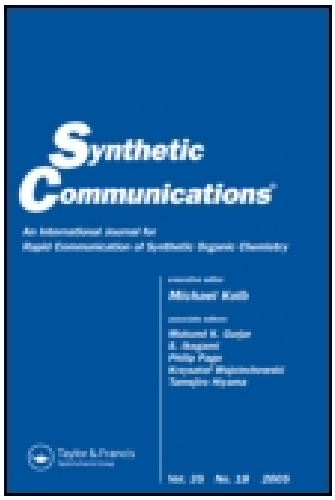

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Yanxing Qi [a] , Haixiang Gao [a] , Min Yang [a] , Chun-Gu Xia [a] & Jishuan Suo [a]

[a] State Key Laboratory for Oxo Synthesis and Selective Oxidation , Lanzhou Institute of Chemical Physics , Chinese Academy of Sciences , Lanzhou, China

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Synthesis of Guanidine Derivatives and Molecular Recognition

Yanxing Qi, Haixiang Gao, Min Yang, Chun-Gu Xia, and Jishuan Suo*

State Key Laboratory for Oxo Synthesis and Selective Oxidation, Lanzhou Institute of Chemical Physics, Chinese Academy of Sciences, Lanzhou, China

ABSTRACT

Five Guanidine Derivatives bearing acyl group were synthesized by the reaction of acyl chloride with 1,1,3,3-tetramethylguanidine. Their structures were confirmed by IR, ^{1}H-NMR, EI-MS, HRMS and elementary analysis. One of them (**4a**) was also characterized by X-ray. Preliminary results of interaction with phosphate-containing biomolecules and adipate showed that all of them exhibited the abilities of molecular recognition.

*Correspondence: Jishuan Suo, State Key Laboratory for Oxo Synthesis and Selective Oxidation, Lanzhou Institute of Chemical Physics, Chinese Academy of Sciences, Lanzhou-730000, China; E-mail: jssuo@ns.lzb.ac.cn.

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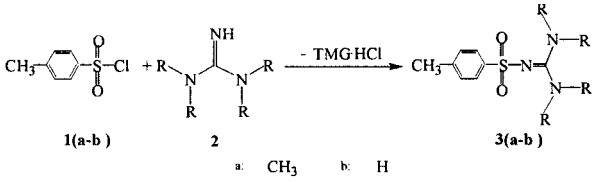
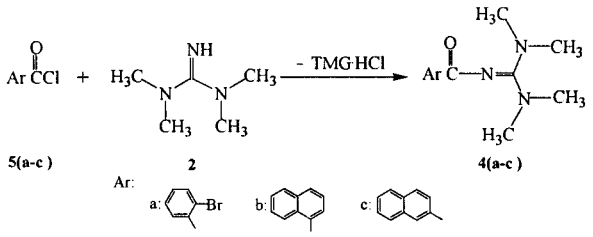
Guanidine groups have been found in many important natural products such as guanine and arginine, and are known to play significant roles in their biological activities.[1] For example, many of the novel metabolites, which isolated from microorganisms, terrestrial invertebrates, and marine and freshwater organisms, contains single or multiple guanidine units and possess unprecedented biological activity ranging from antimicrobial, antiviral, and antifungal to neurotoxic.[2] In addition, guanidine's molecular recognition features are used for DNA base pairing[3] and in the active sites of many enzymes,[4] and this functional group also has high affinity for carboxylates, phosphates and metals. Consequently, preparation of new guanidines and their hydrogen-bond-mediated interaction of guanidinium ions with phosphate- and carboxylate-containing biomolecules molecular recognition are of considerable interest to chemists and biochemists.[5,6] Here we wish to report the new synthesis and structural characterization of five guanidine derivatives bearing acyl groups **3a–3b** (Sch. 1) and **4(a–c)** (Sch. 2).

The condensation of acyl chloride with 1,1,3,3-tetramethyl-guanidine (TMG) gave the products **3a** and **4a–c**. The TMG acts not only as nucleophilic reagent, but also as a base. Their IR spectra have corresponding strong characteristic C=N absorption (about 1600 cm^{-1}), and in their ^{1}H-NMR spectra, the signal of *N*-methyl appeared as a singlet at



Scheme 1.



Scheme 2.

about 3.0 ppm, and confirmed that all of them are guanidine derivatives bearing chromophores. These compounds **3a–3b** and **4a–c** are all new compounds to the literature. In addition, the complexes of transition metals with guanidine and their derivates, including 1,1,3,3-tetramethyl-guanidine, were of considerable interest to chemists.[7–10] To our knowledge, however, there were few previous examples of complexes containing acyl guanidine ligands which have been structurally characterized.[11] When we attempt to prepare new guanidine complexes with transition metals, unexpectedly, we obtained crystal of **4a**, which is suitable for X-ray analysis. As ^{1}H NMR spectroscopy has been widely used to investigate receptor-substrate interactions,[12] ^{1}H NMR spectra of nucleotide and adipate with or without host receptors (**3–4**) were recorded and the selected data are listed in Table 1. Upon addition of host receptors (**3–4**), the proton signals of substrates (Fig. 1) are shifted significantly, which indicated that, as host receptors, all of the new gua-

Table 1. ^{1}H NMR chemical shifts (ppm) for host receptors (**3–4**) in the absence or presence of guest substrates (**6–10**).

Sample	δa	δb	δc	δd	δe	δf	δg
6[a]	3.86	4.55	4.17	4.33	5.70	7.99	
4a + 6[a]	3.33	4.38	3.87	4.20	5.87	8.10	
4b + 6[a]	3.23	4.37	3.90	4.18	5.72	8.05	
6[b]	2.12	4.44	3.98	4.24	5.84	8.16	
4c + 6 [b]	3.23	4.45	4.23	3.94	5.83	8.14	
7[a]	2.65	4.43	3.98	4.19	6.47	8.27	8.50
4a + 7[a]	2.49	4.54	3.82	4.14	6.38	8.12	8.45
8[a]	3.88	4.60	4.23	4.37	5.94	8.00	8.37
4a + 8[a]	3.33	4.50	4.27	3.90	6.01	8.08	8.48
9[c]	3.98	4.61	4.22	4.06	5.96	8.21	8.55
3a + 9[c]	4.02	4.62	4.23	4.12	5.97	8.23	8.42
10[a]	2.01	1.44		4.12	5.97	8.24	8.44
4b + 10[a]	2.05	1.42					
10[c]	2.20	1.52					
3a + 10[c]	2.24	1.52					
3b + 10[c]	2.21	1.52					
10[b]	2.30	1.53					
4c + 10[b]	2.11	1.51					

Solvent:
[a]D_2O.
[b]D_2O:$(CD_3)_2CO$=4:1.
[c]DMSO-d_6.

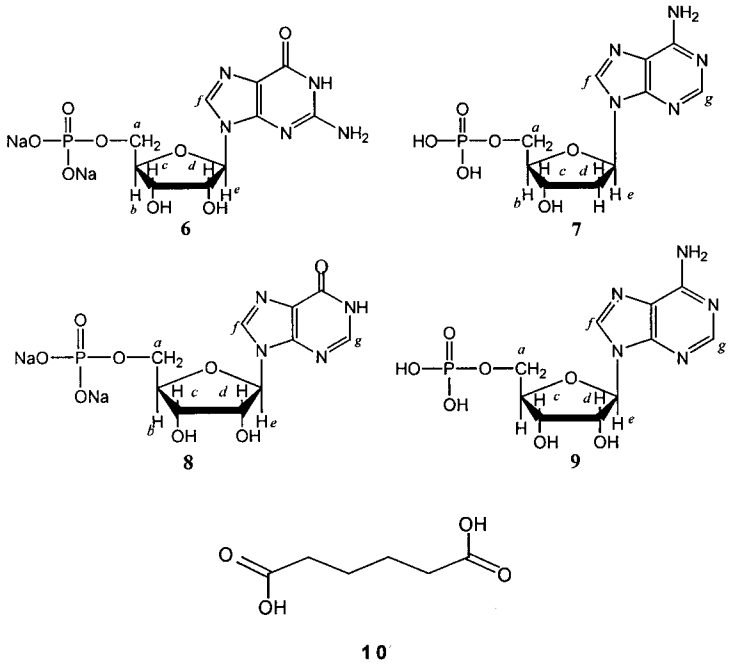


Figure 1. Structures of substrates **6**, **7**, **8**, **9** and **10**.

nidine derivatives (**3–4**) have the abilities of molecular recognition for phosphate (**6–9**) and adipate (**10**). The other molecular recognition details of these compounds will be published elsewhere.

EXPERIMENTAL

The TMG (1,1,3,3-tetramethylguanidine) were obtained from Berqi Chemical Co. All melting points were uncorrected. The yields refer to isolated products. FT-IR spectra were recorded on a Nicolet 10 DX spectrometer (KBr). ^{1}H-NMR spectra were obtained on a Bruker AC-P 200 M NMR instrument in $CDCl_3$ or DMSO-d_6 solution with TMS as internal reference. EI-MS spectra were obtained with a VG AB-HS instrument. HRMS (ESI) spectra were obtained with a Bruker Daltonics APEX II 47e FTICR-HRMS instrument. A Rigaku AFC 7R X-ray diffraction instrument was used for crystal analysis.

General Procedure for the Preparation of Compound 3a and 4

In a flame-dried round-bottomed flask were placed 20 mmol TMG and 20 mL THF. The mixture was cooled to 9°C by an ice water bath. 10 mmol acyl chloride in 10 mL THF was added dropwise to this stirred solution. A white precipitate ($[TMGH]^+ \cdot Cl^-$) was formed immediately. During the addition, the reaction temperature was maintained at 9–18°C about 1 h. After naphthoyl chloride or derivatives of benzoyl chloride solution had been added, the ice water bath was removed. The resulting white slurry was allowed to stir for additional 2 h at room temperature, filtered, and the precipitate was washed with chloroform. The solvents were removed by rotary evaporator to yield yellow syrup. The crude product was dissolved in benzene, and the white precipitate ($[TMGH]^+ \cdot Cl^-$) was removed by filtering. Removal of the solvent in vacuo left a residue, which was recrystallized from H_2O to give products **3a**, or column chromatographed on silica gel (eluted with $CHCl_3$: $CH_3OH = 15{:}1$) (products **4a–4c**).

Preparation of Compound 3b

In a round-bottomed flask was placed 27 mmol Guanidine hydrochloride and 4.5 g 50% aqueous NaOH. The mixture was warmed to 40°C and stirred for 10 min. To this stirred solution were added 15 mL acetone and the mixture was cooled to 0°C. Then 27 mmol *p*-toluenesulfonyl chloride in 20 mL acetone was added dropwise to the above mixture. After acyl chloride had been added, the solution was allowed to stir for additional 0.5 h at 0°C, The pH value was adjusted to 4–5 with 80% acetic acid. The solvent was removed by rotary evaporator to yield white syrup. Crystallization of the residue from pyridine yielded compound **3b**.

Preparation of Crystal of 4a · $HClO_4$

To a stirred solution of **4a** in CH_3OH was added 1 equiv. of $HClO_4$ in water. The mixture was stirred for 10 min, filtered, and left at room temperature for two weeks to give colorless crystals, which are suitable for X-ray analysis. The X-ray structure of **4a · $HClO_4$** is shown in Fig. 2.

4-methylbenzenesulfonyl-(1,1,3,3-tetramethylguanidine) (3a). Yield, 79%; M.p.:142–144°C; ^{1}H NMR (DMSO-d_6): δ ppm 7.63 (d, 2H), 7.28

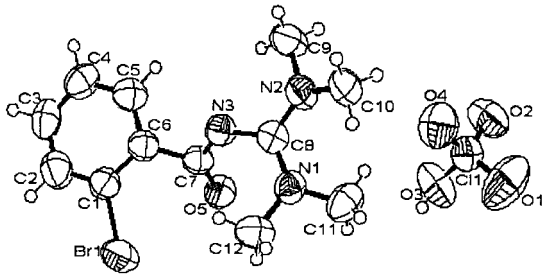


Figure 2. Molecular structure of **4a·HClO$_4$** (ORTEP view).

(d, 2H), 2.83 (s, 12H), 2.34 (s, 3H); HRMS for $C_{12}H_{20}O_2N_3S$ (M +1), Calcd. 270.1271, Found, 270.1267; IR (KBr): 2948, 2893, 1561, 1527, 1471, 1394, 1331, 1264, 1161, 1132, 887, 811, 676 cm^{-1}; Anal. calcd. for $C_{12}H_{19}O_2N_3S$: C, 53.51; H, 7.12; N, 15.61; S, 11.88. Found: C, 53.23; H, 7.27; N, 15.74; S, 11.81.

4-methylbenzenesulfonylguanidine (3b). Yield, 65%; M.p.: 213–215°C; ^{1}H NMR (DMSO-d_6): δ ppm 7.63(d, 2H), 7.29 (d, 2H), 3.33 (s, 4H), 2.35 (s, 3H); HRMS for $C_8H_{12}O_2N_3S$ (M +1), Calcd. 214.0645, Found, 214.0639; IR (KBr): 3491, 3436, 3353, 1621, 1531, 1241, 1181, 1134, 834, 818, 677 cm^{-1}; Anal. calcd. for $C_8H_{11}O_2N_3S$: C, 45.06; H, 5.20; N, 19.72; S, 15.01. Found: C, 44.91; H, 5.10; N, 19.59; S, 14.89.

2-bromobenzyl-(1,1,3,3-tetramethylguanidine) (4a). Yield, 90%; M.p.: 93.3–95°C; ^{1}H NMR (DMSO-d_6): δ ppm 7.58 (d, 1H), 7.55 (d, 1H), 7.19–7.38 (m, 2H), 2.91 (s, 12H); EI/MS (*m*/*z*): 297 (M^+), 282, 253, 218, 183 (100), 155, 130, 76; IR (KBr): 3057, 2956, 1588, 1522 (C=N), 1398, 1229, 1170, 865 cm^{-1}; Anal. calcd. for $C_{12}H_{16}BrN_3O$: C, 48.48; H, 5.43; N, 14.14. Found: C, 48.53; H, 5.51; N, 14.21.

1-naphthoyl-(1,1,3,3-tetramethylguanidine) (4b). Yield, 91%; M.p.: 108–110°C; ^{1}H NMR ($CDCl_3$): δ ppm 9.01 (d, 1H), 8.09 (d, 1H), 7.86 (m, 2H), 7.55–7.43 (m, 3H), 3.01 (s, 12H); EI-MS (*m*/*z*): 269 (M^+), 252, 226, 225 (100), 182, 155, 142, 127; IR (KBr): 3010, 2866, 1583, 1522, 1405, 1359, 1227, 1160, 1037, 810 cm^{-1}; Anal. calcd. for $C_{16}H_{19}N_3O$: C, 71.33; H, 7.12; N, 15.61. Found: C, 71.18; H, 7.23; N, 15.69.

2-naphthoyl-(1,1,3,3-tetramethylguanidine) (4c). Yield, 87%; M.p.: 126–127°C; ^{1}H NMR ($CDCl_3$): δ ppm 8.69 (s, 1H), 8.25 (m, 1H), 7.93 (m, 1H), 7.83 (m, 2H), 7.46 (m, 2H), 2.93 (s, 12H); EI/MS (*m*/*z*): 269 (M^+), 226, 225, 155 (98), 127 (100), 126, 71; IR (KBr): 2925, 2866, 1604, 1519, 1401, 1357, 1154, 1018, 981 cm^{-1}; Anal. calcd. for $C_{16}H_{19}N_3O$: C, 71.33; H, 7.12; N, 15.61. Found: C, 71.18; H, 7.26; N, 15.70.

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