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Dong Hoon Lee[a]; Hae-Jo Kim[b]; Jong-In Hong[a]
[a] Department of Chemistry, College of Natural Sciences, Seoul National University, Seoul, South Korea
[b] Department of Chemistry, Kyonggi University, Suwon, South Korea

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Carbohydrate Recognition by C_3-Symmetric Polypyridine Hosts

DONG HOON LEE[a], HAE-JO KIM[b,*] and JONG-IN HONG[a,*]

[a]*Department of Chemistry, College of Natural Sciences, Seoul National University, Seoul 151-747, South Korea;* [b]*Department of Chemistry, Kyonggi University, Suwon 443-760, South Korea*

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Conformationally preorganized C_3-symmetric polypyridine hosts were designed to recognize monosaccharides in organic solvent through complementary intermolecular hydrogen bonds. Hydrogen bonding acceptor sites are introduced to the host in a systematic way to evaluate the effect of a H-bond number for carbohydrate recognition. The degree of affinity was adjustable by the number of hydrogen bonding acceptors in the peripheral pyridine unit. The anomeric and diastereomeric selectivities were observed to be moderate to high. Molecular modeling studies and ^{1}H NMR titration data reveal that these conformationally well-defined receptors bind to the carbohydrates through multiple intermolecular hydrogen bonds.

Keywords: Carbohydrate; Hydrogen bonding; Host; Molecular recognition

INTRODUCTION

The molecular recognition of saccharides is an attractive research topic in the field of supramolecular chemistry [1], due to the various cellular recognition processes of oligosaccharides on cell surfaces [2,3] and partly due to the 3D complexity even in monosaccharide structures [4,5]. X-ray crystallographic structures of sugar–protein complexes reveal that multiply charged hydrogen bonds as well as neutral hydrogen bonds are involved in the hydrophobic protein cavity for efficient sugar–protein interactions [6–8]. However, the hydrophilic nature of simple saccharides allows even a conformationally well defined tricyclic cage-like receptor to form very weak hydrogen-bonded complexes in water [9]. They can be strongly bound only under solvophobic conditions, i.e. in organic media [10–16]. Recently, acyclic polypyrimidine and naphthyridine amide receptors were reported by Mazik *et al.*, which show a higher affinity to β-D-glucopyranoside with up to $K_a = 10^4\,M^{-1}$ owing to cooperative interactions of hydrogen bonding donors from amide NH's, H-bonding acceptors from pyrimidine/naphthyridine N's, and aromatic π surfaces of the central phenyl unit in the hosts [17,18]. We have developed C_3-symmetric sugar receptors with hydrogen-bonding acceptors [19] and donors [20]. Herein we report how the monosaccharide affinity is affected by the number of hydrogen bonding acceptors of triethylbenzene-based polypyridine receptors.

RESULTS AND DISCUSSION

Towards this end, complementary hydrogen bonding sites for sugars can be introduced in a preorganized way to the 2, 4, and 6 positions of 1,3,5-triethylbenzene. The designed hosts (**1**, **2**, and **4**) have pyridine amide or *N*-pyridylamide units as hydrogen bonding donors and acceptors. The lowest energy conformations of the hosts (**1**–**4**) reveal that all the hydrogen bonding groups at the 1, 3, and 5 positions of the central benzene are pointing to the same face of the aryl ring, while the rest of the ethyl groups is directed in the opposite direction for the avoidance of nonbonded interactions of the adjacent methylene hydrogens [21–23]. All the amide NH's in the hosts are expected to be hydrogen-bonded with hydroxyl oxygens in octyl-D-pyranosides.

*Corresponding authors . E-mail: jihong@snu.ac.kr; haejkim@kyonggi.ac.kr

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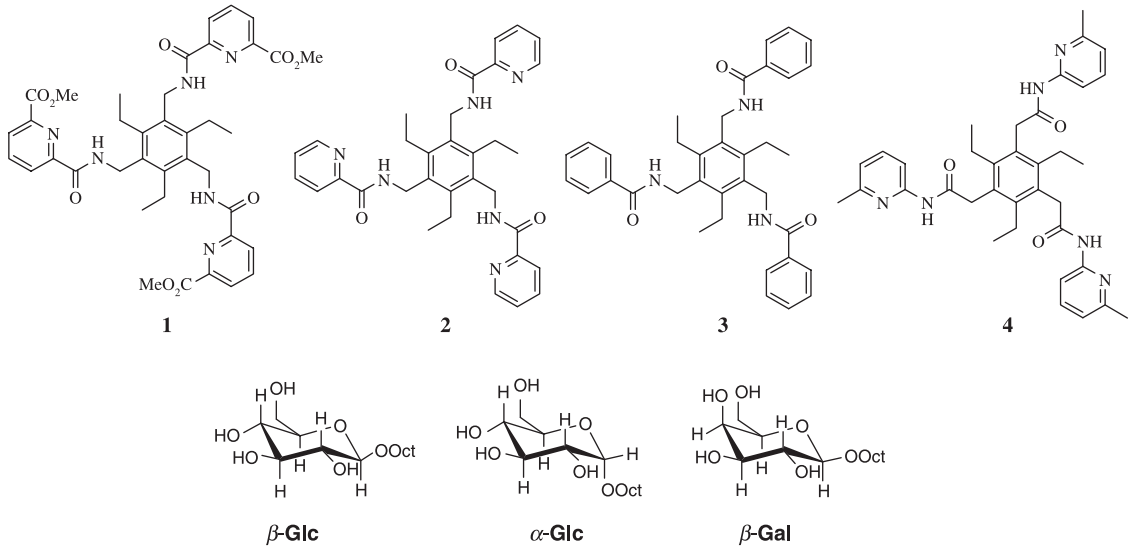


FIGURE 1 Structures of hosts and guests.

Compared to the reference host (**3**) [20], **1** possesses additional six hydrogen bonding acceptors, three from pyridine N's and three from ester O's, while **2** has additional three hydrogen bonding acceptors from pyridine N's. **4** is similar to **2** except in that the position of the amide group is switched (Fig. 1).

The synthesis of C_3-symmetric polypyridine hosts (**1**, **2**, and **4**) is described in the Experimental section. The interaction between host **1** and 1-octyl-*β*-D-glucopyranoside (*β*-**Glc**), 1-octyl-*α*-D-glucopyranoside (*α*-**Glc**) and 1-octyl-D-galactopyranoside (*β*-**Gal**) was investigated by ^{1}H NMR spectroscopy. The complexation of hosts and saccharides was evidenced by a significant downfield shift of the amide NH proton of each host, which reflects the formation of an intermolecular hydrogen-bonded complex between host and guest. This NH peak shift was the average value of the free host and the complex in the limit of fast chemical exchange. The chemical shifts were monitored after stepwise addition of each guest in deuterated chloroform at room temperature by ^{1}H NMR spectroscopy, and were analyzed by a nonlinear regression method [24]. The calculated association constants (K_a) are summarized in Table I. The stoichiometry between **1** and guests was evaluated to be 1:1 by the continuous variation method for the binding experiments [25].

Host **1** shows a moderate *β*-anomer selectivity to a degree of 3.5 times ($\Delta\Delta G = 0.8$ kcal/mol) (entry 1 vs. 2) as well as a high diastereoselectivity (C-4 epimeric selectivity) to a degree of 8.1 times ($\Delta\Delta G = 1.3$ kcal/mol) (entry 1 vs. 3). This indicates that the stereochemistry at the position of C-4 in the pyranosides ring is more crucial than that of C-1 for the effective host–guest complexation. The degree of the observed complexation-induced chemical shift (CIS) $\Delta\delta_{max}$ values is consistent with the calculated K_a's; 0.84 ppm, 0.29 ppm and 0.12 ppm for *β*-**Glc**, *α*-**Glc** and *β*-**Gal**, respectively (Fig. 2).

Compared to benzamide **3** [20], pyridine amide **1** leads to larger binding constants for all 1-octyl-D-pyranosides and a much higher affinity toward *β*-**Gal**: 4.2 fold ($-\Delta\Delta G = 0.9$ kcal/mol), 3.4 fold ($-\Delta\Delta G = 0.8$ kcal/mol) and 23 fold ($-\Delta\Delta G = 1.8$ kcal/mol) increases for *β*-**Glc**, α-**Glc** and *β*-**Gal**, respectively (entries 1–3 vs. 7–9). The higher association constants of **1** are possibly due to six additional hydrogen bonding acceptors. Host **2** exhibits a slightly enhanced binding affinity to *β*-**Glc** compared to **3** (entry 4 vs. 7), but an attenuated affinity to *β*-**Glc** compared to **1** (entry 1 vs. 4). This is consistent with the characteristics of host **2** which possesses three additional hydrogen bonding acceptors from pyridine nitrogen. With host **4** having the switched amide sequence, the binding affinity to *β*-**Glc** decreases more than 4-fold compared to host **2** (entry 4 vs. 10). Similar trends are observed with

TABLE I Binding constants of hosts with guests†

entry	host	guest	K_a(M^{-1})	$-\Delta G$(kcal/mol)
1	**1**	*β*-Glc	3000	4.8
2	**1**	*α*-Glc	860	4.0
3	**1**	*β*-Gal	370	3.5
4	**2**	*β*-Glc	1100	4.2
5	**2**	*α*-Glc	400	3.6
6	**2**	*β*-Gal	95	2.7
7	**3**‡	*β*-Glc	710	3.9
8	**3**‡	*α*-Glc	250	3.2
9	**3**‡	*β*-Gal	16	1.7
10	**4**	*β*-Glc	260	3.3
11	**4**	*α*-Glc	200	3.2
12	**4**	*β*-Gal	90	2.7

† ^{1}H NMR titration of 1.0 mM of [**H**] in $CDCl_3$ at 300 K. Chemical shift of NH of hosts was monitored after each addition of guests. Uncertainty in K_a's was less than 10%. ‡ Reference [20].

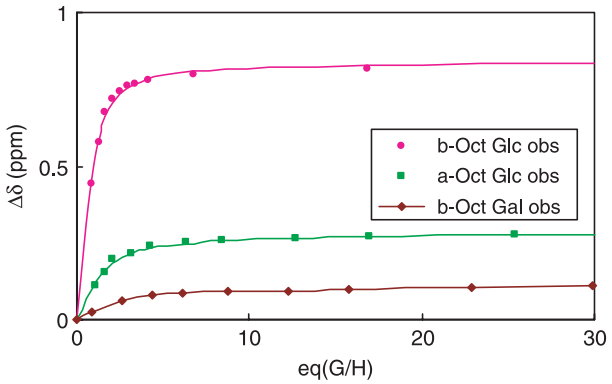


FIGURE 2 Binding isotherms between **1** and 1-octyl-D-pyranosides.

guests of *α*-**Glc** (entry 5 vs. 11) and *β*-**Gal** (entry 6 vs. 12), which implies the significance of the amide and pyridine unit sequence for effective host–guest complexation.

Molecular modeling [26] reveals a possible structure for the complex of **2** and *β*-D-glucopyranoside, which suggests the formation of an additional hydrogen bond between pyridine N of **2** and 4-OH of *β*-D-glucopyranoside compared to **3**. Ester functionality in the pyridine unit of host **1** contributes to another hydrogen bond with OH of *β*-Glc to lead to higher association constants as observed in the NMR titration experiment. Host **4** showed a stacking interaction between *β*-Glc and the peripheral pyridyl ring ($\Delta\delta_{max} = -0.026$ ppm 1-H of *β*-**Glc**) of **4** as well as one intermolecular hydrogen bonding ($\Delta\delta_{max} = 0.144$ ppm in NH of **4**). Even though one intermolecular hydrogen bonding interaction would contribute to weak binding, the moderate binding affinity for *β*-Glc results from cooperative interaction of the stacking interaction and hydrogen bonding interaction. The observed binding affinity of **4** for *β*-Glc was up to 11 times lower than **1** for *β*-**Glc**. This result indicates that the geometric size of the hydrogen bonding pocket as well as the number of hydrogen bonds are important for saccharide binding. The minimized structure between **4** and *β*-**Glc** showed one intermolecular hydrogen bonding interaction whereas **1** and *β*-**Glc** showed four intermolecular hydrogen bonds (Fig. 3).

To clearly observe the intermolecular hydrogen bonding patterns between host and guest, a reverse titration was performed in acid-free chloroform (Fig. 4). Upon addition of **1**, all the OH protons of 1-octyl-D-pyranosides moved downfield while the anomeric proton shifted to the upfield region. Downfield shifts of OH protons suggest intermolecular H-bonding interactions between 1-octyl-D-pyranosides and **1**. Upfield shifts of the anomeric protons of *β*-**Glc**, *α*-**Glc** and *β*-**Gal** imply that the anomeric proton comes into contact with the aromatic surfaces of **1**. The CIS values of the 1-H, 2-OH, 3-OH, 4-OH, and 6-OH resonances of *β*-**Glc**, *α*-**Glc** and *β*-**Gal** for the complex are determined by extrapolation to the maximum complexation and listed in Table II (the assignments of the resonances of the four hydroxyl protons were made on the basis of a reference article [13]). The chemical shift changes of OH protons at the 2, 3, 4, and 6 positions are largest with *β*-**Glc** while they are smaller with *α*-**Glc** and *β*-**Gal**. The larger upfield shift of 1-H of *β*-**Glc**, compared to *α*-**Glc** and *β*-**Gal** also implies that 1-H of *β*-**Glc** is in closer contact with the aromatic surface of **1**, leading to a higher affinity. From the reverse titration, it can be elicited that the intermolecular hydrogen bonding and shielding effects were in the following order: **1** > **2** > **4**. These observed results are consistent with the degree of the association constants.

CONCLUSION

In summary, the conformationally well-defined polypyridine hosts with variable hydrogen bonding acceptors were synthesized from triethylbenzene, which were effective for saccharide recognition. The degrees of affinity were adjustable by the number of hydrogen bonding acceptors in the peripheral pyridine unit. The anomeric and diastereomeric selectivities were observed to be moderate to high.

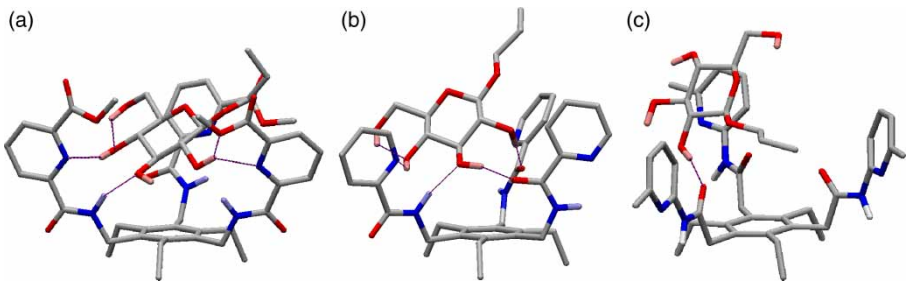


FIGURE 3 Minimized structures of complexes between hosts and *β*-**Glc**. (a) host **1**/*β*-**Glc**: four intermolecular H-bonds and one intra H-bond (b) host **2**/*β*-**Glc**: four intermolecular H-bonds and one intra H-bond (c) host **4**/*β*-**Glc**: one intermolecular H-bond and stacking interaction.

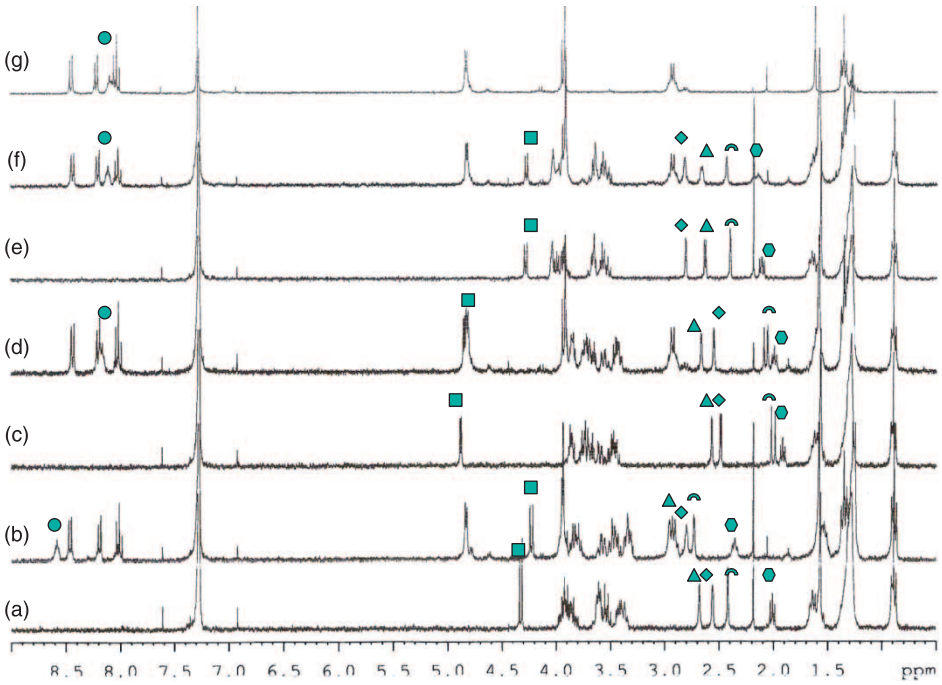


FIGURE 4 Partial reverse titration spectra of 1-octyl-D-pyranosides with 0.5 eq. of **1**, [sugar] = 1.5 mM in $CDCl_3$. (a) β-Glc (b) β-Glc and host (c) α-Glc (d) α-Glc and host (e) β-Gal (f) β-Gal and host (g) host **1**. Filled circle for NH of **1**, square for 1-H, triangle for 3-OH, rhombus for 4-OH, crescent for 2-OH and hexagon for 6-OH of sugars, respectively.

EXPERIMENTAL

Dichloromethane and triethylamine (TEA) were purified by distillation from calcium hydride before use. Oxalyl chloride (2 M solution in dichloromethane) was purchased from Aldrich chemical company. Analytical thin layer chromatography was performed using Kieselgel 60F-254 plates from Merck. Column chromatography was carried out on Merck silica gel 60 (70–230 mesh). Melting points were measured on a Kimax capillary melting point apparatus and were uncorrected. Infrared (IR) spectra were measured using a Perkin Elmer spectrometer. Proton and carbon NMR spectra were recorded on an AM-300 Bruker spectrometer. Chemical shifts are reported as ppm downfield from tetramethylsilane ($\delta = 0.0$) using the residual solvent signal as an internal standard: [D_1] chloroform (^{1}H NMR: $\delta = 7.28$; ^{13}C NMR: $\delta = 77.0$). Mass spectral data were recorded on a Jeol JMS-AX505WA and are reported in units of mass to charge (m/z). HR-MS was performed by the National Center for Inter-University Research Facilities at Seoul National University.

TABLE II Complexation-induced shifts (CIS) of guests upon addition of **1**[†]

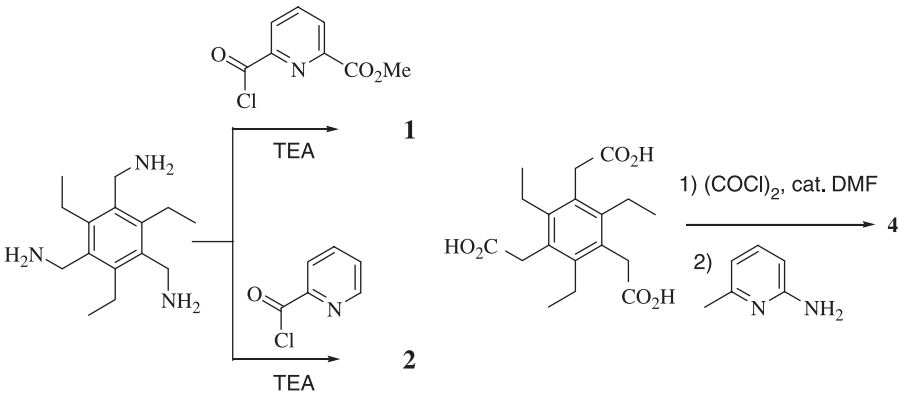
	$\Delta\delta_{max}$ of CIS (δ of free ligand) in ppm		
Guest	α-Glc	β-Glc	β-Gal
1-H	−0.161 (4.85)	−0.334 (4.29)	−0.061 (4.25)
2-OH	+0.349 (1.96)	+0.727 (2.38)	+0.292 (2.37)
3-OH	+0.463 (2.52)	+0.831 (2.63)	+0.300 (2.60)
4-OH	+0.316 (2.44)	+0.763 (2.52)	+0.101 (2.76)
6-OH	+0.378 (1.88)	+1.15 (1.97)	+0.247 (2.08)

[†] ^{1}H NMR reverse titration of 1.0 mM of [**G**] in $CDCl_3$ at 300 K.

Representative Syntheses of the Tris(pyridylamides)

C_3-symmetric tris(amides) hosts (**1**, **2**, and **4**) were synthesized from 1,3,5-triethylbenzene. The precursor, 1,3,5-tris(aminomethyl)-2,4,6-triethylbenzene was synthesized from 1,3,5-triethylbenzene according to the literature [27,28] while (2,4,6-triethylbenzene)-1,3,5-triacetic acid was synthesized by acidic hydrolysis of 1,3,5-tris(cyanomethyl)-2,4,6-triethylbenzene [29,30]. Coupling of 1,3,5-tris(aminomethyl)-2,4,6-triethylbenzene with pyridine acid chloride in the presence of DIPEA in dichloromethane afforded the desired tris(amides) hosts **1** and **2** while tris(acid chlorides) from (2,4,6-triethylbenzene)-1,3,5-triacetic acid was treated with 6-methyl-2-aminopyridine to afford host **4** in high yields (Scheme 1).

1 and **2**; To a solution of 200.7 mg (0.802 mmol) of 1,3,5-tris(aminomethyl)-2,4,6-triethylbenzene and 0.5 mL of TEA (6 Eq. 3.58 mmol) in 20 mL of dichoromethane was added dropwise a solution of 2.775 mmol of pyridine acid chloride in 10 mL of dichloromethane at 0°C under nitrogen. The resulting brown solution was stirred at rt for an additional 8 h. After all volatiles were evaporated under



SCHEME 1 Synthetic scheme of polypyridine hosts.

reduced pressure, the crude product was purified by column chromatography on silica gel and then by recrystallization to afford an analytically pure product.

1,3,5-Tris(2-pyridinecarboxamidomethyl)-2,4,6-triethylbenzene (2)

Quantitative yield; $R_f = 0.10$ (ethylacetate/hexane 2:1); column chromatographic purification on silica gel (eluting solvent, from ethylacetate/hexane 2:1 to ethylacetate/dichloromethane 2:1) afforded a white solid. mp 183–185°C (dec.). IR (KBr): 3394 (s, NH), 2964 (w, ArH), 1670 (s, CONH). ^{1}H NMR (300 MHz, $CDCl_3$): 8.52 (d, J = 4.4 Hz, 3H of pyH_α), 8.26 (d, J = 7.9 Hz, 3H of pyH_β), 7.98 (br, 3H of NH), 7.88 (m, 3H of pyH_γ), 7.43 (m, 3H of pyH_β), 4.74 (d, J = 4.7 Hz, 6H of $ArCH_2N$), 2.85 (q, J = 7.4 Hz, 6H of $ArCH_2C$), 1.28 (t, J = 7.4 Hz, 9H of $ArCH_2CH_3$). ^{13}C NMR (75 MHz, $CDCl_3$): 164.4, 149.9, 148.4, 144.9, 137.9, 38.5, 23.7, 16.8. HR-MS (FAB^+, m-NBA): *m/z* 565.2917 $(M + H)^+$, calc'd for $C_{33}H_{37}N_6O_3$ 565.2927.

1,3,5-Tris(6-methyloxycarbonyl-2-pyridinecarboxamidomethyl)-2,4,6-triethylbenzene (1)

Yield 90%; $R_f = 0.25$ (ethylacetate); column chromatographic purification on silica gel (eluting with ethylacetate) and then recrystalization in ethylacetate by diffusion of ether afforded an analytically pure white solid. mp 190–192°C (dec.). IR (KBr): 3400 (s, NH), 2954 (m, ArH), 1729, 1670 (s, carbonyl in CO_2Me and CONH). ^{1}H NMR (300 MHz, $CDCl_3$): 8.41 (d, J = 7.7 Hz, 3H of pyH_α), 8.20 (br, 3H of NH), 8.17 (d, J = 7.8 Hz, 3H of pyH_α), 8.00 (t, J = 7.7 Hz, 3H of pyH_β), 4.75 (d, J = 4.3 Hz, 6H of $pyCH_2N$), 3.84 (s, 9H of CO_2CH_3), 2.85 (q, J = 7.0 Hz, 6H of $ArCH_2C$), 1.30 (t, J = 7.0 Hz, 9H of $ArCH_2CH_3$). ^{13}C NMR (75 MHz, $CDCl_3$): 165.3, 150.5, 146.9, 145.0, 139.0, 132.3, 127.7, 126.0, 53.1, 38.5, 23.7, 16.8. HR-MS (FAB^+, m-NBA): *m/z* 739.3076 $(M + H)^+$, calc'd for $C_{39}H_{43}N_6O_9$ 739.3092.

N-(6-methylpyridin-2-yl)-2-{2,4,6-triethyl-3,5-Bis-[(6-methyl-pyridin-2-ylcarbamoyl)-methyl]-phenyl}-acetamide (4)

Yield 72%; $R_f = 0.50$ (ethylacetate); column chromatographic purification on silica gel (eluting solvent from ethylacetate/hexane 2:1 to dichloromethane/methanol 10:1) afforded an analytically pure white solid. mp 186–188°C (dec.). IR (KBr): 3404 (m, NH), 1685 (m, CONH). ^{1}H NMR (300 MHz, $CDCl_3$): 8.33 (br, 3H of NH), 7.98 (d, J = 8.2 Hz, 3H of pyH_β), 7.56 (dd, J = 8.2 Hz, J = 7.5 Hz, 3H of pyH_γ), 6.86 (d, J = 7.5 Hz, 3H of pyH_β), 3.94 (s, 6H of $ArCH_2N$), 2.73 (q, J = 7.4 Hz, 6H of $ArCH_2C$), 2.32 (s, 9H of $pyCH_3$), 1.19 (t, J = 7.4 Hz, 9H of $ArCH_2CH_3$). ^{13}C NMR (75 MHz, $CDCl_3$): 170.4, 156.8, 150.8, 143.9, 139.1, 130.1, 119.8, 112.0, 39.1, 24.6, 24.2, 14.7. HR-MS (FAB^+, m-NBA): *m/z* 607.3414 $(M + H)^+$, calc'd for $C_{36}H_{43}N_6O_3$ 607.3397.

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