

- [4] S. Mecking, L. K. Johnson, L. Wang, M. Brookhart, *J. Am. Chem. Soc.* **1998**, *120*, 888.  
 [5] M. P. Coles, C. I. Dalby, V. C. Gibson, W. Clegg, M. R. J. Elsegood, *J. Chem. Soc. Chem. Commun.* **1995**, 1709.  
 [6] V. C. Gibson, E. L. Marshall, C. Redshaw, W. Clegg, M. R. J. Elsegood, *J. Chem. Soc. Dalton Trans.* **1996**, 21, 4197.  
 [7] J. D. Scollard, D. H. McConville, *J. Am. Chem. Soc.* **1996**, *118*, 10008.  
 [8] J. D. Scollard, D. H. McConville, J. J. Vittal, *Organometallics* **1995**, *14*, 5478.  
 [9] D. W. Stephan, F. Guérin, R. E. v. Spence, L. Koch, X. Gao, S. J. Brown, J. W. Swabey, Q. Wang, W. Xu, P. Zoricak, D. G. Harrison, *Organometallics* **1999**, *17*, 2046.  
 [10] D. W. Stephan, J. C. Stewart, F. Guérin, R. E. v. Spence, W. Xu, D. G. Harrison, *Organometallics* **1999**, *17*, 1116.  
 [11] X. Yang, C. L. Stern, T. J. Marks, *J. Am. Chem. Soc.* **1994**, *116*, 10015.  
 [12] X. Yang, C. L. Stern, T. J. Marks, *J. Am. Chem. Soc.* **1991**, *113*, 3623.  
 [13] Y.-X. Chen, C. L. Stern, T. J. Marks, *J. Am. Chem. Soc.* **1997**, *119*, 2582.  
 [14] P. A. Deck, T. J. Marks, *J. Am. Chem. Soc.* **1995**, *117*, 6128.  
 [15] X. Y. Chen, C. L. Stern, S. Yang, T. J. Marks, *J. Am. Chem. Soc.* **1996**, *118*, 12451.  
 [16] Z. Wu, R. F. Jordan, J. L. Petersen, *J. Am. Chem. Soc.* **1995**, *117*, 5867.  
 [17] R. F. Jordan, W. E. Dasher, S. F. Echols, *J. Am. Chem. Soc.* **1986**, *108*, 1718.  
 [18] R. F. Jordan, C. S. Bajgur, R. Willett, B. Scott, *J. Am. Chem. Soc.* **1986**, *108*, 7410.  
 [19] M. Bochmann, S. J. Lancaster, M. B. Hursthouse, K. M. A. Malik, *Organometallics* **1994**, *13*, 2235.  
 [20] Catalyst screening experiments were performed as detailed in ref. [10]. Polymers obtained by using this catalyst have been described in ref. [9].  
 [21] Crystal structure analysis of **3**: monoclinic, space group *C2/c*,  $a = 23.417(9)$ ,  $b = 14.776(6)$ ,  $c = 22.678(8)$  Å,  $\beta = 109.98(3)^\circ$ ,  $V = 7374.2(49)$  Å<sup>3</sup>,  $Z = 4$ ,  $\rho_{\text{calcd}} = 1.535$ ,  $\mu = 0.421$ , 5661 reflections, 486 parameters,  $R = 0.0823$ ,  $R_w = 0.1827$ , GOF = 1.002. Diffraction experiments were performed on a Siemens SMART System CCD diffractometer, and the structure was solved with the SHELX-TL software package. Crystallographic data (excluding structure factors) for the structure reported in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication no. CCDC-134941. Copies of the data can be obtained free of charge on application to CCDC, 12 Union Road, Cambridge CB21EZ, UK (fax: (+44) 1223-336-033; e-mail: deposit@ccdc.cam.ac.uk).  
 [22] W. Lasser, U. Thewalt, *J. Organomet. Chem.* **1986**, *331*, 69.  
 [23] R. F. Jordan, S. F. Echols, *Inorg. Chem.* **1987**, *26*, 383.  
 [24] P. N. Billinger, P. P. K. Claire, H. Collins, G. R. Willey, *Inorg. Chim. Acta* **1988**, *149*, 63.  
 [25] T. K. Hollis, N. P. Robinson, B. Bosnich, *J. Am. Chem. Soc.* **1992**, *114*, 5464.  
 [26] B. Bosch, G. Erker, R. Frohlich, O. Meyer, *Organometallics* **1997**, *16*, 5449.  
 [27] M. L. H. Green, J. Sassmannshausen, *Chem. Commun.* **1999**, 115.

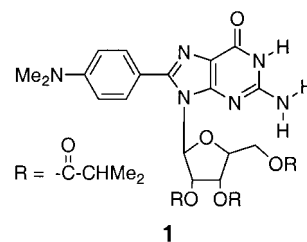
## A G-Quartet Formed in the Absence of a Templating Metal Cation: A New 8-(*N,N*-dimethylaniline)guanosine Derivative\*\*

Jonathan L. Sessler,\* Muhunthan Sathiosatham, Katherine Doerr, Vincent Lynch, and Khalil A. Abboud

Dedicated to Professor Jean-Marie Lehn on the occasion of his 60th birthday

Self-assembly is one of the more intriguing subfields within the general area of molecular recognition. Indeed, quite a number of natural and unnatural molecules form ordered supramolecular ensembles by self-assembly.<sup>[1]</sup> Notable among these is guanosine, a compound known to self-assemble into dimeric,<sup>[2]</sup> tetrameric,<sup>[3]</sup> ribbonlike,<sup>[4]</sup> and helical structures<sup>[5]</sup> as the result of Watson–Crick and Hoogsteen base-pairing interactions. The tetrameric forms of guanosine, known also as G-quartets, have drawn considerable attention over the past three decades. They have been implicated in a variety of biological functions<sup>[6]</sup> and have seen application in a range of nonbiological areas such as ionophores<sup>[7]</sup> and phase-transfer catalysts.<sup>[8]</sup> X-ray analyses of crystals obtained from aqueous solutions of 5'- and 3'-guanosine monophosphate revealed that the constituent bases adopt a tetrameric planar arrangement, which then stacks in a helical fashion with other tetramers to form columnar aggregates.<sup>[9]</sup>

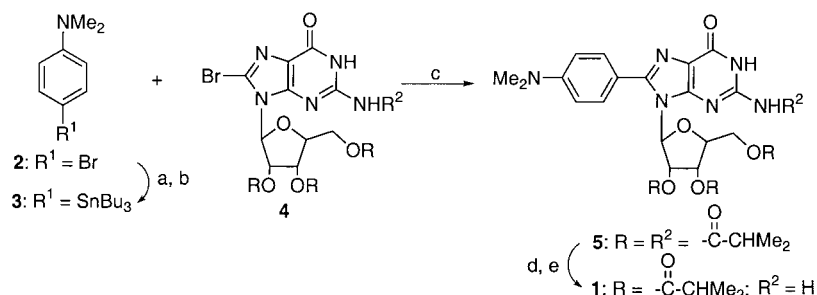
Currently, it is believed that templating alkali metal cations such as Na<sup>+</sup> and K<sup>+</sup> are needed to stabilize the formation of G-quartets.<sup>[10]</sup> The need for such cations to stabilize self-assembled and higher order aggregates formed from lipophilic deoxyguanosine derivatives in chlorinated organic solvents (that is, G-quartet model systems) has also been explicitly noted.<sup>[4,7]</sup> Indeed, in the absence of alkali metal cations these compounds were found to adopt a ribbonlike structure (but not G-quartets) in both chloroform solution<sup>[4a]</sup> and in the solid state.<sup>[4b]</sup> Here, we report the synthesis of the new (*N,N*-dimethylaniline)guanosine derivative **1** that forms a G-quartet in the absence of alkali metal



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Scheme 1. Synthesis of guanosine derivative **1**. a) BuLi, THF,  $-78^{\circ}\text{C}$ ; b)  $n\text{Bu}_3\text{SnCl}$ ,  $-78^{\circ}\text{C}$   $\rightarrow$  room temperature, 90%; c)  $[\text{Pd}(\text{PPh}_3)_4]$ , toluene, reflux, 95%; d)  $\text{NH}_3$ , MeOH,  $\text{CH}_2\text{Cl}_2$ ; e)  $(\text{Me}_2\text{CHCO})_2\text{O}$ , DMAP, TEA, MeCN, 50%. DMAP = 4-dimethylaminopyridine, TEA = triethylamine.

communications in both chlorinated organic solvents and in the solid state.

Scheme 1 outlines the synthesis of **1**. Briefly, *N,N*-dimethyl-4-(tri-*n*-butylstannyl)aniline (**3**) was synthesized from commercially available 4-bromo-*N,N*-dimethylaniline (**2**) by treatment with BuLi in THF at  $-78^{\circ}\text{C}$ , followed by tri-*n*-butylstannyl chloride. Coupling of this tin derivative with the 8-bromoguanosine derivative **4**<sup>[11]</sup> under Stille cross-coupling conditions afforded *N*-protected **5** which was converted to **1** by using standard deprotection and protection procedures.<sup>[11]</sup>

Crystals of **1**<sup>[12]</sup> were obtained by slow evaporation of a solution of **1** in acetonitrile/isopropyl alcohol. An X-ray crystallographic analysis of **1** revealed that it forms H-bonded head-to-tail<sup>[10a]</sup> tetramers in the absence of an alkali metal cation template (Figure 1). Each individual tetramer (see Figure 2 for a schematic representation) possesses  $C_4$  symmetry along the *c* axis and has all four guanine bases within an essentially planar array. The protected ribose subunits occupy the space above this plane and adopt *syn* conformations with

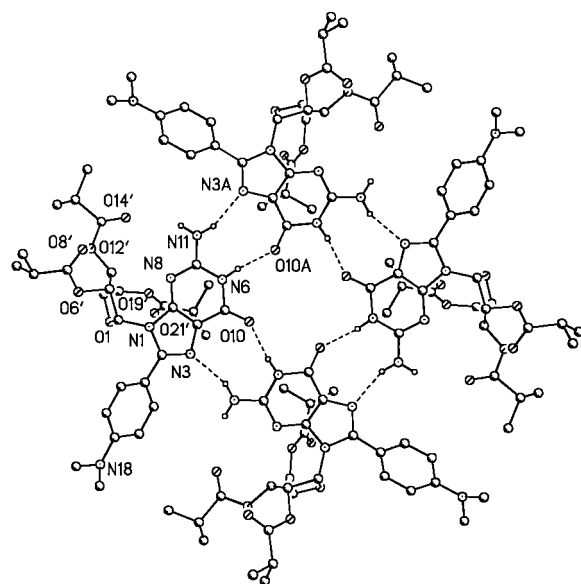


Figure 1. Ball-and-stick representation of the tetrameric arrangement of molecules of **1** in the solid state. The geometry of the hydrogen bonding interaction is:  $\text{N}11\text{---H}11\text{b}\cdots\text{N}3\text{A}$  (related by  $y, 1-x, z$ ),  $\text{N}\cdots\text{N}$  2.927(2) Å,  $\text{N}\cdots\text{H}$  2.107(2) Å,  $\text{N}\text{---H}\cdots\text{N}$  159.1(1) $^{\circ}$ ;  $\text{N}6\text{---H}6\cdots\text{O}10\text{A}$  (related by  $y, 1-x, z$ ),  $\text{N}\cdots\text{O}$  2.778(2) Å,  $\text{H}\cdots\text{O}$  1.92(3) Å,  $\text{N}\text{---H}\cdots\text{O}$  172(2) Å.

respect to the relevant N9–C1' glycosidic bonds. Such an all-*syn* arrangement presumably reflects either a) unfavorable steric interactions between the isobutyryl protecting group and the dimethylaniline moiety that would exist in the *anti* conformation,<sup>[13]</sup> or b) the possibility of hydrogen bond formation between the C5' isobutyryl carbonyl group and the (N2)H\*, or c) some combination of these two effects.

The various guanosine and deoxyguanosine derivatives soluble in organic solvents whose self-assembly properties were studied previously all lack the aryl substituent present in **1**. They thus adopt an *anti* conformation both in sol-

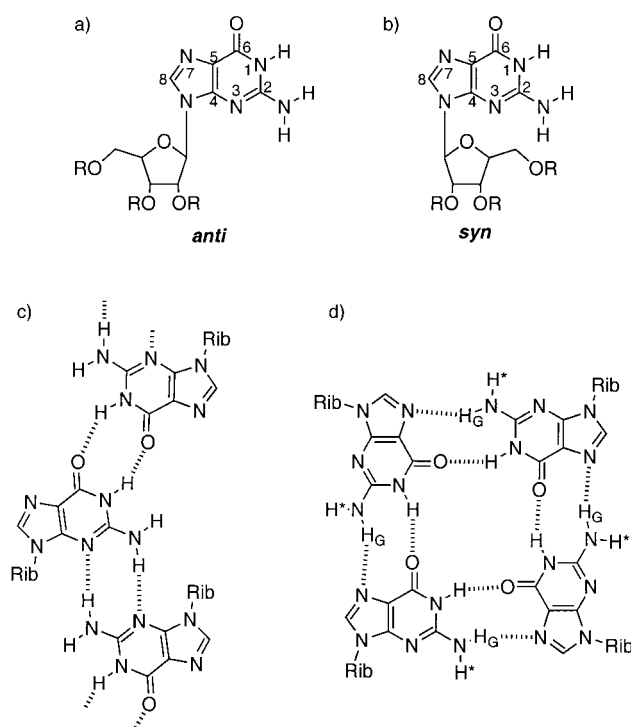


Figure 2. Schematic representations of *anti* (a) and *syn* conformers of guanosines (b) that can arise as the result of rotation about the purine–ribose bond. c) Truncated view of the ribbonlike structures observed for lipophilic guanosine derivatives that are capable of adopting an *anti* conformation. d) Idealized view of G-quartet-like tetramer formed from **1** both in solution in dichloromethane and in the solid state (the *p*-NMe<sub>2</sub>C<sub>6</sub>H<sub>4</sub> substituent at C8' has been omitted for clarity). This structure displays a *syn* arrangement of the ribose (Rib) and purine subunits. H<sub>G</sub> and H\* indicate the amino protons that are, and are not, participating in G-quartet formation, respectively.

ution and in the solid state. They also self-assemble in the form of ribbonlike structures rather than G-quartets in the absence of K<sup>+</sup> or other templating cations.<sup>[4]</sup> By contrast **1**, presumably as a consequence of adopting a *syn* conformation, self-assembles to form a cyclic tetramer. In the *syn* conformation, one of the faces on the guanosine subunit is blocked (Figure 2). Apparently, this prevents the formation of ribbonlike supramolecular structures as is seen in the case of compounds that are capable of adopting an *anti* conformation.

The putative formation of a G-quartet-like structure from **1** was studied in organic solutions by <sup>1</sup>H NMR spectroscopy. In

[D<sub>6</sub>]DMSO, where intermolecular H-bonding interactions are minimized,<sup>[14]</sup> no significant self-assembly was observed at room temperature (as indicated by the presence of NH<sub>2</sub> and (N1)H signals at  $\delta = 6.40$  and 10.80, respectively; Figure 3a). By contrast the <sup>1</sup>H NMR spectrum of a 58 mM solution of **1** in CD<sub>2</sub>Cl<sub>2</sub> at room temperature showed evidence for self-assembly. Under these conditions a broad signal, exchangeable with D<sub>2</sub>O, is observed between  $\delta = 7.0$  and 7.8 (Figure 3b). While such a signal, assigned on the basis of integration to (N2)H<sub>G</sub>, is consistent with the formation of a tetramer that is in fast equilibrium with other self-assembled species (dimers, trimers, oligomers, etc.), it could also indicate the incomplete formation of the proposed G-quartet-like ensemble. We currently favor the first of these interpretations since re-recording the spectrum at  $-30^\circ\text{C}$  produces well-defined spectral patterns that are considered consistent with the formation of a G-quartet (Figure 3c). In particular, new exchangeable signals at  $\delta = 9.81$  and 5.15, ascribed to (N2)H<sub>G</sub> and (N2)H\*, respectively, are observed that are coincident, in terms of chemical shift, with those of previously described guanine-derived tetramers that are stabilized by alkali metal cations.<sup>[7, 15]</sup> Furthermore, the fact that under these low-temperature conditions only a single signal is seen for each of the (N3)H<sub>G</sub> and (N3)H\* protons leads us to suggest that, in contrast to other G-quartets,<sup>[7, 15]</sup> only one of two possible *syn/anti* ribose conformers, presumably *syn*, is present in solution.

To probe more fully the solution-phase characteristics of **1**, the number-averaged molecular weight of putative aggre-

gate(s) in dichloroethane was estimated at  $40^\circ\text{C}$  by using vapor-pressure osmometry (VPO).<sup>[16]</sup> These studies, carried out at initial concentrations<sup>[17]</sup> of 28, 42, 57, and 71 mM (in **1**), revealed an averaged molecular weight of  $2170 \pm 150$  amu, that is, close to the molecular weight expected for a tetramer of **1** (2448 amu). We thus conclude that the tetrameric form, although subject to exchange, constitutes the predominant species in solution as well as in the solid state.

We have shown that G-quartets can be stabilized in the absence of a templating alkali metal cation. This leads us to suggest that this kind of structural motif may be more fundamental in its origin and easier to form than previously assumed.

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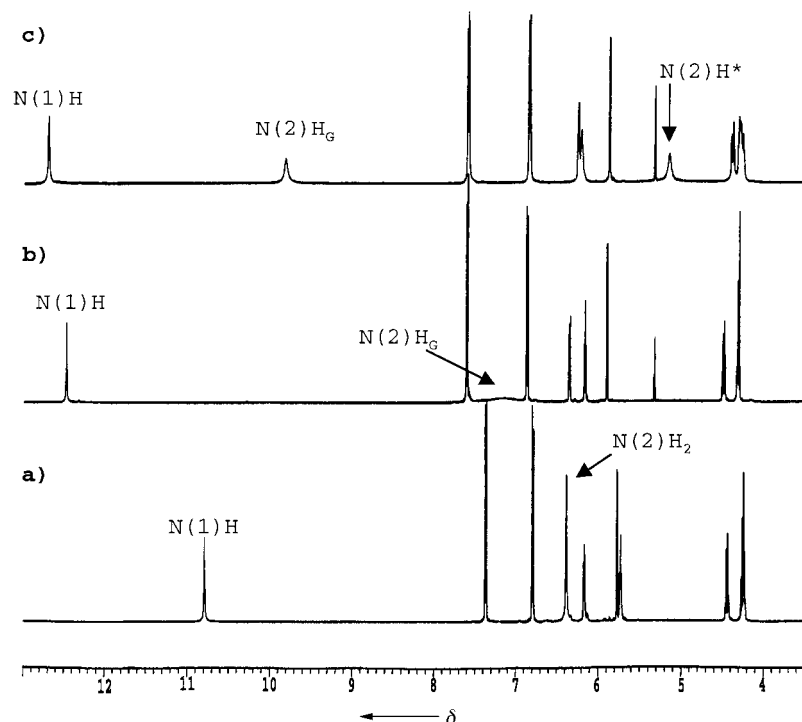


Figure 3. Portion of the proton NMR spectrum of **1** showing changes consistent with the formation of a G-quartet: a) 70 mM solution of **1** in [D<sub>6</sub>]DMSO at room temperature; b) 58 mM solution of **1** in CD<sub>2</sub>Cl<sub>2</sub> at room temperature; c) 58 mM solution of **1** in CD<sub>2</sub>Cl<sub>2</sub> at  $-30^\circ\text{C}$ . The signals ascribed to (N1)H are observed at  $\delta = 10.80$ , 12.47, and 12.70 in the case of spectra a), b), and c), respectively. By contrast, the (N2)H<sub>2</sub> signal observed at  $\delta = 6.40$  in [D<sub>6</sub>]DMSO at room temperature appears in the form of two signals at  $\delta = 5.15$  and 9.81 when the spectrum is recorded at  $-30^\circ\text{C}$  in CD<sub>2</sub>Cl<sub>2</sub>. See text for further discussion. For definitions of H<sub>G</sub> and H\* see caption to Figure 2.

- [1] a) D. Philp, J. F. Stoddart, *Angew. Chem.* **1996**, *108*, 1242–1286; *Angew. Chem. Int. Ed. Engl.* **1996**, *35*, 1154–1196; b) M. M. Conn, J. Rebek, Jr., *Chem. Rev.* **1997**, *97*, 1647–1668; c) J.-M. Lehn, M. J. Krische, *Struct. Bonding* **2000**, in press.
- [2] J. L. Sessler, R. Wang, *Angew. Chem.* **1998**, *110*, 1818–1821; *Angew. Chem. Int. Ed.* **1998**, *37*, 1726–1729.
- [3] V. Andrisano, G. Gottarelli, S. Masiero, E. H. Heijne, S. Pieraccini, G. P. Spada, *Angew. Chem.* **1999**, *111*, 2543–2544; *Angew. Chem. Int. Ed.* **1999**, *38*, 2386–2388.
- [4] a) G. Gottarelli, S. Masiero, E. Mezzina, G. P. Spada, P. Mariani, M. Recanatini, *Helv. Chim. Acta* **1998**, *81*, 2078–2092; b) K. Arakik, M. Abe, A. Ishizaki, T. Ohya, *Chem. Lett.* **1995**, 359–360.
- [5] J. A. Walmsley, J. F. Burnett, *Biochemistry* **1999**, *38*, 14063–14068.
- [6] S. Borman, *Chem. Eng. News* **1999**, *77*(27), 36–37.
- [7] A. L. Marlow, E. Messina, G. P. Spada, S. Masiero, J. T. Davis, G. Gottarelli, *J. Org. Chem.* **1999**, *64*, 5116–5123.
- [8] A. L. Marlow, J. T. Davis, *Tetrahedron Lett.* **1999**, *40*, 3539–3542.
- [9] S. B. Zimmerman, *J. Mol. Biol.* **1975**, *106*, 663–672.
- [10] a) J. A. Walmsley, R. T. G. Barr, E. Bouhoutsos-Brown, T. J. Pinnavaia, *J. Phys. Chem.* **1984**, *88*, 2599–2605; b) E. Bouhoutsos-Brown, C. L. Marshall, J. T. Pinnavaia, *J. Am. Chem. Soc.* **1982**, *104*, 6576–6584.
- [11] J. L. Sessler, B. Wang, A. Harriman, *J. Am. Chem. Soc.* **1995**, *117*, 704–714.
- [12] X-ray crystal data for **1**: Thin colorless needles were grown from a CH<sub>3</sub>CN/*i*PrOH mixture (1:1 ratio). C<sub>30</sub>H<sub>40</sub>N<sub>6</sub>O<sub>8</sub> · ½ CH<sub>3</sub>CN, tetragonal, *I*4, *Z* = 4, *a* = 28.3035(11), *c* = 8.2683(5) Å, *V* = 6623.6(5) Å<sup>3</sup>,  $\rho_{\text{calcd}} = 1.27 \text{ g cm}^{-3}$ , *F*(000) = 2696. A total of 23013 reflections were measured, 7585 unique (*R*<sub>int</sub> = 0.029), on a Siemens SMART PLATFORM equipped with a CCD area detector using graphite-monochromated MoK $\alpha$  radiation ( $\lambda = 0.71073 \text{ \AA}$ ) at  $-100^\circ\text{C}$ . The structure was refined on *F*<sup>2</sup> to an *R*<sub>w</sub> = 0.107, with a conventional *R* = 0.0455 (5821 reflections with *F*<sub>o</sub> > 4[ $\sigma$ (*F*<sub>o</sub>)]), GOF = 1.21 for 437 refined parameters. The tetramer resides around the crystallographic fourfold rotation axis. A molecule of acetonitrile resides between layers of tetramers, spaced 8.2 Å apart, and is disordered along the fourfold rotation axis. Crystallographic data (excluding structure factors) for the structure reported in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication no. CCDC-134040. Copies of the data can be obtained free of charge on application to CCDC, 12 Union Road, Cambridge CB21EZ, UK (fax: (+44) 1223-336-033; e-mail: deposit@ccdc.cam.ac.uk).

- [13] Destabilization of the *anti* conformation due to steric interactions has also been reported: a) S. N. Rao, P. A. Kollman, *J. Am. Chem. Soc.* **1986**, *108*, 3048–3053; b) S. H. Krawczyk, N. Bischofberger, L. C. Griffin, V. S. Law, R. G. Shea, S. Swaminathan, *Nucleosides Nucleotides* **1995**, *14*, 1109–1116; c) F. Seela, Y. Chen, C. Mittelbach, *Helv. Chim. Acta* **1998**, *81*, 570–583, and references therein.
- [14] J. L. Sessler, R. Wang, *J. Org. Chem.* **1998**, *63*, 4079–4091.
- [15] In these previous systems both *syn* and *anti* ribose conformers were observed as implied in the text. Proper comparison was thus made to the signals assigned to the *syn* form.
- [16] a) D. E. Burge, *Am. Lab.* **1977**, *9*, 41–51; b) D. E. Burge, *J. Appl. Polym. Sci.* **1979**, *24*, 293–299.
- [17] In contrast to various previously reported lipophilic deoxyguanosine derivatives that were all found to form gels in chlorinated organic solvents in the absence of cations (that is, self-assembled ribbonlike aggregates)<sup>[4a]</sup>, compound **1** was not found to form a gel even at concentrations as high as 0.2 M. As discussed in the text, we rationalize this in terms of **1**, but not these other compounds, being present in a *syn* conformation. The observation that the less sterically hindered compound, (2',3',5'-tri-*O*-isobutyrylribofuranosidyl)-2-aminopurin-6-one, which lacks an aryl substituent and which should be present mostly in *anti* conformation, forms a gel at concentrations as low as 0.02 M is considered consistent with this theory.

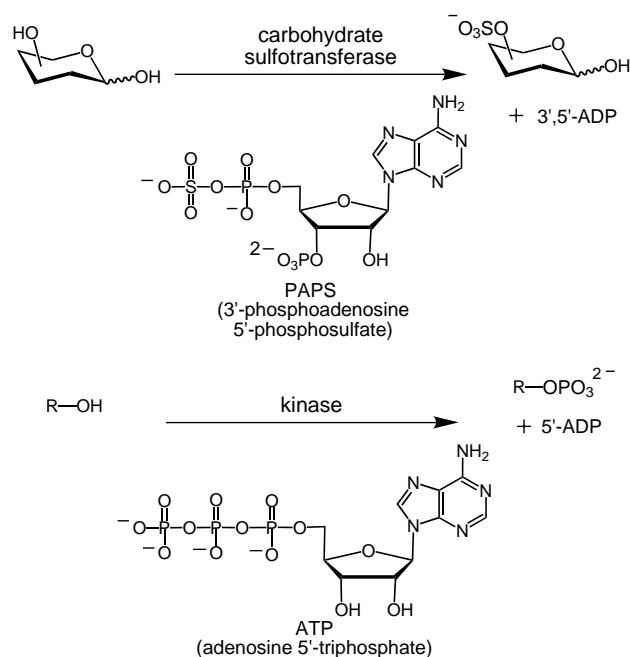
## Discovery of Carbohydrate Sulfotransferase Inhibitors from a Kinase-Directed Library\*\*

Joshua I. Armstrong, Adam R. Portley, Young-Tae Chang, David M. Nierengarten, Brian N. Cook, Kendra G. Bowman, Anthony Bishop, Nathanael S. Gray, Kevan M. Shokat, Peter G. Schultz, and Carolyn R. Bertozzi\*

Carbohydrate sulfotransferases have recently emerged as an important and relatively unexplored class of therapeutic targets.<sup>[1]</sup> For example, the seminal discovery that sulfated sialyl Lewis<sup>x</sup> mediates the adhesion of leukocytes to inflamed

endothelium established carbohydrate sulfotransferases as potential targets for anti-inflammatory therapy.<sup>[2]</sup> Ongoing genome sequencing projects have uncovered numerous carbohydrate sulfotransferase genes in the past few years.<sup>[1, 3]</sup> It is now apparent that carbohydrate sulfotransferases comprise a large family of enzymes with overlapping tissue distribution and substrate specificities. To deconvolute the precise role of each sulfotransferase gene product and elucidate its contribution to normal and pathological processes, cell-permeable and highly specific small-molecule antagonists need to be identified. Surprisingly, no inhibitor of a carbohydrate sulfotransferase has been reported to date. At present, the limited structural and mechanistic information about this class of enzymes impedes rational approaches to inhibitor design. To identify lead inhibitors of carbohydrate sulfotransferases, we therefore adopted a strategy that involved the screening of small-molecule libraries.

To narrow our search, we focused on the similarities between the substrates utilized by sulfotransferases and kinases, a widely studied family of enzymes for which diverse and potent inhibitors are available.<sup>[4]</sup> Carbohydrate sulfotransferases catalyze the transfer of a sulfonyl group from the universal sulfate donor 3'-phosphoadenosine 5'-phosphosulfate (PAPS) to a hydroxy (or amino) group of the acceptor oligosaccharide (Scheme 1).



Scheme 1. Reactions catalyzed by carbohydrate sulfotransferases and kinases.

Kinases catalyze a similar anionic group transfer reaction using adenosine 5'-triphosphate (ATP) as a phosphoryl donor. Thus, both enzyme classes recognize adenosine-based substrates, PAPS and ATP. Furthermore, the hydrophobic adenine binding pockets of the recently crystallized estrogen sulfotransferase,<sup>[5]</sup> and heparin N-sulfotransferase<sup>[6]</sup> are similar to those of several kinases. On the basis of these parallels, we chose to screen a panel of previously reported kinase-

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