ALBION®
HUMAN NUTRITION

RESEARCH NOTES

A COMPILATION OF VITAL RESEARCH UPDATES ON HUMAN NUTRITION

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Molecular Weight and the Metal Amino Acid Chelate

In the July, 1994 (Vol. 3 No. 3) issue of Albion® Research Notes, an official definition for the term, "metal amino acid chelate" was given. One of the key components of this definition was that a bioavailable metal amino acid chelate should have a molecular weight which is no greater than 800 daltons. To determine the molecular weight of a chelate, one should total the atomic weight of all the atoms in the ligand(s) plus the atomic weight of the metal being chelated. The heaviest metal normally supplemented is molybdenum, with an atomic weight of 95.94 daltons. In its +3 oxidation state, molybdenum can be bonded to three amino acids. Tryptophan is the heaviest amino acid, having a molecular weight of 204.22 daltons. An amino acid chelate of molybdenum and tryptophan, with a 1:3 molar ratio (metal: amino acid), would then have a molecular weight of 708.60 daltons. This illustrates why the upper limit for a true metal amino acid chelate can be set at 800 daltons. As seen in Figure 1, a true bioavailable amino acid chelate can be formed with one, two, or three amino acids. It is physically impossible to chelate any more amino acids to the metal. Additional amino acids must be bonded to other amino acids which results in the product no longer being a bioavailable chelate (as seen in Figure 3).

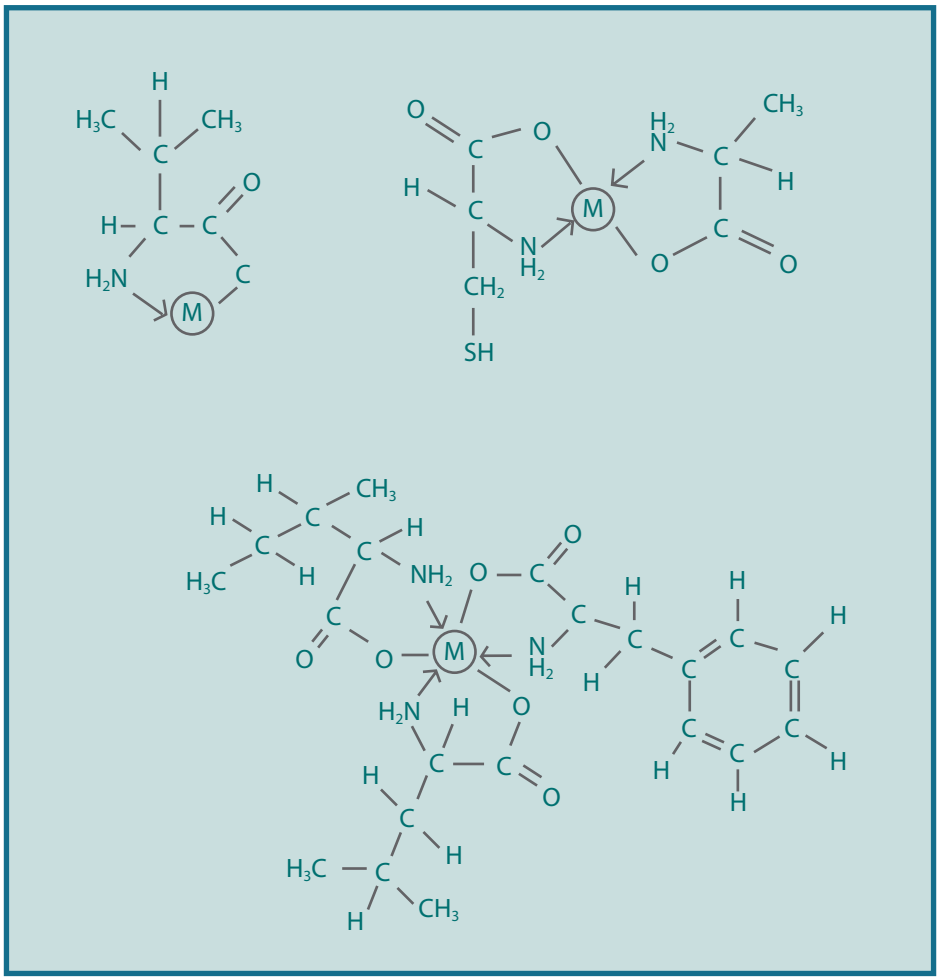


Figure 1.
M = Polyvalent Metal Atom

Chelate examples formed between free soluble metals and free amino acid acids.

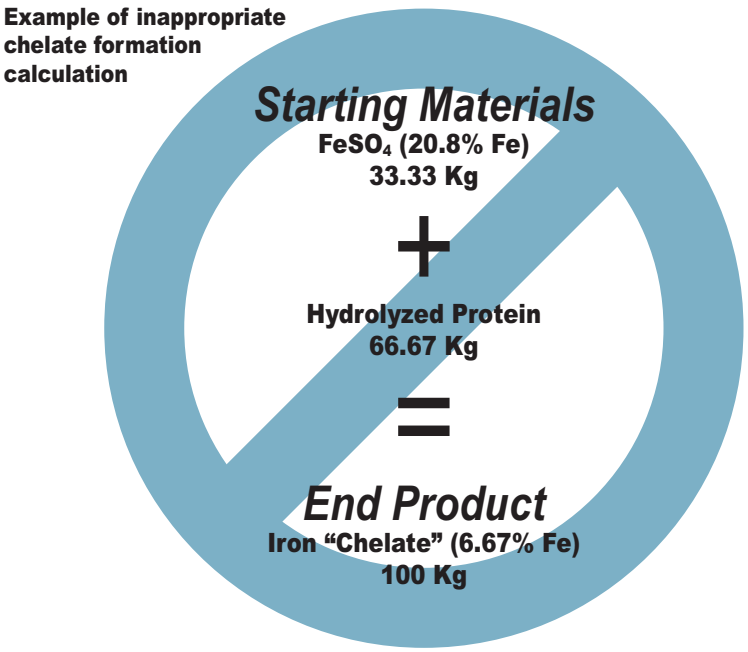
Bell, C.F., Metal Chelation Principles and Applications (Oxford: Clarendon Press) 1977.

A Word of Caution on Chelates using the terms Hydrolyzed Amino Acids and Hydrolyzed Protein

It has been commonplace to find "chelate" suppliers stating that their products are formed from metal salts and hydrolyzed protein or amino acids from hydrolyzed protein. The ability to interchange words like hydrolyzed protein or amino acids from hydrolyzed protein has lead to a wide disparity as to what those suppliers call "metal amino acid chelates." Hydrolyzed proteins and amino acids from hydrolyzed protein come in a wide assortment of specifications. They can have different average molecular weights, different ranges of molecular weights, different protein sources, variances in color, as well as nitrogen content (which is involved in chelation). All of these variations can lead to different products, none of which is a true bioavailable chelate.

The terms, "average" and "range" are critical. Individual amino acids have known molecular weights. Hydrolyzed proteins and amino acids from hydrolyzed protein materials do not. They have average molecular weights that can range from 1000 to 100,000 daltons, or greater.

Companies using hydrolyzed proteins as ligands, often talk about manufacturing metal chelates using weight ratios or percentages in determining quantities of starting materials to produce an end product containing a percentage of mineral in "chelate" form, as if it were a simple math ratio, as illustrated in the *following incorrect formula:*



This approach in trying to make a chelate shows a lack of understanding of basic chemistry. Chemical reactions take place in molar ratios and usually do not have an end product that has the weight which is the sum of the weights of the starting materials. In the above example even though the molecular weight of the iron sulfate can be determined, the sulfate in the starting material was included in the total weight of the product formed. The sulfate should not have been counted in the weight of the chelate even though most so-called chelate manufacturers do not take the trouble to remove the sulfate from their finished products. (Albion has patents that describe how to do this.)

As noted above, hydrolyzed protein has an average molecular weight, which has a wide range. The actual molecular weight is never really known. Because of this, the quantity and nature of the end product in the above example cannot be predicted. There is no guarantee that a chelate will ever be formed. If individual amino acids had been used in the above example, their molecular weights could have been determined, the quantity and nature of the end product would have been predictable, and the end product could have been defined as a true amino acid chelate.

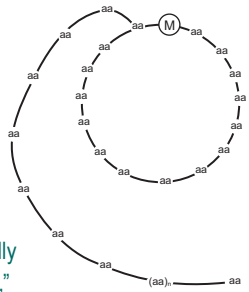
Bailer, J. C.m Chemistry (Orlando: Academic Press) 144-146, 1984.

Protein Absorption: A Consideration in Metal Amino Acid Chelate Molecular Size

Setting upper limits on the molecular weight of a true metal amino acid chelate has implications beyond mere definition. It is the key to a chelate's nutritional functionality. How large can a metal amino acid chelate be and still not require digestion? Can a chelate above a certain size avoid the digestive process? The size of the ligand is the main variable, and logically, the limiting factor in chelate absorption. In a paper given at an international nutrition seminar, Dr. Robert Jeppsen illustrated several "small" molecular weight chelates made with "hydrolyzed" protein. None of these chelates, which are illustrated in Figure 2, is bioavailable because their molecular weights are so large they cannot be absorbed intact. Yet in molecular terms, each is considered to be a small molecule[1].

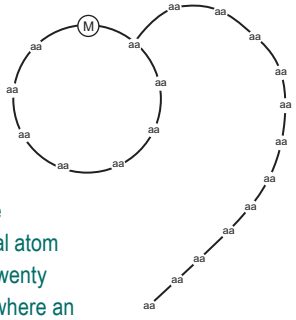
1. Jeppsen, R.B., "Differences in Trace Minerals and Their Relationship to Bioavailability," Albion International Nutrition Seminar, 1992.

Figure 2.



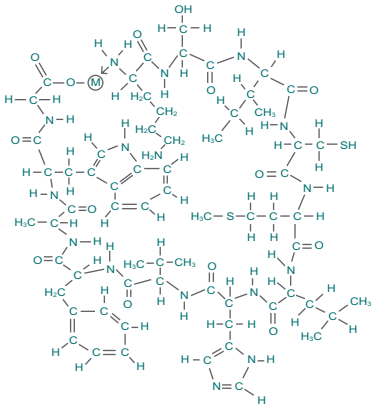
M=Metal Atom

Unlikely chelate between a metal atom and a "partially hydrolyzed protein," where n can approach 100 or more residues and molecular weights can range from several thousand to several tens of thousands of daltons.



M=Metal Atom

Unlikely chelate between a metal atom and a peptide twenty residues long, where an extra reactive moiety occurs on the eighth amino acid in the chain. Molecular weight equals 2796 (if M = Fe and the average molecular weight for the twenty different amino acids = 137).



M = Metal Atom

Unlikely chelation between a metal and the terminal ends of a peptide consisting of twelve amino acid residues (glycine, tryptophan, alanine, phenylalanine, valine, histidine, leucine, methionine, cysteine, isoleucine, serine, and lysine). With iron as the metal, molecular weight equals 1381.

The Number of Glycine Residues Limits Intact Absorption of Glycine Oligopeptides in Human Jejunum

This study was undertaken to determine the capacity of the peptide carrier system in the intestine for transporting peptides consisting of four or more amino acids. Among the 160,000 theoretically possible tetrapeptides containing the 20 amino acids found in protein, the researchers chose tetraglycine because it is highly soluble and because they had previously investigated the absorption of di- and triglycine, in the presence of glycylleucine. Glycylleucine was added for its ability to inhibit the transport of di- and triglycine into intestinal epithelial cells. The glycylleucine had no effect on the disappearance rate of tetraglycine, but increased (over six-fold) appearance rates of triglycine and diglycine (products of tetraglycine hydrolysis). These products were the result of the hydrolysis to tetraglycine by the brush-border enzymes, because the cytosol fraction was seen to lack any hydrolase activity against tetraglycine. Furthermore,

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when jejunal rings were incubated with tetraglycine, there was an intracellular accumulation of di- or triglycine, but not of tetraglycine.

These observations led the researchers to conclude: (a) the disappearance of tetraglycine in the human jejunum was accomplished principally by brush-border oligopeptidases; (b) the rate limiting step in the uptake of glycine from tetraglycine or higher peptides was due to the hydrolysis of these peptides into absorbable products. Peptide carrier systems were not involved in the absorption of peptides that were larger than three amino acids[1].

While the investigators did not study chelates, these data suggest that amino acid chelates made with one, two, or three amino acids are absorbed without digestion in the intestines, whereas so-called chelates made with more than three amino acids require digestion.

1. Adibi, S.S. and Morse, E.L.; the Journal of Clinical Investigation Vol 60 Nov. 1977:1008-1010.

Intestinal Absorption of the Intact Peptide Carnosine in Man, and Comparison with Intestinal Permeability to Lactulose

Peptide transport systems in the small intestinal brush-border are well documented and are thought to play a major role in absorption of the digestion products of dietary protein. It has been a common assumption that these absorbed peptides are hydrolyzed in the epithelial cytosol, and that only free amino acids enter the circulation. In this study the researchers investigated the absorption of a specific dipeptide (carnosine), in an attempt to determine if dipeptides could be absorbed intact into the circulation. Their results showed that up to 14% of the ingested carnosine was excreted into the urine as intact carnosine. In view of the remarkably short half-life observed for carnosine in the plasma, the researchers believed that it was likely that the amount crossing the border, intact, greatly exceeded the amount excreted in the urine. Indeed, it is possible that the majority, or even all, of the carnosine was absorbed intact. The researchers considered it unlikely that the pericellular route played any significant role in the absorption of the dipeptide, and that the transcellular route was the major route for the absorption of the dipeptide[1].

This suggests that correctly made amino acid chelates with a molar ratio of no more than 1:3 can be absorbed intact from the intestine into the blood. Other research has proven this to be correct[2].

1. Gardner, M.L.G., et al; Journal of Physiology (1991), 439, pp. 411-422.

2. Ashmead, H.D., Intestinal Absorption of Metal Ions and Chelates, (Springfield: Charles C. Thomas) 1985.

Micro Electrode Study of Oligopeptide Absorption By The Small Intestinal Epithelium Of Necturus Maculosus

Researchers measured the effects of certain amino acids and oligopeptides (smaller peptides) on the electrical properties of the brush-border membrane of the small intestine, using in vitro microelectrodes. A number of the amino acids (glycine, l-proline, and l-leucine) and small peptides (carnosine, glycyl-l-proline, l-leucyl-l-leucine, glycylclycine, glycylglycylglycine) depolarized the brush-border membrane. The oligopeptide, tetraglycine, showed no appreciable evidence of depolarization of the brush-border membrane. Depolarization of the brush-border membrane is essential for the influx of the substances into the intestinal epithelial cells (first phase of absorption). The researchers stated that the experiments on the glycine peptides showed that only the di- and triglycine were transported by rheogenic mechanisms. The tetraglycine was transported very slowly across the brush-border membrane into the intestinal

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epithelium, suggesting an upper limit of three amino acid residues for intestinal oligopeptide transport[1].

This is exactly the upper limit requirement for absorption of a true bioavailable amino acid chelate.

1. Boyd, C.A.R. and War, M.R.; J Physiol (1982). 324, pp. 411-428.

Not Beyond a Tripeptide

It has been shown that di- and tri-peptides are absorbed intact via active transport carrier systems. Indeed, there have been a considerable number of other studies that have substantiated this. Active transport systems for tetrapeptides and larger peptides do not exist. (Thus, there is probably no transport system for chelates that are greater than 800 daltons in size. They must be further hydrolyzed before absorption and thus, destroyed by digestion.) Adibi[1] furthermore showed that the luminal disappearance of glycine containing dipeptides occurs largely as intact dipeptides, rather than as free amino acids.

Adibi, A.A., Intestinal Transport of Dipeptides in Man: Relative Importance of Hydrolysis and Intact Absorption. J Clin Invest 1971; 50: 2266-75.

Albion's Metal Amino Acid Chelates 'Dipeptide Like'

Most of Albion's metal amino acid chelates consist of one mole of metal chelated to two moles of amino acid. The absorption characteristics of these chelates are similar to the absorption of dipeptides. As the above studies have shown, dipeptides are very well absorbed as intact molecules in the jejunal area of the small intestine.

In his exhaustive text *Protein Absorption*[1], Dr. Matthews stated that the total evidence strongly indicates that intestinal absorption of protein matter by active transport is limited to di- and tripeptides. While minute quantities of longer chain peptides may be absorbed, the amounts are not significant. Matthews further reported that it is the peptide chain-length, rather than molecular volume, that limits the absorption of the peptide by active transport.

When applied to absorption of amino acid chelates, Jeppsen illustrated this concept very well by using a screen to simulate the intestinal cell membrane.[2] As shown in Figure 3, even if chelation were a remote outcome using partially hydrolyzed protein as chelating ligands, those "chelates" would still need to be digested before absorption could occur because true amino acid chelates are absorbed via the dipeptide absorption pathway.[3] In the case of an amino acid chelate with a molecular weight of less than 800 daltons, there is no need for digestion prior to absorption which results in greater bioavailability.

1. Matthews, D.M., Protein Absorption (NY: Wiley-Liss), 245-247, 1991.

2. Jeppsen, R.B., "Differences in Trace Minerals and their Relationship to Bioavailability", Albion Inter. Nutrition Seminar, 1992.

3. Ashmead, H.D., et al., Intestinal Absorption of Metal Ions and Chelates (Springfield: Charles C. Thomas) 1985.

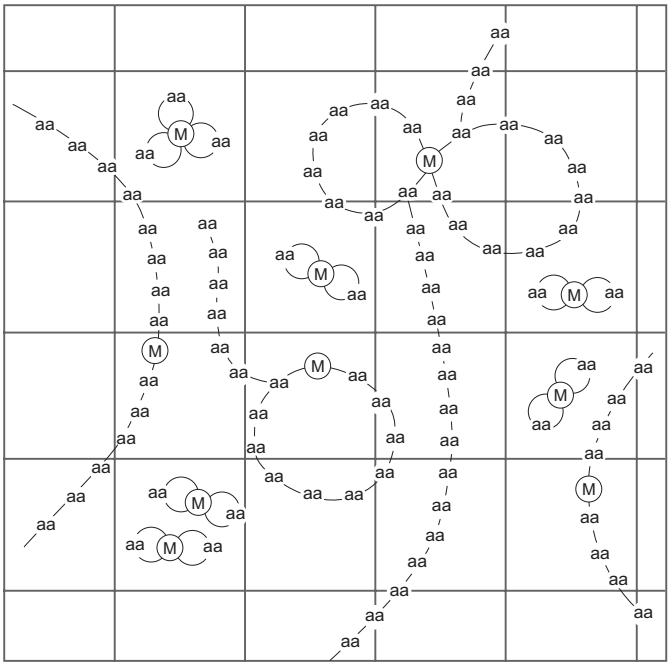

Figure 3. ►
M = Polyvalent Metal Atom

Which chelates can enter through the cell wall membrane (screen) without digestion?

A Final Note on Molecular Weight and Metal Amino Acid Chelates

The upper limit for the molecular weight of a metal amino acid chelate should be less than 800 daltons. The research findings state that tripeptides are upper limit for peptide absorption. As shown previously, the largest possible true metal amino acid chelate (containing 3 amino acids) has a molecular weight of 708.60 daltons. The setting of this limit for the molecular weight of a metal amino acid chelate at 800 daltons does more than guarantee a certain molecule will be a true metal amino acid chelate. It makes it a nutritionally functional chelate. It is a chelate that can be absorbed as an intact molecule. A larger chelate requires digestion prior to absorption, thus destroying the chelate structure and taking away the advantages of consuming a metal amino acid chelate.

All of Albion's patented metal amino acid chelates are formed with less than four amino acids (most are just two). Only Albion has patents describing the formation of amino acid chelates with less than four amino acids. Consequently, they have molecular weights well below the 800 dalton limit. Albion metal amino acid chelates are nutritionally functional mineral chelates that are capable of being absorbed as intact chelates. In fact, only Albion Laboratories has patents guaranteeing absorption of amino acid chelates. Only Albion Laboratories' can bring you the advantages of nutritionally functional mineral chelates.

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