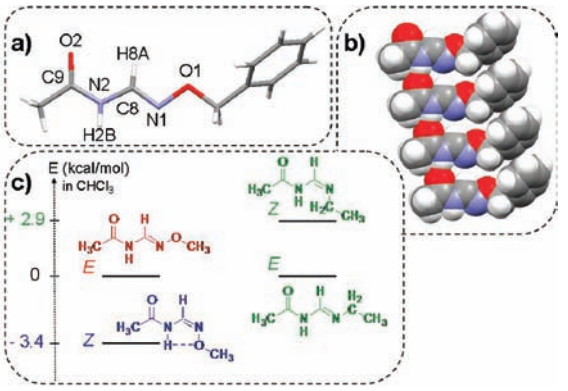


Figure 3. (a) Molecular structure of E-**2Bn**; (b) solid-state self-assembly; selected bond distances (Å): C9−O2 1.225(2), C9−N2 1.358(2), N2−C8 1.380(2), C8−N1 1.281(2); (c) comparison of calculated relative energies of E and Z isomers of *N*-acylformamidoxime and *N*-acylformamidine in $CHCl_3$ (MP2/6-311++G(d,p)).

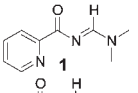
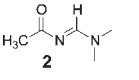
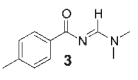
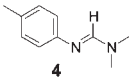
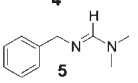
E form, the C=N double-bond is still localized between the formamidine carbon atom (C8) and the nitrogen atom of what belonged to the alkoxyamine (N1). The molecular structure correlates well with the ^{1}H NMR chemical shifts in $CDCl_3$, with H8A in an electron-rich environment (O2, O1), and (N)H2B exposed to the surrounding and available to participate in intermolecular interactions.

Interestingly, the solid-state self-assemby is very different from most *N*,*N*′-disubstituted formamidines (Figure 3b): those commonly self-assemble into dimers (through (N2)-H2B····N1 mutual interactions).[6c] Importantly, in the present case, the carbonyl oxygen is the major interaction partner to the formamidine NH (intermolecular O2····N2: 2.780 Å), with a very weak interaction between the slightly acidic formamidine H8A proton and basic N1 nitrogen (C8····N1 3.928 Å), in a strikingly similar structure to that of *N*,*N*′-disubstituted ureas.[13,14] In solution, dilution experiments support the fact that hydrogen-bonded directed self-assembly also takes place in $CDCl_3$, and mostly involves the acetyl carbonyl group, NH and formamidine protons (see the Supporting Information for ^{1}H NMR experimental details).[14]

Calculations in the gas phase and in $CHCl_3$ also confirm the reversed relative stabilities of the Z and E isomers of *N*-acylformamidoximes and *N*-acylformamidines (Figure 3c, the Supporting Information). Interestingly, the Z isomer is as much stabilize in *N*-acylformamidoxime (through intramolecular H-bonding) as it is destabilized in the carbon-based analog (Figure 3c, left; the Supporting Information). Therefore, the E isomer can only be isolated when trapped under kinetic conditions, through a careful control of the relative kinetics of the condensation and isomerization processes, as presented below.

Conditions for Isolation of the E Isomer and E to Z Conversion. The reactive *N*,*N*-dimethylformamidine electrophile is known to be sensitized toward nucleophilic attack (e.g., by alkoxyamines) by protonation. However, the strength and amount of the introduced acid turn out to be critical to the stereochemical outcome of the reaction (Table 1). For instance, when *N*,*N*′-dimethyl-*N*-acetylformamidine **2** was condensed in the presence of 2 equivalents of trifluoroacetic acid (TFA, entry 1.2a), the Z isomer was exclusively formed within the first 10 min (see the Supporting Information). Using less acidic conditions (*e.g.*, only 1 equivalent of TFA, entry 1.2c, or of a weaker acid such as AcOH, entry 1.2d), the E isomer was formed nearly exclusively. Similar behavior was observed with an arylamide-derived electrophile (entries 1.3a and 1.3b).

Table 1. Effect of the Strength and Amount of Acid on the E/Z Proportions[a]

electrophile	amine	acid	% E	% Z	
 1	$BnONH_2$	TFA [2]	0	100	1.1a
	$BnONH_2$	AcOH [1]	58	40	1.1b
	$MeONH_2$	Et_3NHCl [1]	32[b]	40[b]	1.1c
 2	$BnONH_2$	TFA [2]	0	100	1.2a
	$MeONH_2$	HCl [1]	57	43	1.2b
	$BnONH_2$	TFA [1]	93	5	1.2c
	$BnONH_2$	AcOH [1]	97	3	1.2d
 3	$BnONH_2$	TFA [2]	5	95	1.3a
	$BnONH_2$	AcOH [1]	80[b]	5[b]	1.3b
 4	$BnONH_2$	AcOH [1]	0	70[b]	1.4
 5	$BnONH_2$	AcOH [1]	0[b]	60[b]	1.5a
	$MeONH_2$	Et_3NHCl [1]	0[b]	0[b]	1.5b

[a] As Determined by ^{1}H NMR in $CDCl_3$* after 30 min at 298 K. A graphical representation of the kinetics for each set of conditions is given in Supporting Information. In brackets, number of equivalents. [b] Complement to 100% is composed of starting material.

These results suggest that the first species that is formed in the acid-promoted condensation is the E isomer and that when an electron-withdrawing group such as a carbonyl function is present,[15a] the condensation reaction may be rendered fast enough and isomerization to the Z isomer slow enough for the E intermediate to be isolated. In order to achieve those conditions, a sufficient amount of acid to promote just the condensation step allows the analytical and preparative isolation of the never-seen-before E isomer.

To better understand the role of acids in the subsequent isomerization step, cascade reactions were investigated (Figure 4). Activation of the condensation step by 1 equivalent of TFA leads to immediate formation of the exclusive E isomer, with less than 5% of the Z isomer. The dimethylammonium trifluoroacetate byproduct is not acidic enough to efficiently catalyze the E to Z isomerization. However, addition of a second equivalent of TFA accelerates isomerization,

(13) (a) Zhao, X.; Chang, Y.-L.; Fowler, F. W.; Lauher, J. W. *J. Am. Chem. Soc.* **1990**, *112*, 6627–6634. (b) Chang, Y.-L.; West, M.-A.; Fowler, F. W.; Lauher, J. W. *J. Am. Chem. Soc.* **1993**, *115*, 5991–6000. (c) Hollingsworth, M. D.; Brown, M. E.; Santarsiero, B. D.; Huffman, J. C.; Goss, C. R. *Chem. Mater.* **1994**, *6*, 1227–1244. (d) Coe, S.; Kane, J. J.; Nguyen, T. L.; Toledo, L. M.; Wininger, E.; Fowler, F. W.; Lauher, J. W. *J. Am. Chem. Soc.* **1997**, *119*, 86–93. (e) Nguyen, T. L.; Scott, A.; Dinkelmeyer, B.; Fowler, F. W.; Lauher, J. W. *New J. Chem.* **1998**, *22*, 129–135.

(14) Attempts to compare to the self-assembly of the little studied N-acylformamidines were made unsuccessful by their difficult synthesis and instability. See (a) Bechstein, U.; Liebscher, J. *Journal f. prakt. Chemie* **1989**, *1*, 153–156. Supporting Information of: (b) Díaz, D. D.; Finn, M. G. *Chem. Commun.* **2004**, 2514–2516.

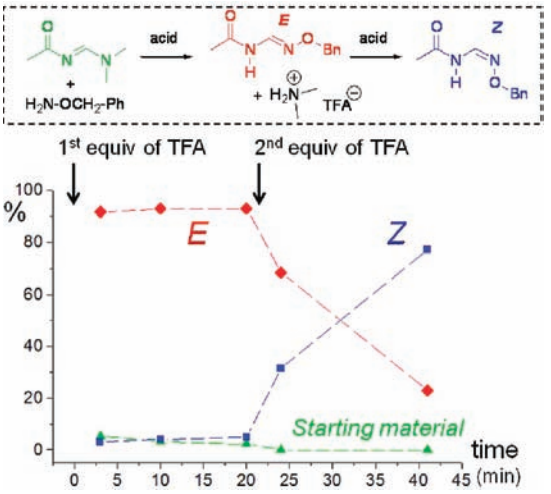


Figure 4. Kinetic study of the condensation and isomerization reactions (^{1}H NMR, $CDCl_3$*, 500 MHz).

leading to full conversion to the Z isomer (see the Supporting Information for NMR details on E/Z isomerization).

Looking back at the reaction of the pyridine-derived formamidine (**1**), no conditions were found to exclude the Z isomer all together. At best, 58:40 mixtures of the E and Z isomers were isolated (AcOH 1 equiv, entry 1.1b). Comparing with the alkyl (**2**)- or aryl (**3**)-carbonyl derivatives, one may suggest that the more acidic pyridylamide proton accelerates the isomerization step[15b,c] through intramolecular H-transfer,[6a] a process which cannot be completely prevented.

In an effort to understand the role of the carbonyl group in influencing the relative kinetics of condensation and isomerization, similar studies were carried out with *N*-aryl (**4**)- and *N*-alkyl (**5**)-*N*′,*N*′-dimethylformamidines. In these cases, the condensation is slower, allowing for isomerization to take place while the chemical reaction is still occurring (see the Supporting Information). As a result, under all conditions tested, the starting material was converted to the Z isomer only (entries 1.4, 1.5a) without detectable traces of the E isomer.

In conclusion, the present study reports, for the first time, details on the structural, self-assembly, calculated relative stability and preparation of the E isomer derived from *N*-carbonyl-*N*′-substituted formamidoxime. The carbonyl group plays a critical role in accelerating the condensation step. Controlling the acidic conditions of the reaction allows to prevent fast isomerization, and to isolate the pure E isomer. Interestingly, formamidoximes display fungicidal properties which have been tentatively associated with the E isomer based on an analogy with *N*-phenylcarbamate pesticides.[10] However, the E isomer had never been isolated to test this hypothesis prior to our work. The methodology described herein allows easy access to pure E isomers and should facilitate the study of their biological properties. As a matter of fact, their mode of self-assembly evidenced in the solid-state (Figure 3) and in solution (see the Supporting Information) bodes well for possible interactions with natural systems through a combination of H-bonds. In addition to the effect of the static E/Z stereoisomerism on biological interactions, the present work suggests the potential use of the dynamic pH-induced E to Z isomerization to tune the biological properties of formamidoximes, and as a release mechanism for possible applications to the pH-induced drug delivery.[16] Finally, formamidoximes of both the E and Z forms may be interesting mimics of the amide motif in Biomimetic Chemistry.[7f,17]

Acknowledgment. We thank Queen's University, the National Science and Engineering Research Council of Canada, the Canadian Foundation for Innovation, and the Ontario Ministry of Research and Innovation (Early Researcher Award) for financial support.

Supporting Information Available. Synthetic procedures and characterizations of formamidoximes and precursors. ^{1}H NMR and UV−vis kinetic studies. ^{1}H NMR dilution experiments for (*E*)-**2Bn** and (*Z*)-**2Bn** ($CDCl_3$). ^{1}H NMR details for NOESY and E to Z conversion. Theoretical calculations for simple E and Z isomers. Crystallographic details for (*Z*,*E*)-**1Bn$_2$** (CCDC 834517), (*E*)-**2Bn** (CCDC 828088), (*E*)-**1Me** (CCDC 828089) and (*Z*)-**1Bn** (CCDC 828090). This material is available free of charge via the Internet at http://pubs.acs.org.

(15) (a) Díaz, D. D.; Finn, M. G. *Chem.—Eur. J.* **2004**, *10*, 303–309. (b) Hegarthy, A. F.; Chandler, A. *J. Chem. Soc. Chem. Commun.* **1980**, 131–132. (c) Hegarthy, A. F.; Cunningham, I. D. *J. Chem. Soc., Perkin Trans. II.* **1986**, 537–541.

(16) (a) Leblond, J.; Gao, H.; Petitjean, A.; Leroux, J.-C. *J. Am. Chem. Soc.* **2010**, *132*, 8545–8555. (b) Lee, E. S.; Gao, Z.; Bae, Y. H. *J. Controlled Release* **2008**, *132*, 164–170. (c) Harguindey, S.; Arranz, J. L.; Wahl, M. L.; Orive, G.; Reshkin, S. J. *Anticancer Res.* **2009**, *29*, 2127–2136. (d) Ulbrich, K.; Šubr, V. *Adv. Drug Delivery Rev.* **2004**, *56*, 1023–1050. (e) Jain, R.; Standley, S. M.; Frechet, J. M. *Macromolecules* **2007**, *40*, 452–457. (g) Tong, R.; Cheng, J. *Polym. Rev.* **2007**, *47*, 345–381.

(17) (a) Davis, J. M.; Tsou, L. K.; Hamilton, A. D. *Chem. Soc. Rev.* **2007**, *36*, 326–334. (b) Li, X.; Wu, Y.-D.; Yang, D. *Acc. Chem. Res.* **2008**, *41*, 1428–1438. (c) Stevenson, C. L. *Curr. Pharm. Biotechnol.* **2009**, *10*, 122–137. (d) Patel, T.; Sheth, A.; Doshi, N.; Dave, J. B.; Patel, C. N. *J. Chem. Pharm. Res.* **2010**, *2*, 197–208. (e) Boyden, T.; Niosi, M.; Vaz, A. *RSC Drug Discovery Ser.* **2010**, *1*, 370–389. (f) Cummings, C. G.; Hamilton, A. D. *Curr. Opin. Chem. Biol.* **2010**, *14*, 341–346. (g) Liskamp, R. M. J.; Rijkers, D. T. S.; Kruijtzer, J. A. W.; Kemmink, J. *ChemBioChem* **2011**, *12*, 1626–1653. (h) Inokuchi, E.; Yamada, A.; Hozumi, K.; Tomita, K.; Oishi, S.; Ohno, H.; Nomizu, M.; Fujii, N. *Org. Biomol. Chem.* **2011**, *9*, 3421–3427.