

## Origins of Life

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# Darwin's Warm Little Pond: A One-Pot Reaction for Prebiotic Phosphorylation and the Mobilization of Phosphate from Minerals in a Urea-Based Solvent

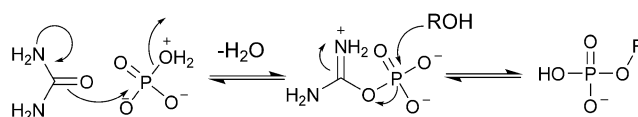
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**Abstract:** The poor reactivity of insoluble phosphates, such as apatite-group minerals, has been a long-appreciated obstacle for proposed models of prebiotic organophosphate formation. This obstacle presents a significant challenge to the nascent development of an RNA world and other models for the origins of life on Earth. Herein, we demonstrate that a scenario based on the formation of a urea/ammonium formate/water (UAFW) eutectic solution leads to an increase in phosphorylation when compared to urea alone for phosphate sources of varying solubility. In addition, under evaporative conditions and in the presence of  $\text{MgSO}_4$ , the UAFW eutectic mobilizes the phosphate sequestered in water-insoluble hydroxyapatite, giving rise to a marked increase in phosphorylation. These results suggest that the prebiotic concentrations of urea in a geologically plausible evaporitic environment could solve the problem of organic phosphorylation on a prebiotic Earth.

The synthesis of the first organophosphates has been a major question in origin of life studies at least as far back as 1871 when Charles Darwin mused about a “warm little pond, with all sorts of ammonia and phosphoric salts,...that a protein compound was chemically formed ready to undergo still more complex changes.”<sup>[1]</sup> This question captivates prebiotic chemists owing to the indispensable role of phosphate in modern biochemistry; a role it attains by ensuring the aqueous solubility of biomolecules, such as DNA and RNA, and by also forming kinetically stable phosphate ester and phosphodiester bonds.<sup>[2]</sup> These properties can be lost when phosphate is replaced with similar, alternate molecules,<sup>[3]</sup> indicating a strong evolutionary pressure for the early incorporation of

phosphate in nucleic acids.<sup>[4]</sup> If organophosphates can be readily formed in “warm little ponds” then these compounds could have been abundant on the prebiotic Earth and played important roles leading to the origins of life. However, owing to the strong affinity of phosphate towards divalent cations, it is assumed that most phosphate would have been sequestered in low-solubility minerals on a prebiotic Earth, rendering it unavailable for use in prebiotic chemical reactions and leading to the phosphate problem for the origin of RNA.<sup>[5]</sup> Additionally, the most plausible routes to phosphorylation of organic molecules are through condensation reactions, reactions that are thermodynamically unfavored in aqueous solutions. Consequently, a fundamental question raised by the phosphate problem is what are the appropriate geochemical settings and mineral assemblages that could lead to the origin of the first organophosphates of prebiotic relevance?

To address the problems associated with the initial entry of phosphate into biochemistry, model prebiotic phosphorylation reactions have been investigated using condensation agents,<sup>[6]</sup> under dry and elevated temperature conditions ( $\geq 85^\circ\text{C}$ ),<sup>[7]</sup> in water-free solvent systems,<sup>[8]</sup> and with reduced phosphorus species.<sup>[9]</sup> Notably, the dry and organic solvent-based reactions have demonstrated significant phosphorylation when soluble phosphate salts are used, or when insoluble apatite is used in the presence of oxalate chelators.<sup>[7e]</sup> Results from these studies have been invaluable for characterizing abiotic phosphorylation reaction pathways, such as the role of reduced pH environments, or the importance of urea as a catalyst for phosphorylation (Scheme 1),<sup>[6,7f,10]</sup> which generates a reaction intermediate similar to the intermediate of carbodiimide crosslinking chemistry.<sup>[11]</sup> However, these reactions do not fully address the question of the origin of phosphate in biochemistry as they are problematic in their use of potentially rare phosphorus species, elevated temperatures, compounds that are insoluble in the presence of divalent cations, and/or solvent systems that are unlikely to have been common under realistic geochemical and environmental conditions on a prebiotic Earth.



**Scheme 1.** Proposed mechanism for urea-catalyzed synthesis of phosphate esters.<sup>[6,7f,10]</sup>

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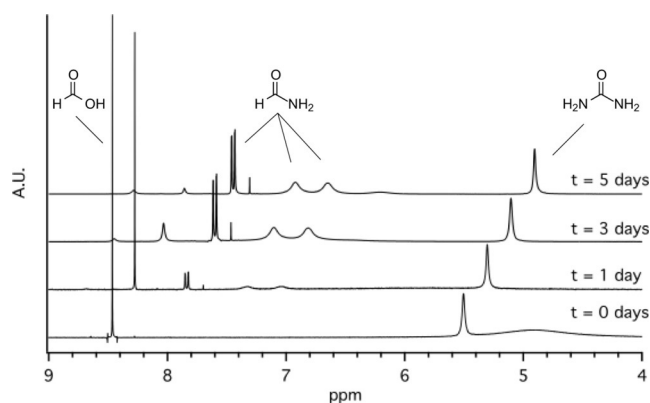
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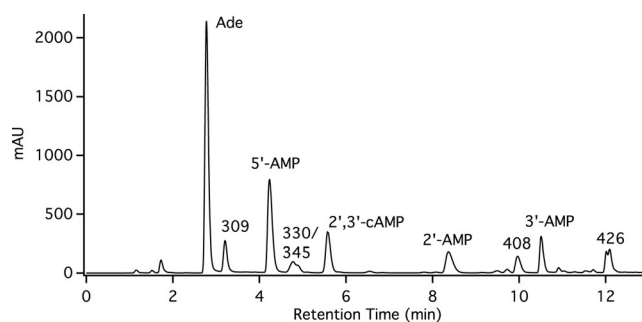
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Eutectic solvents with no water, or low water activity, have recently been shown to exhibit properties that could have facilitated prebiotic RNA synthesis. Specifically, the 3:1 urea:choline chloride eutectic supports Watson–Crick base pairing<sup>[12]</sup> and can serve as a milieu for the phosphorylation of sugars and nucleosides at 60–70 °C.<sup>[8a]</sup> However, the prebiotic relevance of choline eutectics is questionable and phosphorylation is limited by competitive phosphorylation of the choline in the eutectic itself. We therefore decided to investigate the effectiveness of a urea/ammonium formate/water (UAFW) eutectic solvent system (molar ratio of 1:2:4)<sup>[13]</sup> as a milieu for direct phosphorylation from soluble phosphate sources and for the solubilization of secondary phosphate minerals formed by urea-driven remobilization of primary phosphates accumulated in an evaporitic environment. The UAFW eutectic is a prebiotically plausible solvent. Urea is produced in Miller–Urey type reactions,<sup>[14]</sup> when ammonium cyanide is exposed to sunlight,<sup>[15]</sup> and is a hydrolysis product of cyanamide;<sup>[16]</sup> ammonium formate is a hydrolysis product of HCN.<sup>[17]</sup> Upon heating, the UAFW eutectic is partially converted to formamide (Figure 1, Table S1), creating a four-component solvent, and providing a facile pathway for generating this co-solvent of considerable prebiotic interest<sup>[8c, 18]</sup> that has also been shown, by itself, to enhance phosphorylation from mineral sources.<sup>[8b]</sup> This UAFW/formamide solvent system provides a fluidic, low-water environment that can be generated by the moderate heating of urea/ammonium formate solutions of various concentrations. Dilute urea/ammonium formate solutions initially stabilize near the UAFW eutectic point through evaporative loss of water and ammonium formate, or precipitative loss of urea, ensuring a consistent starting concentration of components regardless of their initial abundances (Table S2).

To investigate organophosphate synthesis in the UAFW eutectic, adenosine was mixed separately with Na<sub>2</sub>HPO<sub>4</sub> and hydroxyapatite Ca(PO<sub>4</sub>)<sub>3</sub>OH (believed to be one of the most common Hadean phosphate minerals)<sup>[19]</sup> in the eutectic and heated, open, for multiple days at 65 or 85 °C. Efficient phosphorylation was observed for this reaction with Na<sub>2</sub>HPO<sub>4</sub> at both temperatures, yielding a diverse collection of phosphorylated species (Figure 2), and for all of the canonical ribonucleotides (Table S3). These products, when compared to dry-down reactions with water and urea instead of the UAFW eutectic, show an increase in total phosphorylation at both temperatures, with a marked increase in phosphorylation for all of the characterized species that were observed at 65 °C (Table 1, Figure S1). Upon extended heating, a transition from noncyclic to cyclic nucleotides was observed (Tables S4 and S5), and oligomers with masses corresponding to dimers and trimers are detected (Figure S2). Phosphoryla-



**Figure 1.** <sup>1</sup>H-NMR spectra of UAFW eutectic heated, open, at 85 °C as a function of time. The appearance of formamide in UAFW is observed beginning at 1 day after the preparation of the solvent. Sequential spectra are offset by 0.2 ppm. Spectra are normalized to the intensity of the urea resonances at 5.5 ppm.

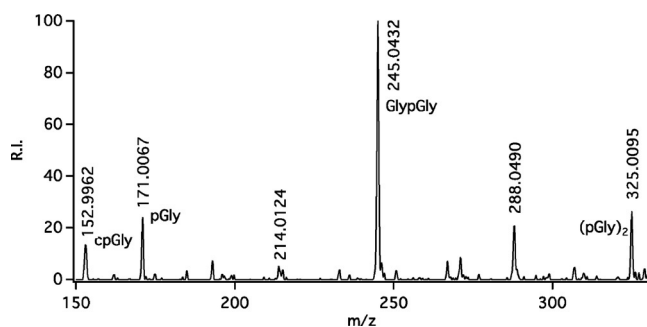


**Figure 2.** HPLC-MS chromatogram of a representative adenosine phosphorylation reaction carried out in the UAFW eutectic at 85 °C for 5 days with Na<sub>2</sub>HPO<sub>4</sub> as the phosphate source. Masses and presumptive compounds for uncharacterized species: 309, adenosine-formamide; 330/345, 5'-amidophosphate adenosine; 408, monophosphorylated 2',3'-cAMP; 426, mixed diphosphates of adenosine.

**Table 1:** Phosphorylation (%adenine by HPLC) in urea solution vs. UAFW.

Temp. [°C]	Solvent	P-Source	5'-AMP [%]	2',3'-cAMP [%]	T-Org-PO <sub>4</sub> [%] <sup>[c]</sup>
65 <sup>[a]</sup>	water/urea	Na <sub>2</sub> HPO <sub>4</sub>	3.7		6.9
	UAFW	Na <sub>2</sub> HPO <sub>4</sub>	21.7	9.4	58
	water/urea	hydroxyapatite			N.D.
	UAFW	hydroxyapatite			N.D.
85 <sup>[b]</sup>	water/urea	Na <sub>2</sub> HPO <sub>4</sub>	14.5	6.2	27
	UAFW	Na <sub>2</sub> HPO <sub>4</sub>	14.4	4.8	34
	water/urea	hydroxyapatite			N.D.
	UAFW	hydroxyapatite	2.9	0.8	4.0

[a] 19 days. [b] 5 days. [c] Total organic phosphate. N.D.: None Detected.



**Figure 3.** Negative mode ESI-MS spectrum of a glycerol (Gly) phosphorylation (p) reaction carried out in the UAFW eutectic with  $\text{Na}_2\text{HPO}_4$  after 22 days. cpGly, cyclic glycerol monophosphate; pGly, glycerol monophosphate; GlypGly, diglycerol monophosphate; (pGly)<sub>2</sub>, diglycerol diphosphate. Additional peaks are the major side products resulting from carbamylation of glycerol phosphates (Figure S3).

tion with dimerization is also observed for glycerol under identical conditions (Figure 3). Both the phosphorylation and oligomerization of nucleosides is consistent with reported higher temperature, urea-catalyzed results,<sup>[7d]</sup> but with the current reactions taking place at lower temperatures than these previous reports. Control experiments run without urea showed no detectable phosphorylation at either temperature, for any solvent composition, or any phosphate source.

Following these experiments, the impact of the UAFW eutectic on insoluble mineral phosphate sources was explored. Emulating conditions similar to those used for the phosphorylation reactions, an increase in solubilization was observed for representative phosphate minerals (Table S6). Correlating with their observed solubility in water, an impact on phosphorylation efficacy is also observed for different synthetic mineral phosphate sources in the UAFW eutectic (Table 2, Figure S4). These results are indicative of phosphorylation in the UAFW eutectic being primarily limited only by the availability of phosphate in solution.

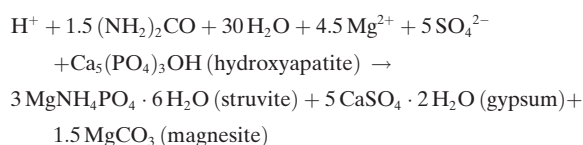
**Table 2:** Phosphorylation (%adenine by HPLC) of adenosine in UAFW at 85 °C with different  $\text{PO}_4$  sources.

P-Source	5'-AMP [%]	2',3'-cAMP [%]	T-Org- $\text{PO}_4$ [%]
$\text{Na}_2\text{HPO}_4$	14.4	4.8	33.8
Struvite	11.2	4.3	25.2
Newberyite	10.4	3.9	23.8
Struvite/Brushite/ Gypsum <sup>[a]</sup>	6.8	2.9	12.8
Processed Hydroxyapatite <sup>[b]</sup>	4.1	1.3	6.9
Hydroxyapatite	2.9	0.8	4.0

[a] Mixture from precipitation by  $\text{H}_3\text{PO}_4$  by equimolar  $\text{CaCl}_2$  and  $\text{MgSO}_4$  in urea solution. [b] Processed by successive additions of  $\text{MgSO}_4$  followed by drying to a suspension of hydroxyapatite in urea solution at 65 °C.

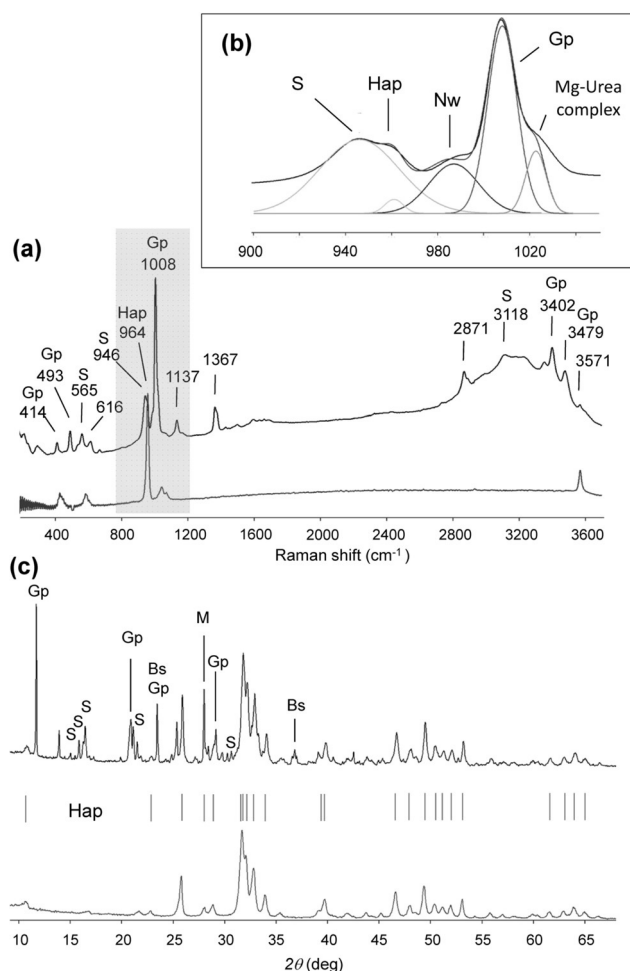
Given the importance of mobile phosphate for these phosphorylation reactions, we hypothesize that the UAFW eutectic formed from urea- and ammonia-rich ponds could be vital for generating moderately soluble struvite and newberyite on the prebiotic Earth, as these minerals commonly form on the present Earth in urea-rich solutions from biological sources.<sup>[20]</sup> Simulating an evaporitic environment with urea or UAFW eutectic as an ammonium source, along with initial concentrations of 50 mM  $\text{MgSO}_4$  and 10  $\mu\text{M}$  free phosphate (concentrations within the ranges found in modern seawater and geological systems, with phosphate provided, for example, from apatite dissolution by acidic steam-heated surface waters),<sup>[21]</sup> the formation of struvite ( $\text{NH}_4\text{MgPO}_4 \cdot 6\text{H}_2\text{O}$ ) and newberyite ( $\text{MgHPO}_4 \cdot 2\text{H}_2\text{O}$ ) is observed for both solutions after three days of drying-rewetting cycles (Figure S5). The formation of newberyite or struvite is pH- and redox-dependent and struvite eventually loses ammonia to form newberyite (Figure S6).<sup>[20b,22]</sup> In the presence of 50 mM  $\text{CaCl}_2$ , this solution forms a combination of brushite ( $\text{CaHPO}_4 \cdot \text{H}_2\text{O}$ ) and newberyite.

In addition to generating struvite and newberyite, it is important to know if the eutectic can release phosphate from insoluble source minerals. The conversion of hydroxyapatite to struvite is calculated to be thermodynamically favorable in the presence of water, urea, and  $\text{MgSO}_4$ , with  $K = 10^{59}$  at 298 K:



Experimentally, the UAFW eutectic with an initial concentration of 50 mM of  $\text{MgSO}_4$  was found to alter the hydroxyapatite ( $\text{Ca}_5(\text{PO}_4)_3(\text{OH})$ ) upon drying and rewetting with 50 mM  $\text{MgSO}_4$ , mobilizing the phosphate and forming an assemblage of secondary evaporitic mineral phases, mainly struvite, gypsum ( $\text{CaSO}_4 \cdot 2\text{H}_2\text{O}$ ), and ammonium sulfates. XRD analysis of the converted hydroxyapatite shows 60 % unreacted hydroxyapatite, 25 % struvite, and 10 % gypsum comprising the solid residue (Figure 4). Without  $\text{MgSO}_4$  the treatment of hydroxyapatite with urea or UAFW under the same conditions, or in the presence of  $\text{MgCl}_2$ , was not found to alter the original mineral phase, suggesting that phosphate solubilization is due to phosphate substitution by sulfate. Urea-negative experiments showed no phosphate solubilization from hydroxyapatite in the presence of  $\text{MgSO}_4$ . These results demonstrate that urea-rich solutions, such as a UAFW eutectic, not only increase the solubility of phosphate minerals, but also allow the formation of a secondary evaporitic paragenesis of urea-soluble classic “cave minerals” from primary phosphate sources, even in the presence of  $\text{Ca}^{2+}$  and the absence of biological agents (Figures S5–S9).

These experiments suggest that an environment rich in ammonia, small organics such as urea and formate,  $\text{MgSO}_4$ , and phosphate could be an ideal location for prebiotic organophosphate synthesis. These organics would theoretically be abundant near prebiotic geothermal fields and from



**Figure 4.** Phosphate solubilization from hydroxyapatite in urea +  $\text{MgSO}_4$  solutions. a) Raman spectrum of hydroxyapatite before (lower line) and after (upper line) drying-rewetting cycles at  $65^\circ\text{C}$  with urea solution and  $\text{MgSO}_4$ . Note the formation of gypsum (Gp) and struvite (S). b) Deconvolution of the  $900\text{--}1050\text{ cm}^{-1}$  zone of the Raman spectrum. The sum of contributions of the main phosphate vibrations of hydroxyapatite (Hap), newberyite (Nw), gypsum, and struvite fits with the observed spectrum. c) Powder X-ray diffractogram of the partially converted hydroxyapatite in UAFW +  $\text{MgSO}_4$ . Characterized conversion products: struvite (S), gypsum (Gp), boussingaultite (Bs), and manganite (M). Original hydroxyapatite and reference reflections (blue vertical lines) are shown for comparison.

Miller-Urey type reactions,<sup>[14,16]</sup> with magnesium as the dominant divalent cation due to the higher solubility of its salts and an abundant source from weathering of mafic and ultramafic rocks.<sup>[23]</sup> Additionally, the availability of  $\text{SO}_4^{2-}$  on a prebiotic Earth is possible through disproportionation of volcanic  $\text{SO}_2$ .<sup>[24]</sup> Even if phosphate was initially present in insoluble apatites or similar minerals, successive evaporative inflows with urea-rich water containing  $\text{MgSO}_4$  would greatly enhance the solubility of these phosphate minerals.<sup>[23b]</sup> Local heating from the hydrothermal systems along with evaporation would form the UAFW eutectic in this pond, which would then act to dissolve and convert the insoluble phosphate minerals to struvite, newberyite, and brushite, which can then

be readily utilized for organophosphate synthesis (Figure S10).

To test this evaporative scenario, we conducted experiments in which we allowed samples to completely dry during heating, followed by reforming the UAFW eutectic by rewetting with either deionized water or an aqueous solution containing  $50\text{ mM MgSO}_4$ . These reactions exhibited significant phosphorylation at  $65$  and  $85^\circ\text{C}$  for  $\text{Na}_2\text{HPO}_4$  and struvite, with a  $3\text{--}6\times$  increase in phosphorylation for apatite when rewet with  $50\text{ mM MgSO}_4$  (Table 3). These reaction conditions simulate environmental drying-rewetting cycles that are useful for providing extreme dehydrating conditions to facilitate condensation reactions followed by increased mobility within a fluidic phase to promote solution-based chemistry. These conditions are particularly interesting as they simulate some of the best environments for the formation of struvite and newberyite minerals from apatites, and may be the most prebiotically viable scenario.

For these reactions, the addition of  $\text{MgSO}_4$  to the system inhibits phosphorylation in the presence of soluble  $\text{Na}_2\text{HPO}_4$  while promoting phosphorylation when moderately soluble struvite or insoluble apatite is used (Tables 3 and S7). These results are indicative of magnesium sequestering phosphate when only soluble phosphate is present, while promoting the solubility of phosphate when less soluble minerals are used as the phosphate source. In fact, the  $\text{MgSO}_4$ -doped phosphorylation reactions with  $\text{Na}_2\text{HPO}_4$  and struvite are nearly identical, supporting the premise that equilibrium is reached with these ions in solution regardless of their initial source.

Overall, our observations suggest that a simple evaporitic environment rich in urea, whose formation is plausible during the Early Archean, could address the phosphate problem by promoting thermodynamically favored phosphate solubility or by forming secondary phosphate species with higher solubility in a UAFW eutectic solvent. Also, it is shown that newberyite is equivalent to struvite as a phosphate source for the phosphorylation of nucleosides, extending the redox, pH, and composition spaces for the formation of efficient phosphate donors. Most importantly, these reactions are shown to work efficiently even under one-pot synthetic conditions by solubilization of phosphate from plausibly abundant prebiotic minerals, such as hydroxyapatite, making prebiotic organophosphate synthesis possible under mild conditions with enhanced yields, and much less complicated than multi-environment synthetic scenarios. Finally, we have shown that Darwin's intuition regarding a "warm little pond" could be right, as an evaporating urea-rich pond with ammonium salts and phosphates (even water-insoluble phosphates) could be the ideal environment for the origin of organophosphates.

### Experimental Section

Identification of mineral phases was done by Raman and X-ray diffraction spectroscopy. Analysis of nucleoside phosphates and the UAFW eutectic was done by HPLC-DAD, ESI-MS, and  $^1\text{H-NMR}$ . Method information and synthesis of mineral phases are described in the Supporting Information.



**Table 3:** Phosphorylation (% nucleobase by HPLC) for adenosine and uridine using drying–rewetting cycles.

Temp. [°C]	Phosphate Source	5'-XMP [%]		2',3'-cXMP [%]		T-Organic-PO <sub>4</sub> [%]	
		A <sup>[a]</sup>	U <sup>[b]</sup>	A <sup>[a]</sup>	U <sup>[b]</sup>	A <sup>[a]</sup>	U <sup>[b]</sup>
65	Na <sub>2</sub> HPO <sub>4</sub>	10.0	13.3	1.5	2.7	18.8	27.0
	struvite	5.4	10.5	1.3	3.4	10.2	20.4
	hydroxyapatite	0.6	0.9	N.D.	0.3	0.6	1.2
	hydroxyapatite with MgSO <sub>4</sub>	2.8	2.5	1.2	1.4	4.9	4.7
85	Na <sub>2</sub> HPO <sub>4</sub>	17.0	22.0	5.5	12.9	39.9	55.4
	struvite	7.4	5.3	4.6	3.4	16.8	14.2
	hydroxyapatite	2.3	2.6	N.D.	1.5	4.1	5.2
	hydroxyapatite with MgSO <sub>4</sub>	6.8	6.9	4.6	3.8	15.8	14.1

[a] Adenosine. [b] Uridine.

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