

c-diGMP in Bacterial Signalling:

Research Tools for Use in Bacterial Signal Transduction and Biofilm Formation

The cyclic dinucleotide c-diGMP is an essential signalling molecule in bacteria

c-diGMP (aka cyclic diguanylate or cyclic bis(3'→5')diguanylic acid) was first described in the 1980s as a modulator of cellulose synthesis in the fruit-degrading bacterium *Gluconacetobacter xylinus*. Subsequently, the c-diGMP-metabolizing enzymes were identified to be diguanylate cyclases carrying GGDEF domains and specific phosphodiesterases that carry EAL or HD-GYP domains. EAL and HD-GYP domain proteins linearize c-diGMP to pGpG, which is then further degraded to 5'-GMP (Fig. 1).

Another second messenger candidate in bacteria was recently discovered: **c-diAMP** (Fig. 2) is considered to be a messenger molecule that signals DNA integrity in *Bacillus subtilis* during sporulation. A *Bacillus subtilis* protein exhibiting phosphodiesterase activity towards c-diAMP and generating the linear pApA has also been described. However, the occurrence of c-diAMP in bacteria, the mechanisms controlling its production and breakdown, as well as its role in bacterial signalling remain to be discovered.

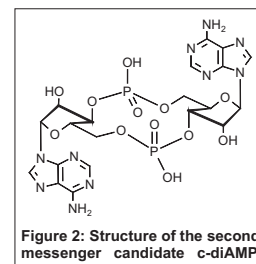


Figure 2: Structure of the second messenger candidate c-diAMP.

BIOLOG Life Science Institute is the exclusive source for the cyclic dinucleotides c-diGMP and c-diAMP and their metabolites. An expanding product line of chemically modified c-diGMP and c-diAMP analogues for research of bacterial signalling mechanisms is also available.

Selected References: Ross et al., *Nature*, **325**, 279 - 281 (1987): "Regulation of Cellulose Synthesis in *Acetobacter xylinum* by Cyclic Diguanylic acid" • Römmling et al., *Mol. Microbiol.*, **57**, 629 - 639 (2005): "C-di-GMP: the Dawning of a Novel Bacterial Signalling System" • Jenal & Malone, *Annu. Rev. Genet.*, **40**, 385 - 407 (2006): "Mechanisms of Cyclic-di-GMP Signaling in Bacteria" • Karaolis et al., *J. Immunol.*, **178**, 2171 - 2181 (2007): "Bacterial c-di-GMP is an Immunostimulatory Molecule" • Witte et al., *Mol. Cell*, **30**, 167 - 178 (2008): "Structural Biochemistry of a Bacterial Checkpoint Protein Reveals Diadenylate Cyclase Activity Regulated by DNA Recombination Intermediates" • Hengge, R., *Nat. Rev. Microbiol.*, **7**, 263 - 273 (2009): "Principles of c-di-GMP Signalling in Bacteria" • Jonas et al., *Future Microbiol.*, **4**, 341 - 358 (2009): "Regulation of c-di-GMP Metabolism in Biofilms" • Rao et al., *J. Biol. Chem.*, **285**, 473 - 482 (2010): "YybT is a Signaling Protein that Contains a Cyclic Dinucleotide Phosphodiesterase Domain and a GGDEF Domain with ATPase Activity"

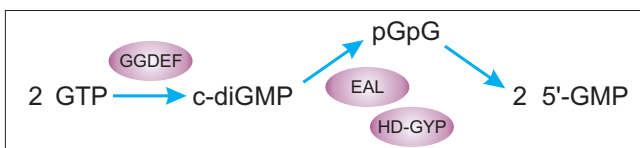


Figure 1: Metabolism of c-diGMP. GGDEF domain proteins (diguanylate cyclases) produce c-diGMP from two molecules of GTP. EAL and HD-GYP domain proteins (c-diGMP-specific phosphodiesterases) linearize c-diGMP to pGpG, which is then further degraded to two 5'-GMP molecules.

Based on the near ubiquitous presence of the GGDEF and EAL domains in bacteria, c-diGMP is currently believed to be a universal bacterial second messenger involved in the regulation of many complex and diverse physiological processes including bacterial motility, adhesion, cell-to-cell communication (quorum sensing) and exopolysaccharide synthesis. It was also found to exhibit immunostimulatory action in mice and to play a role in virulence and in the formation of biofilms, thus identifying the c-diGMP signalling network to be an important target in medical research and health care. However, many aspects of the complex c-diGMP signalling system such as the integration of external signals are not yet fully understood and need to be further investigated.

c-diGMP / Metabolite of c-diGMP

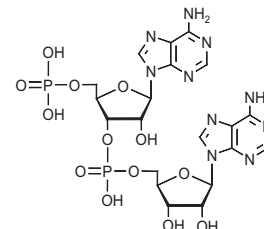
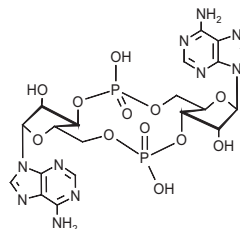
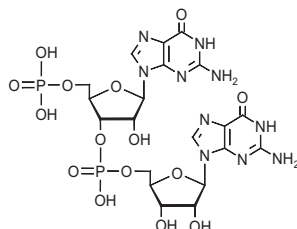
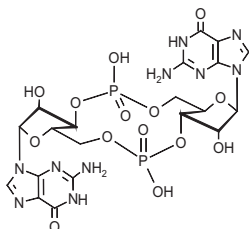
c-diGMP is a near ubiquitous bacterial second messenger that was found to be involved in a wide variety of physiological processes in bacteria.

pGpG is the first physiological metabolic degradation product of the bacterial signalling nucleotide c-diGMP.

c-diAMP / Metabolite of c-diAMP

c-diAMP is considered to be an additional purine-based signalling nucleotide in prokaryotes.

pApA is a potential metabolic degradation product of the second messenger candidate c-diAMP.



c-diGMP

C 057-01, 1 µmol/~0.7 mg
C 057-05, 5 x 1 µmol

pGpG

P 023-001, 0.1 µmol/~71 µg
P 023-005, 5 x 0.1 µmol

c-diAMP

C 088-001, 0.1 µmol/~66 µg
C 088-005, 5 x 0.1 µmol

pApA

P 033-001, 0.1 µmol/~68 µg
P 033-005, 5 x 0.1 µmol

See back page for analogues of c-diGMP and c-diAMP.

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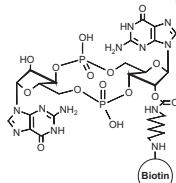
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c-diGMP in Bacterial Signalling:

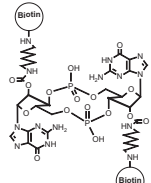
Research Tools for Use in Bacterial Signal Transduction and Biofilm Formation

Biotinylated Analogues of c-diGMP

Biotin connected to one of the two ribose 2'-hydroxy groups in c-diGMP via a 16 atom spacer.



Biotin connected to both ribose 2'-hydroxy groups in c-diGMP via 16 atom spacers.



2'-[Biotin]-AHC-c-diGMP

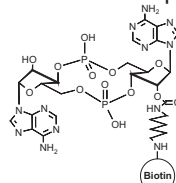
B 098-001, 0.1 µmol/~0.1 mg
B 098-005, 5 x 0.1 µmol

2',2''-Di-[Biotin]-AHC-c-diGMP

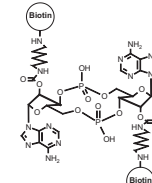
D 111-001, 0.1 µmol/~0.2 mg
D 111-005, 5 x 0.1 µmol

Biotinylated Analogues of c-diAMP

Biotin connected to one of the two ribose 2'-hydroxy groups in c-diAMP via a 16 atom spacer.



Biotin connected to both ribose 2'-hydroxy groups in c-diAMP via 16 atom spacers.



2'-[Biotin]-AHC-c-diAMP

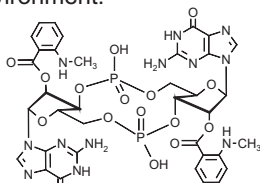
B 106-001, 0.1 µmol/~0.1 mg
B 106-005, 5 x 0.1 µmol

2',2''-Di-[Biotin]-AHC-c-diAMP

D 122-001, 0.1 µmol/~0.2 mg
D 122-005, 5 x 0.1 µmol

Fluorescent Analogues of c-diGMP and c-diAMP

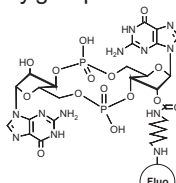
The MANT fluorophore (λ_{exc} 355 nm, λ_{em} 448 nm) is sensitive to its environment.



Di-MANT-c-diGMP

D 101-001, 0.1 µmol/~0.1 mg
D 101-005, 5 x 0.1 µmol

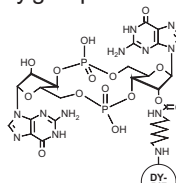
Fluorescein (λ_{exc} 494 nm, λ_{em} 517 nm) connected to one of the two 2'-hydroxy groups in c-diGMP.



2'-Fluo-AHC-c-diGMP

F 009-001, 0.1 µmol/~0.1 mg
F 009-005, 5 x 0.1 µmol

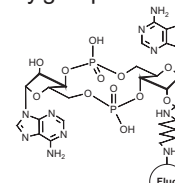
DY-547 (λ_{exc} 557 nm, λ_{em} 574 nm) connected to one of the two 2'-hydroxy groups in c-diGMP.



2'-[DY-547]-AHC-c-diGMP

D 116 Please inquire!

Fluorescein (λ_{exc} 494 nm, λ_{em} 517 nm) connected to one of the two 2'-hydroxy groups in c-diAMP.

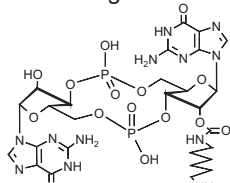


2'-Fluo-AHC-c-diAMP

F 011-001, 0.1 µmol/~0.1 mg
F 011-005, 5 x 0.1 µmol

c-diGMP-based Ligands

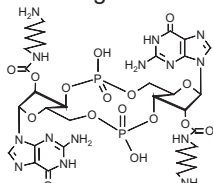
Suitable as a ligand in affinity chromatography or for coupling of various labelling structures.



2'-AHC-c-diGMP

A 151-001, 0.1 µmol/~83 µg
A 151-005, 5 x 0.1 µmol

Suitable as a ligand in affinity chromatography or for coupling of various labelling structures.

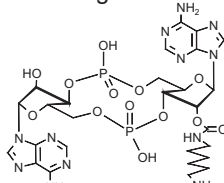


2',2''-Di-AHC-c-diGMP

D 112-001, 0.1 µmol/~97 µg
D 112-005, 5 x 0.1 µmol

c-diAMP-based Ligands

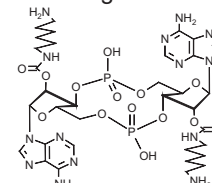
Suitable as a ligand in affinity chromatography or for coupling of various labelling structures.



2'-AHC-c-diAMP

A 182-001, 0.1 µmol/~80 µg
A 182-005, 5 x 0.1 µmol

Suitable as a ligand in affinity chromatography or for coupling of various labelling structures.

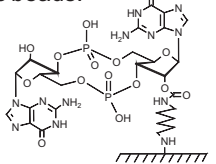


2',2''-Di-AHC-c-diAMP

D 121-001, 0.1 µmol/~94 µg
D 121-005, 5 x 0.1 µmol

Affinity Gels

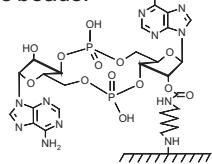
c-diGMP immobilized on agarose gel. Available in pre-packed columns or as free beads.



2'-AHC-c-diGMP-Agarose

A 153-06, 0.6 mL
A 153-25, 2.5 mL
A 153-60, 6 mL

c-diAMP immobilized on agarose gel. Available in pre-packed columns or as free beads.

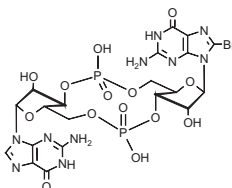


2'-AHC-c-diAMP-Agarose

A 183-06, 0.6 mL
A 183-25, 2.5 mL
A 183-60, 6 mL

Brominated Analogues of c-diGMP

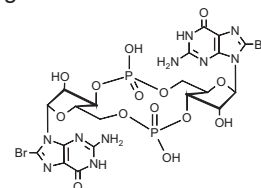
c-diGMP brominated in position 8 of one of the two guanine nucleobases.



8-Br-c-diGMP

B 099 Please inquire!

c-diGMP brominated in the 8-positions of both guanine nucleobases.

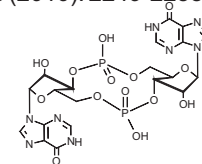


8,8'-Di-Br-c-diGMP

D 113 Please inquire!

c-diIMP

Potential adjuvant for mucosal vaccination (Libanova et al., *Vaccine*, 28 (2010): 2249-2258).



c-diIMP

C 105 Please inquire!

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