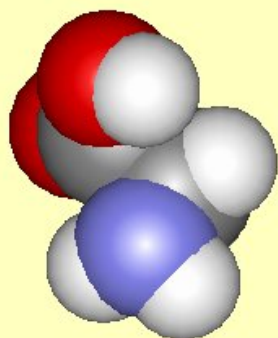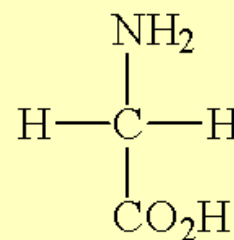# Glycine

The amino acid that may have kick-started life on Earth

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Molecule of the Month April 2010
Also available: JSMol version.

It's an amino acid, right?

Yes, glycine is a colourless crystalline solid (decomposing around 230°C), the smallest α-amino acid there is, with only two carbon atoms, and a Relative Formula Mass of 75.

Why is it called an alpha-amino acid?

The amine (NH_2) group is bound to the first carbon (α-carbon) along from the acid (CO_2H) group. And, incidentally, because there are two hydrogen atoms attached to this carbon, it is the only common α-amino acid not to have optical isomers.

If it is such a small molecule, why is it a high-melting solid?

All these amino acids contain a basic amine group, which can act as a proton acceptor, and an acidic carboxylic acid group, which an act as a proton donor. The COOH donates a proton to the NH_2 group, forming a *zwitterion*, in an internal acid-base reaction.
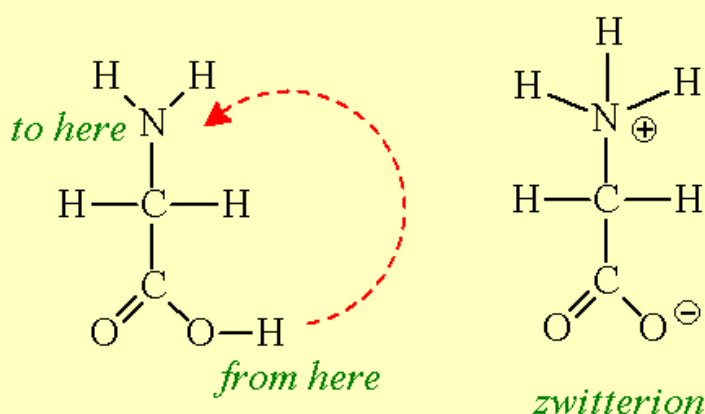
Amino acids exist mainly as the zwitterion in both solution and solid; the solids are held together by electrostatic interactions between the opposite charges. This strong attraction means that amino acids have very high melting points.

The zwitterion has groups that can be protonated or deprotonated; they can accept or donate protons by changing the pH.

ion at low pH   zwitterion   ion at high pH
   neutral pH
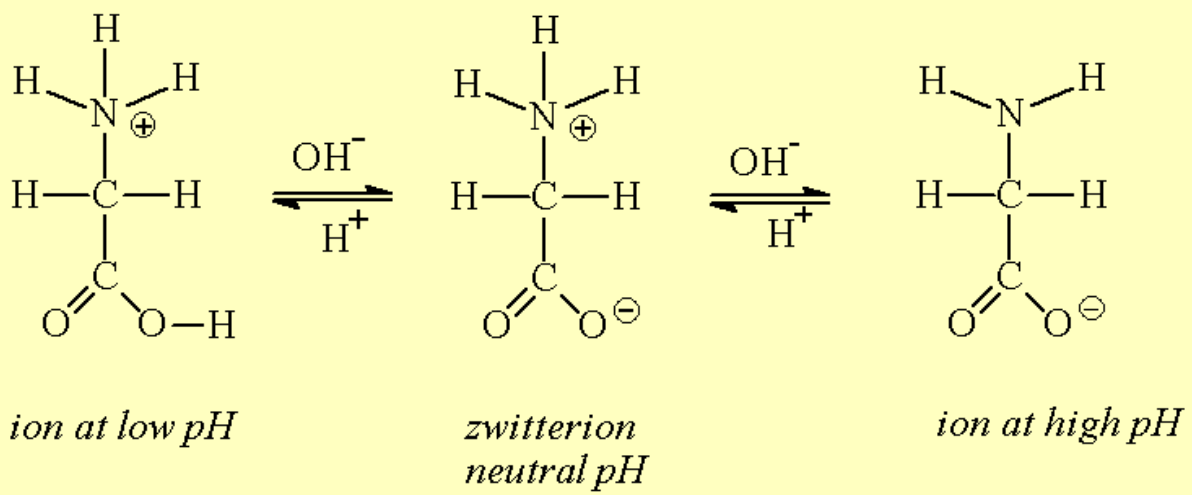
And amino acids are the building blocks of proteins.

Exactly. Amino acids can join together in a condensation reaction, when the amine group of one molecule reacts with the carboxylic acid group of a second molecule, eliminating a molecule of water. They form a peptide link (-CO-NH-). Two amino acids form a dipeptide; three form a tripeptide and so on.
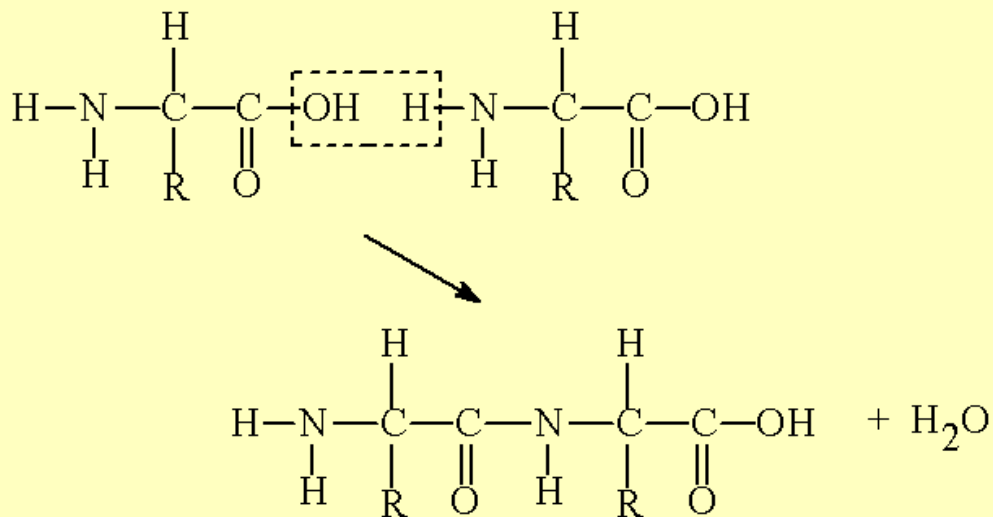

When glycine joins to a different amino acid (R does not equal H), then there are two possible dipeptides.
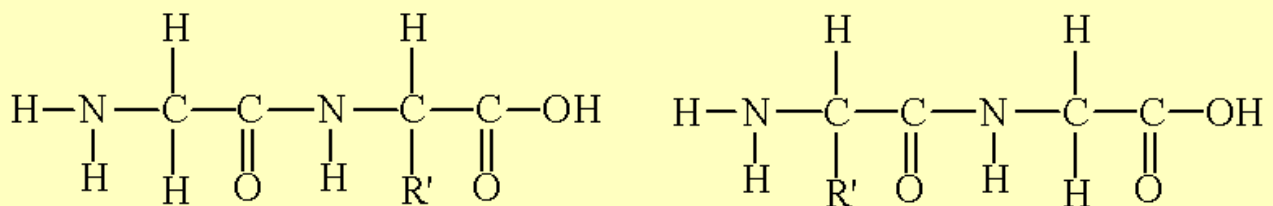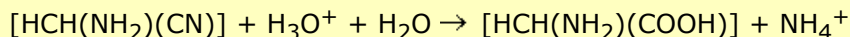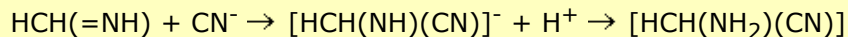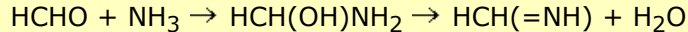

As there are 22 different "natural" amino acids (20 being "common" amino acids), there are huge numbers of different products possible when amino acids join together. When 10 or so amino acid molecules join, the product is called a *polypeptide*. When ~40 or more amino acid molecules join, the product is called a *protein*. Collagen, the fibrous structural protein widely found in mammals, contains some 35% glycine.

Very good. From where can I get this glycine stuff?

Assuming that you don't buy it from a company supplying chemicals, there are three ways in which glycine can be obtained. In the laboratory, chloroethanoic acid reacts with ammonia forming glycine (in the cold, requires a couple of days to go to completion)

$$ClCH_2COOH + 2\ NH_3 \rightarrow H_2N.CH_2COOH + NH_4Cl$$
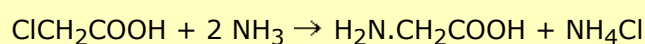
Another route is the classic Strecker synthesis (1850), a route due to Adolf Strecker (1822-1871). Treat methanal with KCN and aqueous ammonia; the reaction forms an intermediate, an α-aminoalcohol, then an imine, which can be converted into a nitrile. This can be hydrolysed with dilute mineral acid to give the amino acid.

$$HCHO + NH_3 \rightarrow HCH(OH)NH_2 \rightarrow HCH(=NH) + H_2O$$

$$HCH(=NH) + CN^- \rightarrow [HCH(NH)(CN)]^- + H^+ \rightarrow [HCH(NH_2)(CN)]$$

$$[HCH(NH_2)(CN)] + H_3O^+ + H_2O \rightarrow [HCH(NH_2)(COOH)] + NH_4^+$$

Secondly, there is biosynthesis. Glycine is a "nonessential" amino acid, as it is synthesised within the human body. In most organisms, it is made from another amino acid, *serine*, in a reaction where the extra methylene group of serine is transferred to tetrahydrofolate, in a reaction catalysed by the enzyme serine hydroxymethyltransferase.

$$serine + tetrahydrofolate \rightarrow glycine + N^5,N^{10}\text{-methylene tetrahydrofolate}$$
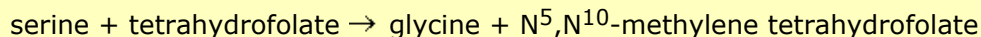
In the liver of vertebrates, the enzyme glycine synthase can catalyse the synthesis of glycine from carbon dioxide and N^5,N^{10}-methylene tetrahydrofolate, with ammonium ions acting as the source of the amine group. This is a reversible reaction.

And the third way?

The Miller-Urey method.

What's that?

In 1951, the Nobel laureate Harold Urey gave a lecture about how life on Earth might have originated. Over a year later, a graduate student named Stanley Miller who had heard the lecture asked Urey about the possibility of trying experiments using a mixture of gases thought to be present in the prebiotic atmosphere of the Earth. The simplest one employed a mixture of water vapour, methane, ammonia, and hydrogen, which had an electric discharge passed through it. Glycine was detected by paper chromatography after a couple of days; after a week, the liquid present had turned brown and a number of other amino acids were detected besides glycine. This important research was immediately submitted for publication in the journal *Science*.
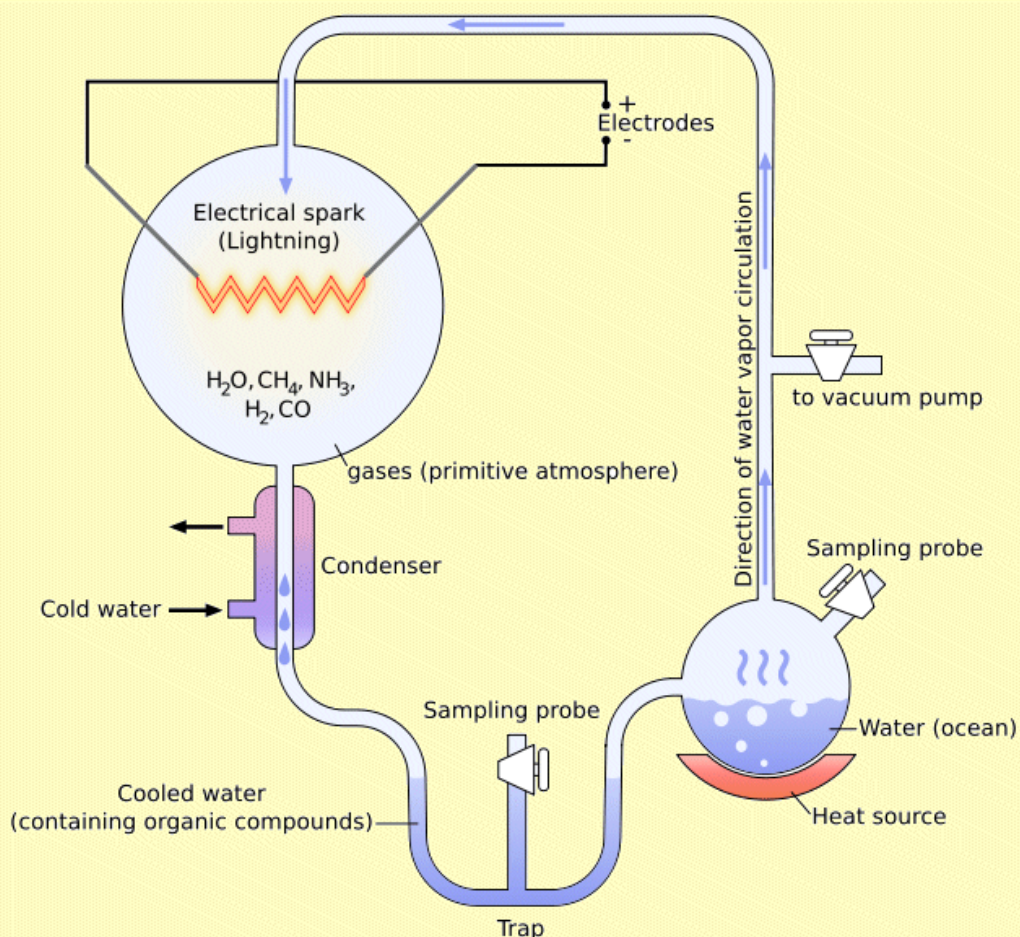

After Miller's death in 2007, it emerged that he kept samples resulting from all the experiments he conducted. His former student Jeffrey Bada carefully analysed these using modern analytical techniques like HPLC and MS. He focussed particularly upon experiments where steam was added to the mixture being sparked, possibly a mimic of the formation of molecules around a volcanic eruption. In all, 22 amino acids were detected, more than Miller had noted, including hydroxyamino acids, previously undetected. But glycine is the principal amino acid product of this reaction.

So that's it?

Well, of course, you can always wait for a passing meteorite or a comet.

What?

Meteorites, such as the 1969 Murchison meteorite, arrive on Earth containing amino acids; the Murchison meteorite contained over 100 amino acids, from glycine upwards. Finding amino acids in deep space has been more problematic, and glycine has defied detection. In 2008, it was reported that, using the Arecibo radio telescope (the largest and most sensitive in the world) scientists had detected emissions from methanimine (CH_2NH), an obvious precursor for glycine, in the Ultraluminous Infrared galaxy, Arp 220. Meanwhile on January 15th 2006, the NASA Stardust craft (image, right) returned to Earth after its 7-year mission to collect space dust with samples taken from the comet 81P/Wild 2.
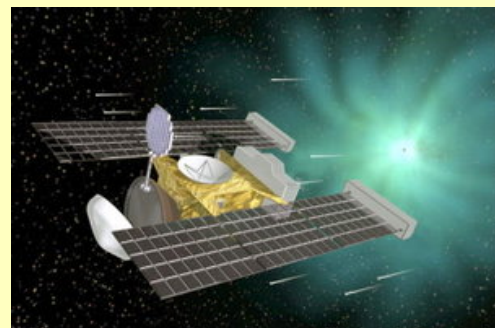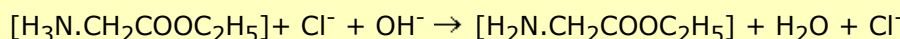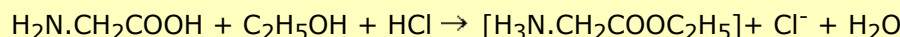
On January 2, 2004, the craft went through the cloud of dust and gas round the core of Wild 2, collecting samples using a collection grid filled with aerogel. The presence of glycine in the sample did not immediately prove it came from space, but analysis of the isotopic composition did; the amount of ^{13}C present in the glycine molecules indicated an extra-terrestrial source for the glycine.
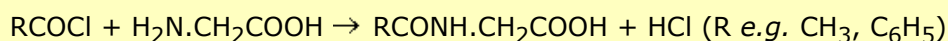
What else does glycine do?

Like other compounds with a primary amine group, it reacts quantitatively with nitrous acid at room temperature, eliminating nitrogen gas effervescently, the van Slyke determination of primary amine content.

$$HNO_2 + H_2N.CH_2COOH \rightarrow HO.CH_2COOH + N_2 + H_2O$$
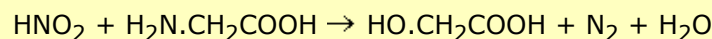
The alcohol function can be esterified in the usual way by the Fischer-Speier method in the presence of HCl. The initial product is a hydrochloride salt, but on treatment with alkali, followed by ether extraction and distillation, the ester itself can be obtained.

$$H_2N.CH_2COOH + C_2H_5OH + HCl \rightarrow [H_3N.CH_2COOC_2H_5]+ Cl^- + H_2O$$

$$[H_3N.CH_2COOC_2H_5]+ Cl^- + OH^- \rightarrow [H_2N.CH_2COOC_2H_5] + H_2O + Cl^-$$

Acyl chlorides (and anhydrides) acylate the amine group: -

$$RCOCl + H_2N.CH_2COOH \rightarrow RCONH.CH_2COOH + HCl \text{ (R } e.g. \text{ } CH_3, C_6H_5)$$

If you heat glycine with iodomethane in methanol, you obtain glycine betaine (often called betaine for short). This occurs naturally in foods, particularly wheat, spinach, shellfish, and sugar beet.

$$3 CH_3I + H_2N.CH_2COOH \rightarrow (CH_3)_3N^+.CH_2COO^- + 3 HI$$
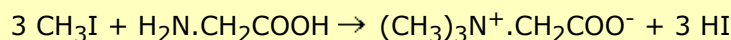
And then there are the transition metal complexes.

Transition metal complexes?

Amino acids can form complexes with transition metals, typically acting as chelating ligands; the formation of blue copper (II) complexes is a diagnostic test for amino acids. This can be done by gently warming the acid with either copper (II) oxide or copper (II) hydroxide. In fact, two isomeric copper(II)-glycine complexes can be isolated.

If hot aqueous glycine solution is added to a hot solution of copper ethanoate in water-ethanol, then the mixture ice-cooled, light blue needles of *cis*-Cu(glycinate)$_2$(H$_2$O) are obtained. If this is then refluxed with some of the filtrate from the reaction and added glycine for an hour or more, it converts to blue-violet platelets of the *trans*-isomer.
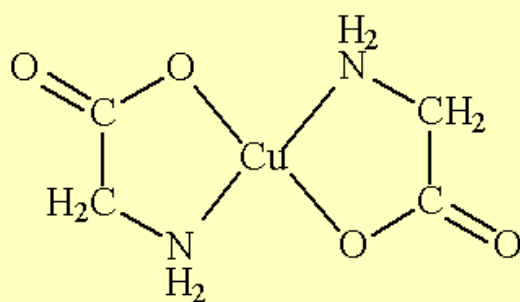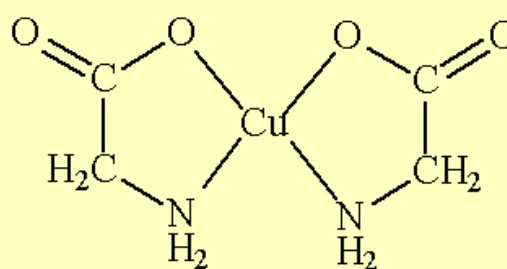
Trans-   Cis-

Why does this happen?

The initial reaction mixture contains both *cis*- and *trans*- isomers in equilibrium, but the *cis*- isomer crystallises faster. However the *trans*- isomer is thermodynamically more stable and less soluble, so on extended heating, the only product is the *trans*- isomer.

Theoretical studies of the *cis*- to *trans*- isomerisation reaction in the gas phase indicate that the *trans*- isomer is more stable above 100 K. A ring-twist mechanism for the isomerisation probably occurs, rather than ring opening, and is likely to happen in the solid state too. It is believed that solid-state packing effects keep the solid-state barrier to twisting much higher, permitting the isolation of the *cis*- isomer.

Studies of the solid-state structures indicate that in the *cis*- form, the copper has distorted octagonal coordination; apart from the two glycine ligands, the first and sixth coordination positions are occupied by an oxygen atom in the water molecule, and by an oxygen atom from a neighbouring glycine. In the case of the *trans*- isomer, the two glycine

ligands occupy four coordination positions, the other two being filled by oxygen atoms from two neighbouring glycines; the water is not coordinated, but sits in a gap in the lattice. X-ray absorption spectroscopy measurements in aqueous solution suggest that here the bis complex has a distorted octahedral structure with two bidentate glycine ligands and two axial water molecules.

Do these complexes have any uses?

Copper glycinate has been found to be effective against oral diseases including plaque, gingivitis and peridontitis, though this has not yet resulted in commercial application.

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