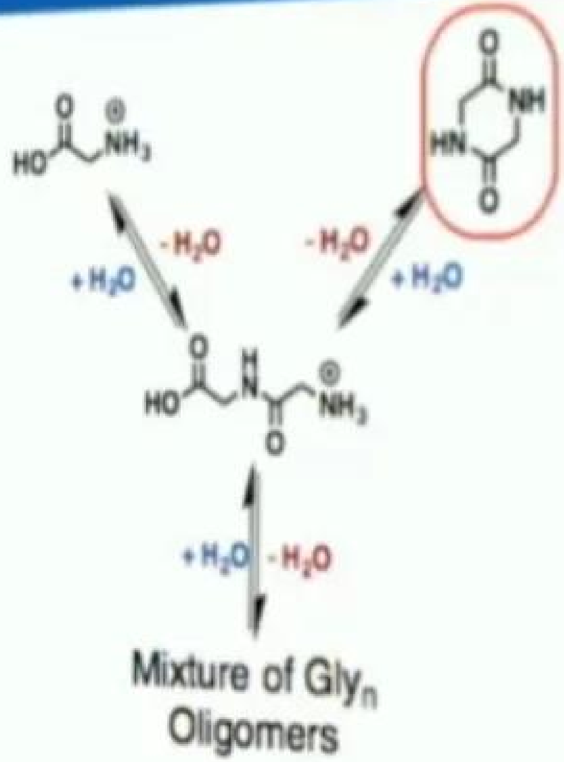
Cyclic Dimers



- In prebiotic conditions, we must consider cyclic dipeptides
- Linear dimers cyclize readily in water
- Their role is subject to some debate
- Typical cGG:GG ratio of 10:1 or 20:1

Danger *et al*, Chem. Soc. Rev., **2012**, 41, 5416–5429.

1
00:00:11,270 --> 00:00:08,450
yeah so for those of you I haven't met

2
00:00:14,089 --> 00:00:11,280
yet my name is Thomas Campbell come from

3
00:00:16,550 --> 00:00:14,099
st. Louis University and I'm in Paul

4
00:00:19,029 --> 00:00:16,560
Brockers lab he's a new assistant

5
00:00:21,769 --> 00:00:19,039
professor so this is kind of the first

6
00:00:24,259 --> 00:00:21,779
let's say coherent story that we have to

7
00:00:27,080 --> 00:00:24,269
talk about and so I'm excited to share

8
00:00:29,599 --> 00:00:27,090
that with you guys and we're interested

9
00:00:32,600 --> 00:00:29,609
in fundamental questions that have been

10
00:00:35,270 --> 00:00:32,610
around for a long long time back in

11
00:00:38,270 --> 00:00:35,280
biblical times matthew was pondering if

12
00:00:41,479 --> 00:00:38,280
salt loses its saltiness how can we make

13
00:00:43,610 --> 00:00:41,489

it salty again and even today on the

14
00:00:47,869 --> 00:00:43,620
Today Show we're still asking questions

15
00:00:49,069 --> 00:00:47,879
of salt and thankfully these questions

16
00:00:52,010 --> 00:00:49,079
have almost nothing to do with my

17
00:00:56,510 --> 00:00:52,020
research but at least I got your

18
00:00:59,569 --> 00:00:56,520
attention so we are interested in salt

19
00:01:01,099 --> 00:00:59,579
though specifically salts of sodium and

20
00:01:03,020 --> 00:01:01,109
potassium and the reason we're

21
00:01:05,810 --> 00:01:03,030
interested in these salts is because we

22
00:01:09,260 --> 00:01:05,820
see a universal enrichment of potassium

23
00:01:11,390 --> 00:01:09,270
across all of modern biology so all

24
00:01:14,300 --> 00:01:11,400
cells today spend a tremendous amount of

25
00:01:18,160 --> 00:01:14,310
energy enriching potassium and expelling

26
00:01:20,990 --> 00:01:18,170
sodium and we won't understand why these

27
00:01:23,600 --> 00:01:21,000
selective gradients are universally

28
00:01:25,760 --> 00:01:23,610
conserved we work under the assumption

29
00:01:28,249 --> 00:01:25,770
that something that's ubiquitous like

30
00:01:30,100 --> 00:01:28,259
this developed early on is conserved

31
00:01:34,819 --> 00:01:30,110
throughout evolution because it's

32
00:01:36,380 --> 00:01:34,829
important and it's probably fundamental

33
00:01:38,870 --> 00:01:36,390
in nature which is what leads us to

34
00:01:41,060 --> 00:01:38,880
prebiotic chemistry so we want to

35
00:01:43,999 --> 00:01:41,070
understand how do these ions impact

36
00:01:45,679 --> 00:01:44,009
reactions their relative relevant to

37
00:01:47,780 --> 00:01:45,689
prebiotic chemistry and we want to start

38
00:01:50,690 --> 00:01:47,790

with the simplest systems we can pretty

39
00:01:52,130 --> 00:01:50,700
much possibly imagine so that brings us

40
00:01:55,060 --> 00:01:52,140
the peptides we've talked a little bit

41
00:01:58,670 --> 00:01:55,070
about peptides over the past couple days

42
00:02:01,130 --> 00:01:58,680
but why why peptides first their obvious

43
00:02:03,289 --> 00:02:01,140
prebiotic relevance second their

44
00:02:05,600 --> 00:02:03,299
relatively well understood by that I

45
00:02:07,850 --> 00:02:05,610
mean we have a lot of information to go

46
00:02:09,680 --> 00:02:07,860
off of they've been studied for a long

47
00:02:12,990 --> 00:02:09,690
time both in the context of prebiotic

48
00:02:15,150 --> 00:02:13,000
chemistry and other context

49
00:02:17,240 --> 00:02:15,160
and why hydrolysis so this is something

50
00:02:20,310 --> 00:02:17,250
that Becky just touched on a little bit

51
00:02:22,320 --> 00:02:20,320
obviously the goal is to drive

52
00:02:25,650 --> 00:02:22,330
condensation that's that's what we need

53
00:02:27,870 --> 00:02:25,660
to build complexity but these reactions

54
00:02:30,449 --> 00:02:27,880
are in competition and in order to

55
00:02:32,580 --> 00:02:30,459
understand the more messy condensation

56
00:02:33,720 --> 00:02:32,590
we first want to understand hydrolysis

57
00:02:36,180 --> 00:02:33,730
because that's going to be going on in

58
00:02:38,490 --> 00:02:36,190
the background all the time and again

59
00:02:40,440 --> 00:02:38,500
it's simpler we have one reactant one

60
00:02:44,280 --> 00:02:40,450
product in the case of a homodimer at

61
00:02:47,070 --> 00:02:44,290
least and so I'll highlight again the

62
00:02:48,810 --> 00:02:47,080
emphasis on fundamental reactions so

63
00:02:52,949 --> 00:02:48,820

hopefully we can just understand the

64
00:02:54,810 --> 00:02:52,959
basics first and then then apply what we

65
00:02:59,280 --> 00:02:54,820
observe to kind of messy your systems

66
00:03:02,040 --> 00:02:59,290
down the line okay that got pretty

67
00:03:04,290 --> 00:03:02,050
blurry but this is just a couple notes

68
00:03:07,830 --> 00:03:04,300
on our methods we are doing the

69
00:03:11,340 --> 00:03:07,840
hydrolysis of dipeptides we do

70
00:03:13,920 --> 00:03:11,350
everything with NMR so it pretty simple

71
00:03:15,630 --> 00:03:13,930
just measure the integration of the

72
00:03:18,509 --> 00:03:15,640
peaks of the reactants and the products

73
00:03:20,729 --> 00:03:18,519
over time get the rate constant but what

74
00:03:24,600 --> 00:03:20,739
I wanted to point out is that you can't

75
00:03:27,660 --> 00:03:24,610
see it but we have one more HCL that's

76
00:03:30,800 --> 00:03:27,670
key because the half life of a peptide

77
00:03:33,930 --> 00:03:30,810
bond neutral pH is painstakingly slow

78
00:03:36,690 --> 00:03:33,940
and I want to graduate eventually so we

79
00:03:38,430 --> 00:03:36,700
use an acid catalysts and we have an

80
00:03:41,250 --> 00:03:38,440
excess of acid which is important

81
00:03:42,900 --> 00:03:41,260
because then we observe a pseudo

82
00:03:44,220 --> 00:03:42,910
first-order reaction kinetics so kind of

83
00:03:49,160 --> 00:03:44,230
simplifies things they're a little bit

84
00:03:53,100 --> 00:03:49,170
also so when we do this experiment for

85
00:03:55,170 --> 00:03:53,110
we did for dipeptides all the all the

86
00:03:59,039 --> 00:03:55,180
possible combinations of glycine and

87
00:04:01,020 --> 00:03:59,049
alanine so glug lie gly ala ala gly and

88
00:04:04,199 --> 00:04:01,030

then ala ala so these are the two most

89
00:04:05,759 --> 00:04:04,209
simple amino acids the most prebiotic ly

90
00:04:08,490 --> 00:04:05,769
abundant amino acids that they're kind

91
00:04:10,860 --> 00:04:08,500
of the obvious choice there and when we

92
00:04:13,080 --> 00:04:10,870
measure this in the presence of sodium

93
00:04:15,960 --> 00:04:13,090
chloride and potassium chloride in every

94
00:04:19,530 --> 00:04:15,970
case the hydrolysis proceeds faster in

95
00:04:22,320 --> 00:04:19,540
the presence of sodium and slightly

96
00:04:25,640 --> 00:04:22,330
slower in the presence of potassium so

97
00:04:28,400 --> 00:04:25,650
this was cool we're excited about that

98
00:04:31,219 --> 00:04:28,410
and you know it's it's definitely

99
00:04:33,860 --> 00:04:31,229
interesting but it gets a little bit

100
00:04:36,080 --> 00:04:33,870
more interesting and that's we got to

101
00:04:39,200 --> 00:04:36,090
talk about cyclic dimers now so whenever

102
00:04:40,520 --> 00:04:39,210
we talk about peptides in the context of

103
00:04:44,450 --> 00:04:40,530
prebiotic chemistry we have to also

104
00:04:47,830 --> 00:04:44,460
consider cyclic dimers because this is

105
00:04:50,749 --> 00:04:47,840
the reactions general reaction scheme of

106
00:04:55,640 --> 00:04:50,759
prebiotic long-chain polypeptide

107
00:04:59,060 --> 00:04:55,650
synthesis the linear dimer will readily

108
00:05:01,010 --> 00:04:59,070
cycle eyes and you get the cyclic dimer

109
00:05:03,469 --> 00:05:01,020
here there's a little bit of debate

110
00:05:05,480 --> 00:05:03,479
about what the role of this is in this

111
00:05:09,590 --> 00:05:05,490
schematic but suffice it to say that

112
00:05:11,570 --> 00:05:09,600
generally researchers will consider the

113
00:05:13,070 --> 00:05:11,580

cyclic dimer to be a problem for

114
00:05:18,620 --> 00:05:13,080
prebiotic synthesis of long-chain

115
00:05:21,800 --> 00:05:18,630
polypeptides within in like a miller

116
00:05:23,749 --> 00:05:21,810
type experiment you see typical ratios

117
00:05:28,040 --> 00:05:23,759
of the cyclic dimer to the linear dimer

118
00:05:30,260 --> 00:05:28,050
somewhere between 10 to 12 20 21 ok so

119
00:05:33,830 --> 00:05:30,270
we wanted to then measure the hydrolysis

120
00:05:36,159 --> 00:05:33,840
of this cyclic dimer basically doing the

121
00:05:39,710 --> 00:05:36,169
same experiment again so we did that and

122
00:05:41,839 --> 00:05:39,720
remarkably we found the exact opposite

123
00:05:44,570 --> 00:05:41,849
trend of what we what we saw before so

124
00:05:48,140 --> 00:05:44,580
in this case all the possible

125
00:05:52,760 --> 00:05:48,150
combinations of glycine alanine all

126
00:05:54,529 --> 00:05:52,770
three of them and in each case they

127
00:05:57,370 --> 00:05:54,539
hydrolyze faster in the presence of

128
00:06:00,409 --> 00:05:57,380
potassium than in the presence of sodium

129
00:06:02,390 --> 00:06:00,419
and this I mean when admittedly when I

130
00:06:05,750 --> 00:06:02,400
first did this experiment I was like a

131
00:06:07,730 --> 00:06:05,760
kind of upset that you know it didn't go

132
00:06:09,350 --> 00:06:07,740
right but then it's actually pretty

133
00:06:13,670 --> 00:06:09,360
interesting for for a number of reasons

134
00:06:17,270 --> 00:06:13,680
so if we look over here this is

135
00:06:19,670 --> 00:06:17,280
basically we're just comparing the rates

136
00:06:21,950 --> 00:06:19,680
of sodium sodium and potassium so

137
00:06:24,080 --> 00:06:21,960
anything that goes up hydrolyzes faster

138
00:06:27,439 --> 00:06:24,090

in sodium anything that goes down

139
00:06:30,610 --> 00:06:27,449
hydrolyzes faster and potassium so if we

140
00:06:32,870 --> 00:06:30,620
this is kind of a cartoon model of the

141
00:06:36,140 --> 00:06:32,880
reaction scheme I just showed you but if

142
00:06:37,909 --> 00:06:36,150
we're in a potassium rich environment

143
00:06:38,850 --> 00:06:37,919
then relative to a sodium rich

144
00:06:41,520 --> 00:06:38,860
environment you're going to have

145
00:06:43,939 --> 00:06:41,530
higher proportion of the linear dimer

146
00:06:48,719 --> 00:06:43,949
which then can go on to react to form

147
00:06:51,510 --> 00:06:48,729
longer chain polypeptides and so this

148
00:06:54,290 --> 00:06:51,520
these results kind of raise the the

149
00:06:58,260 --> 00:06:54,300
possibility emphasize possibility that

150
00:07:01,080 --> 00:06:58,270
life may have needed potassium rich

151
00:07:04,080 --> 00:07:01,090
environments to optimize these kinetics

152
00:07:07,140 --> 00:07:04,090
because although admittedly their modest

153
00:07:10,559 --> 00:07:07,150
changes in kinetics you know given

154
00:07:13,260 --> 00:07:10,569
millions of years a small change good

155
00:07:18,209 --> 00:07:13,270
could kind of be what's needed to tip

156
00:07:21,050 --> 00:07:18,219
the kinetic scales let's say so also i

157
00:07:24,360 --> 00:07:21,060
call it the flip so the the flip in the

158
00:07:27,089 --> 00:07:24,370
relative rates it's useful for a number

159
00:07:29,010 --> 00:07:27,099
of reasons one it rules out the effect

160
00:07:31,110 --> 00:07:29,020
of cations on the structure and

161
00:07:33,659 --> 00:07:31,120
reactivity of water this was our initial

162
00:07:36,689 --> 00:07:33,669
hypothesis that there would be some

163
00:07:40,110 --> 00:07:36,699

difference like for example the activity

164
00:07:41,519 --> 00:07:40,120
of water of a sodium chloride solution

165
00:07:43,950 --> 00:07:41,529
is different than a potassium chloride

166
00:07:45,480 --> 00:07:43,960
solution and that's pretty reasonable we

167
00:07:49,769 --> 00:07:45,490
would think that would expect that would

168
00:07:51,329 --> 00:07:49,779
impact the rate of hydrolysis since the

169
00:07:53,820 --> 00:07:51,339
rate determining step of hydrolysis

170
00:07:55,170 --> 00:07:53,830
involves attack of water so if you lower

171
00:07:58,279 --> 00:07:55,180
the activity of water you should lower

172
00:08:00,899 --> 00:07:58,289
the rate of hydrolysis but if that were

173
00:08:03,089 --> 00:08:00,909
simply the only effect in play then that

174
00:08:04,529 --> 00:08:03,099
would be the case across the board

175
00:08:07,679 --> 00:08:04,539
regardless of which substrate you're

176
00:08:10,769 --> 00:08:07,689
looking at it also rules out any sort of

177
00:08:13,769 --> 00:08:10,779
systematic errors from reagents or our

178
00:08:16,170 --> 00:08:13,779
methods if we're say we're weighing out

179
00:08:18,149 --> 00:08:16,180
a lot of we have a lot of water in our

180
00:08:19,439 --> 00:08:18,159
potassium chloride and so we're not

181
00:08:20,959 --> 00:08:19,449
actually putting as much potassium

182
00:08:24,570 --> 00:08:20,969
chloride in there as we think we are

183
00:08:28,010 --> 00:08:24,580
then that would again present itself as

184
00:08:31,079 --> 00:08:28,020
the same change across all substrates

185
00:08:34,889 --> 00:08:31,089
what it does do is necessitate a direct

186
00:08:38,490 --> 00:08:34,899
role between the ions and the substrates

187
00:08:40,610 --> 00:08:38,500
themselves in the mechanism which a you

188
00:08:42,449 --> 00:08:40,620

know beyond the origin of the

189
00:08:44,159 --> 00:08:42,459
application to the origin of life I

190
00:08:47,579 --> 00:08:44,169
think this is a super interesting

191
00:08:49,559 --> 00:08:47,589
observation because if you ask an

192
00:08:52,380 --> 00:08:49,569
organic chemist that to draw the

193
00:08:54,720 --> 00:08:52,390
mechanism for pepto

194
00:08:58,280 --> 00:08:54,730
hydrolysis even in a sodium chloride

195
00:09:02,460 --> 00:08:58,290
solution not I don't think anyone would

196
00:09:05,090 --> 00:09:02,470
enlist the ions in in that mechanism so

197
00:09:08,520 --> 00:09:05,100
but these results suggest that we should

198
00:09:11,430 --> 00:09:08,530
so the next step for us is how can we

199
00:09:14,340 --> 00:09:11,440
probe that interaction we've we've done

200
00:09:15,630 --> 00:09:14,350
some work to try to do that but so far

201
00:09:17,370 --> 00:09:15,640
all of our studies have been

202
00:09:19,950 --> 00:09:17,380
inconclusive there so i won't i won't

203
00:09:22,500 --> 00:09:19,960
talk more about that but if you have any

204
00:09:26,240 --> 00:09:22,510
ideas about this I'd be happy to hear

205
00:09:29,070 --> 00:09:26,250
them so lastly not to be outdone by

206
00:09:31,560 --> 00:09:29,080
everybody who has these amazing you know

207
00:09:33,390 --> 00:09:31,570
field sites all over the world this is a

208
00:09:39,150 --> 00:09:33,400
picture of the Mississippi River that I

209
00:09:43,950 --> 00:09:39,160
took from just outside my lab it's it's

210
00:09:44,940 --> 00:09:43,960
a really nice place so lastly I just

211
00:09:47,190 --> 00:09:44,950
like to acknowledge my group

212
00:09:49,740 --> 00:09:47,200
specifically Annie and Mark are two

213
00:09:53,100 --> 00:09:49,750

really awesome undergrad surprisingly

214
00:09:54,720 --> 00:09:53,110
great undergrads Rio and Matt are the

215
00:09:57,140 --> 00:09:54,730
other two grad students in the lab they

216
00:09:59,820 --> 00:09:57,150
work on some other stuff and then

217
00:10:17,820 --> 00:09:59,830
funding sources so yeah that'll take

218
00:10:19,560 --> 00:10:17,830
questions thank you hi I for your rate

219
00:10:22,110 --> 00:10:19,570
of cyclization versus the rate of

220
00:10:25,080 --> 00:10:22,120
hydrolysis are they competitive or I

221
00:10:28,430 --> 00:10:25,090
couldn't see so we don't measure the

222
00:10:33,030 --> 00:10:28,440
rate of cyclization that's been done

223
00:10:36,300 --> 00:10:33,040
it's I can't recall the exact rate I

224
00:10:38,070 --> 00:10:36,310
mean it when we have a one more HCL it's

225
00:10:41,820 --> 00:10:38,080
not cycle izing you know it's only

226
00:10:43,530 --> 00:10:41,830
hydrolyzing for the most part does that

227
00:10:45,090 --> 00:10:43,540
answer your question yeah and my other

228
00:10:47,490 --> 00:10:45,100
question is it's safer like it was a

229
00:10:49,740 --> 00:10:47,500
kinetic rate you know if you have a

230
00:10:51,720 --> 00:10:49,750
equilibrium where like the hydrolysis is

231
00:10:54,840 --> 00:10:51,730
faster than the cyclization what about

232
00:10:57,600 --> 00:10:54,850
the do you know the rate of going from

233
00:11:02,580 --> 00:10:57,610
years linear chain to the polypeptides

234
00:11:03,930 --> 00:11:02,590
Oren uh I don't know that again in acid

235
00:11:05,730 --> 00:11:03,940
that's not really happening you're not

236
00:11:08,490 --> 00:11:05,740
condensing at all

237
00:11:10,410 --> 00:11:08,500
you know there's a lot of that's there's

238
00:11:11,790 --> 00:11:10,420

a lot of work on peptide condensation in

239
00:11:13,590 --> 00:11:11,800
general we and that's where we're going

240
00:11:17,280 --> 00:11:13,600
to go next is looking at that in the

241
00:11:23,630 --> 00:11:17,290
presence of sodium and potassium does

242
00:11:27,330 --> 00:11:23,640
that answer your question yeah yeah

243
00:11:29,430 --> 00:11:27,340
there is in more mild conditions but

244
00:11:31,080 --> 00:11:29,440
what you know we're trying to drive it

245
00:11:39,210 --> 00:11:31,090
that direction so that we can so we can

246
00:11:41,400 --> 00:11:39,220
measure that specifically all right that