THE JOURNAL OF BIOLOGICAL CHEMISTRY
Vol. 266, No. 22, Issue of August 5, pp. 14440-14445, 1991

Printed in U.S.A.

Estimation of Standard Gibbs Energy Changes of Biotransformations*

(Received for publication, February 8, 1991)

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Contributions and corrections for the estimation of standard Gibbs energies are given. The group contribution method, applicable to both cyclic and acyclic compounds, permits the approximate estimation of the standard Gibbs energy of a biotransformation, given the stoichiometry and structures of the metabolites involved. Estimated standard Gibbs energies of formation for a number of acyclic biochemical compounds are provided.

The biological standard Gibbs energy change $\Delta G^{0'}$ and the equilibrium constant K', related by the equation

$$\Delta G^{0'} = -RT \ln K'$$

are common tools for the thermodynamic analysis of biotransformations. Throughout this article, these quantities will refer to concentrations rather than activities (Interunion Commission on Biothermodynamics, 1976), expressed in M (mol/liter or kmol/m^3). The standard state is a dilute aqueous solution at pH = 7 and 25 °C. One point requiring particular attention is that the concentration of water is not included (*i.e.* it is taken equal to 1) in the expression of the equilibrium constant K'. The same is true, at pH = 7, for the concentrations $[H^{1+}] = 10^{-7}$ and $[OH^{1-}] = 10^{-7}$. For other values of the pH, the value of K' must be adjusted, based on the stoichiometric coefficients of H^{1+} and OH^{1-} in the transformation; alternatively, one may use the same numerical value for K' but include in its expression the factors $([H^{1+}]/10^{-7})^n$ and $([OH^{1-}]/10^{-7})^m$ where n and m are, respectively, the stoichiometric coefficients of H^{1+} and OH^{1-} in the transformation.

The quantities $\Delta G^{0'}$ and K' depend on the nature of the biochemical compounds involved and the stoichiometry of the transformation, but they are independent of the kinetics of the enzyme or enzymes catalyzing the transformation. With υ_i the stoichiometric coefficient of compound S_i, a transformation with known stoichiometry can be written as shown below,

$$\sum_i \upsilon_i S_i = 0$$

with the usual sign convention for υ_i, specifically $\upsilon_i > 0$ if S_i is a net product and $\upsilon_i < 0$ if S_i is a net reactant or substrate. If $\Delta G_i^{0'}$ is the Gibbs energy of formation of S_i, the standard Gibbs energy change of the transformation can be expressed as shown below.

$$\Delta G^{0'} = \sum_i \upsilon_i \Delta G_i^{0'}$$

Thus, the standard Gibbs energies of formation of a number of biochemical compounds allow the determination of the standard Gibbs energy change (and the equilibrium constant) of any transformation that involves only these biochemical compounds. It was previously mentioned that the concentrations of water (regardless of pH) and the concentrations of H^{1+} and OH^{1-} (for pH = 7) are not included in the expression for K'; it should be emphasized here that the Gibbs energies of formation of these species must nonetheless be included in the derivation of the Gibbs energy change of the transformation. In the rest of this article, the term "Gibbs energy" will be used for both the standard Gibbs energy of formation of a compound and the standard Gibbs energy change of a transformation.

For most compounds and biotransformations, Gibbs energies are not available. Various thermodynamic properties can often be estimated from the structures of the compounds involved, using group contributions (Benson, 1968; Reid *et al.*, 1987). This article presents group contributions and new results on an group contribution estimation approach, whose basic characteristics have been discussed in a previous publication (Mavrovouniotis, 1990a). The method is based on multiple linear regression, using data from several sources (Barman, 1969a; 1969b; 1974; Thauer *et al.*, 1977; Hinz, 1986; Lehninger, 1975; 1986; Sober, 1970; Edsall and Gutfreund, 1983), screened and weighted according to their accuracy. Theoretically, the method could be used for any organic compound in aqueous solution, but it may be less accurate for non-biochemical compounds, because the data from which the contributions were estimated were very heavily biased in favor of biochemical compounds and reactions.

THEORY[1]

Relating Biotransformations to Groups—In group contribution methods, one views a compound as composed of functional groups and sums amounts contributed by each group to the Gibbs energy of formation of the compound. Corrections for special structural features of the compound can also be added to the Gibbs energy. The contributions of groups or features that occur more than once in the structure of a compound must be multiplied by the number of occurrences. Thus, the Gibbs energy $\Delta G_i^{0'}$ of a compound S_i is given by an expression of the form shown in the following equation,

* This research was supported in part by National Science Foundation Grant CTS 9010549 and the University of Maryland Systems Research Center which is also funded by National Science Foundation Grant CDR 8803012. The costs of publication of this article were defrayed in part by the payment of page charges. This article must therefore be hereby marked "*advertisement*" in accordance with 18 U.S.C. Section 1734 solely to indicate this fact.

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[1] Portions of this paper (including Tables I–V and Figs. 1–3) are presented in miniprint at the end of this paper. Miniprint is easily read with the aid of a standard magnifying glass. Full size photocopies are included in the microfilm edition of the Journal that is available from Waverly Press.

$$\Delta G_i^{0\prime} = \sum_j m_{ij} g_j$$

where m_{ij} is the number of occurrences of group j in S_i, and g_j is the contribution of group j. For the Gibbs energy of formation (as well as other thermodynamic quantities, such as the standard enthalpy of formation), these methods entail only linear combination, without any other functional transformation. For the Gibbs energy $\Delta G^{0\prime}$ of a biotransformation,

$$\sum_i \upsilon_i S_i = 0,$$

one can combine the expressions

$$\Delta G^{0\prime} = \sum_i \upsilon_i \Delta G_i^{0\prime}$$

and

$$\Delta G_i^{0\prime} = \sum_j m_{ij} g_j$$

to obtain the following.

$$\Delta G^{0\prime} = \sum_i \upsilon_i \sum_j m_{ij} g_j$$

$$\Rightarrow \Delta G^{0\prime} = \sum_j (\sum_i \upsilon_i m_{ij}) g_j$$

$$\Rightarrow \Delta G^{0\prime} = \sum_j n_j g_j,$$

where

$$n_j = \sum_i \upsilon_i m_{ij}$$

The coefficient n_j represents the net participation of group (or correction) j in the biotransformation; it is obtained by subtracting the number of occurrences of each group in reactants from its occurrences in products, always taking into account the stoichiometric coefficients. Thus, the estimation of the Gibbs energy of a transformation from contributions of groups can be carried out directly, without the intermediate estimation of the Gibbs energies of the participating compounds. A group that occurs the same number of times in reactants and products leads to a corresponding $n_j = 0$; thus, it does not affect the Gibbs energy of the transformation and its contribution is not necessary. Often, a transformation involves complicated reactants and products but affects only a small portion of their structures; only this affected portion must be decomposed into groups for the estimation of the Gibbs energy. The way in which group contribution methods operate will be clarified further in the context of an example, after the detailed group contributions are presented.

Group Contributions—The groups and other features used in the method, along with their contributions to the Gibbs energy, are listed in Table I. The contributions were estimated through multiple linear regression, based on literature data (Barman, 1969a; 1969b; 1974; Thauer *et al.*, 1977; Hinz, 1986; Lehninger, 1975; 1986; Sober, 1970; Edsall and Gutfreund, 1983). Throughout the application of the group contribution method, all compounds and groups must be represented in their common state in aqueous solution, at the standard state of pH = 7 and temperature 25 °C. For example, amine groups should normally have a proton attached, as in R–NH_3^{1+} rather than R–NH_2, carboxylic acids should be in their anion form R–CO–O^{1-} rather than R–CO–OH, amino acids in their zwitter-ion forms, etc. It should be pointed out in particular that the proposed method cannot be used to estimate acid-base equilibria (*e.g.* the K_a dissociation constant for a carboxylic acid or a protonated amine), because the method applies only to the most prevalent of the acid-base forms of a compound. In Table I, one encounters groups that at first appear to permit such acid-base calculations (for example, both –NH_2 and –NH_3^{1+} are listed); the contribution of each form of a group, however, presupposes a biochemical compound structure that makes that form prevalent at pH = 7.

In order to apply the developed group contribution technique, one must determine which groups or features occur in the structure of the compound (and how many times, in the case of multiple occurrences). In this determination, one must always use the most specialized possible group. The arrangement of the groups in Table I is designed to facilitate this.

The first contribution in Table I refers to the *origin*, which is used as the initial quantity for the Gibbs energy of any biochemical compound. The be treated like any other group in the estimation of the Gibbs energy of the transformation; one origin term, multiplied by the appropriate stoichiometric coefficient, must be used for each participating compound. Thus, for a biotransformation of either the form A → B + C or the form A → 2B, the net effect on $\Delta G^{0\prime}$ is the addition of one origin term; for a transformation of the form A + D → B + C the net effect is zero; while for a transformation of the form A + 2D → C the net effect is subtraction of two origin terms.

The next set of contributions in Table I refers to the contributions of features that are not represented by distinct functional groups. When the Gibbs energy of a transformation is sought, the inclusion of these features and contributions must be treated according to the stoichiometry of the transformation, in a way similar to the treatment of the origin.

The presence of one of these features in a compound and the inclusion of the appropriate contribution do not eliminate any portion of the molecule from further consideration. For example, if a molecule consists of only carbon and hydrogen, the hydrocarbon correction of 4.0 kcal/mol must be used in addition to the contributions of the groups that make up the structure of the molecule. Similarly, the amide correction of −10.5 kcal/mol must be used for each occurrence of a nitrogen which attached to a carbonyl group, in addition to the contributions of the actual groups (from the rest of Table I).

The remainder of Table I refers to specific groups and has been organized so that groups are easy to locate, and the more specialized groups are listed first. In contrast to feature-based corrections, occurrence of a group in a compound eliminates the use of the same atoms of the compound in a subsequent group; as noted earlier, the most specialized possible group should be used, and the order of the groups in the table reflects this priority.

In practice, one focuses first on any occurrences of sulfur and/or phosphorus in a compound. Scanning Table I under the appropriate subheading, starting at the top, one locates the groups that must be used. Each group is marked, essentially eliminated from the structure of the compound. One then proceeds similarly to nitrogen atoms, always picking the most specialized group, *i.e.* the first group that matches the structure (based on the order in which they are provided under the nitrogen subheading). Occurrences of oxygen that have not already been included in other groups (nitrogen or phosphorus) are considered next. Finally, the remaining portions of the structure of the compound are broken down, first into unsaturated carbon groups and then saturated carbon groups. In the end, the whole structure must be used up by groups, and if any portion of the structure remains then the method cannot be applied, *i.e.* the structure is outside the scope of the method. Note, in particular, that there is no group for hydrogen (*i.e.* –H); if hydrogens remain in the structure not accounted for in groups, it is likely that an

incorrect group was used in the decomposition. For example, if one incorrectly uses a >C< group instead of a >CH– group, a hydrogen will remain unused.

In Table I, the term "benzene ring" is used for a six-carbon aromatic ring (without heteroatoms). The term "heteroaromatic ring" refers to a ring which contains a heteroatom and, following Hückel's rule, has six delocalized π-electrons.

As mentioned earlier, for biotransformations one is concerned only with that portion of the compounds which actually undergoes a modification. Not only groups but also feature-based corrections affected by the modification must be considered in the estimation of the transformation's $\Delta G^{0'}$.

Group contribution methods are generally inaccurate for very small compounds, including inorganic ions, which in fact cannot be broken down into groups, and some organic compounds with two or fewer carbons (*e.g.* methane, formaldehyde, oxalate), which may or may not be formally decomposable into groups. The Gibbs energies of these small compounds can be obtained either from a reliable source of experimental data (Thauer *et al.*, 1977) or from estimates that were developed in conjunction with group contributions (Mavrovouniotis, 1990a). The same sources can be used for certain complex biochemical compounds with important metabolic roles (such as the pair NAD^+/NADH).

Table II provides the Gibbs energies of formation of common acyclic compounds. The Gibbs energies of common cyclic compounds, from an earlier version of the method, have been previously reported (Mavrovouniotis, 1990a). Improvements in the method have led to changes in the values for cyclic compounds; if one computes a Gibbs energy from the contributions provided here and compares it with that previously reported, a small difference is likely to be observed. However, the changes are not sufficient to warrant the presentation of the new results for cyclic compounds in this article. Table II has been accordingly confined to the estimation results for acyclic compounds, which have never been reported. The energies of Table II can serve as useful *reference points*, when the Gibbs energy of a compound similar to one given in the table is desired. One needs to identify only the *differences* between the compound at hand and the similar compound listed in the table and add and subtract appropriate contributions (and corrections) that correspond to these differences. The Gibbs energies of Table II were estimated from group contributions that had *not* been rounded off; because of this, if one estimates the Gibbs energy for a compound from the contributions of Table I and compares it with a value given in Table II, a small deviation might be observed in the first decimal digit.

As an example of the application of the method, Fig. 1 depicts the decomposition of the structure of cystathionine. The computation of its standard Gibbs energy of formation is shown in Table III. As an illustration of the application of the group contribution method to biotransformations, consider the example of Fig. 2.

Cystathionine + acetate → homocysteine + pyruvate + acetamide

This transformation cannot be achieved in a single enzymatic step, but it represents a legitimate overall transformation for which a pathway of enzymatic and/or nonenzymatic steps might exist. What is essential here is that the transformation is stoichiometrically balanced. Expressing the transformation in terms of molecular formulae,

$$C_7H_{14}O_4N_2S + C_2H_3O_2^{1-} \rightarrow C_4H_9O_2NS + C_3H_3O_3^{1-} + C_2H_5ON$$

one can easily verify that the balances for the electrical charge and all the elements (C, H, O, N, S) are satisfied. It should be emphasized that this is a necessary condition for the estimation of the Gibbs energy of the transformation. One could, naturally, estimate separately the Gibbs energies of formation of the five compounds involved (some of which are also given in Table II), and then derive $\Delta G^{0'}$ for the transformation as shown in the following equation.

$$\Delta G^{0'} = \Delta G^{0'}(\text{homocysteine}) + \Delta G^{0'}(\text{pyruvate}) + \Delta G^{0'}(\text{acetamide}) - \Delta G^{0'}(\text{cystathionine}) + \Delta G^{0'}(\text{acetate})$$

However, one can take advantage of the fact that some portions of the chemical structures do not undergo transformation, leading to a simpler computation. Fig. 3*a* marks the unmodified portions, and Fig. 3*b* shows how the remainders of the structures are decomposed into groups. Based on this decomposition, the computation of the transformation's $\Delta G^{0'}$ is detailed in Table IV. The participation of each group is determined as its total number of occurrences in products and reactants, taking into account the stoichiometric coefficients (which are negative for reactants). Note that, regardless of the cancellation of structures (including all groups in the structure of acetate), the origin contribution must be included with a coefficient of 1, which is equal to the sum of all the stoichiometric coefficients (with the coefficients of reactants being negative). Note also the inclusion of the amide correction.

The examples given above illustrate the mechanics of applying the group contribution method. Some additional examples are presented in Table V, with a comparison between estimated Gibbs energies and those reported in the literature. Deviations of 1–2 kcal/mol, such as the ones in Table V, are typical, but occasional deviations exceeding 5 kcal/mol are possible (Mavrovouniotis, 1990a).

Concluding Remarks—The contributions of Table I allow the estimation of the standard Gibbs energy of formation of a biochemical compound and the standard Gibbs energy and the equilibrium constant of a biotransformation. The typical error of the group contribution approach is less than 2 kcal/mol but errors higher than 5 kcal/mol can occur (Mavrovouniotis, 1990a). Thus, the method provides only an approximate value for the Gibbs energy, correct within a few kcal/mol. Only the rough order of magnitude of the equilibrium constant can be obtained. The method is not accurate enough for those cases in which a precise value of the equilibrium constant is needed. It is, however, quite useful in assessing the feasibility and reversibility of bioreactions and pathways.

While the method presented here is, in theory, also applicable to non-biochemical organic compounds in aqueous solution, there is a considerable bias towards biochemical compounds in the database from which the contributions were derived. Hence, extreme caution should be used when non-biochemical compounds are considered.

To achieve better accuracy and reduce the number of parameters, alternatives to the group contribution approach are currently being considered, including an approach that bases the estimation on alternative formal arrangements of valence electrons (Mavrovouniotis, 1990b).

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Supplemental Material to Estimation of Standard Gibbs Energy Changes of Biotransformations

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The contributions of groups which can be used to estimate the standard Gibbs Energy change of a biotransformation or the standard Gibbs Energy of formation of a biochemical compound in aqueous solution are given in Table I. Compounds and groups must always be represented in their common state in aqueous solution, at pH=7 and temperature 25°C (e.g., R–CO–O^{1-} rather than R–CO–OH). In decomposing the structure of a compound into groups, one must always use the most specialized possible group; the groups in Table I are ordered so that more specialized groups occurring earlier.

Table I includes the *origin* (which is a contribution added to the Gibbs energy of any biochemical compound), and features that are not represented by distinct functional groups. The inclusion of a portion of a molecular structure into a group precludes its inclusion in other groups; the special features however represent corrections that must still be included.

In practice, one focuses first on heteroatoms (sulfur, phosphorous, nitrogen, and oxygen, in that order) and identifies the necessary groups under the appropriate subheading of Table I; each group that is identified can be eliminated from further consideration (except for feature-based corrections). Then, one considers similarly unsaturated carbon groups and finally saturated carbon groups. If any portion of the chemical structure remains unused then the method was either applied incorrectly or is simply not applicable to the structure in question.

Gibbs energies of formation have been precomputed for many acyclic compounds and are reported in Table II. Gibbs energies for many cyclic compounds have been reported (Mavrovouniotis, 1990a) within an earlier version of the method.

Figure 1 shows, as an example, the decomposition of the structure of cystathionine into groups and Table III shows the computation of its standard Gibbs Energy of formation.

Figures 2 and 3 show how one can efficiently estimate the Gibbs Energy change for a biotransformation by taking advantage of the fact that some portions of the chemical structures remain unchanged. Table IV provides the corresponding computation of the transformation's $\Delta G'^{\circ}$. The table shows the net number of occurrences of each group in products and reactants, taking into account the stoichiometric coefficients (which are negative for reactants). Note the inclusion of the origin contribution and the amide correction.

Additional examples in Table V allow a comparison between estimated Gibbs Energies and those reported in the literature.

Table I. Contributions of groups and corrections to the standard Gibbs energy of formation. A ring is considered heteroaromatic if it has, by resonance, 6 delocalized π-electrons (according to Hückel's 4n+2 rule). The term "benzene ring" refers to any aromatic ring that involves six carbon atoms and no heteroatoms; when the term "benzene ring" is applied to fused rings, it should be noted that a benzene ring can be fused to either a non-benzene ring or another benzene ring. The subgroup CO denotes a carbonyl group. The contributions of >C< (participating in two non-benzene rings) and >C= (participating in two fused rings; one benzene ring and one non-benzene ring) are followed by a tilde (~) to indicate that these contributions should be used with extra caution, because they have been estimated indirectly from the contributions of other groups.

GROUP OR CORRECTION	CONTRIBUTION (kcal/mol)
origin (a contribution which must be added to every compound)	**–23.6**
Corrections for various features	
correction for hydrocarbon molecule (i.e., molecule containing only C and H)	4.0
correction for each three-atom ring	28.9
correction for each amide (i.e., each nitrogen which is attached to a carbonyl group)	–10.4
correction for each heteroaromatic ring (following Hückel's rule; except for this correction, heteroaromatic rings are treated like regular non-benzene rings)	–5.9
Sulfur groups	
$-SO_3^{1-}$	–105.8
–SH	13.4
–S–S–	5.8
–S–	9.5
Phosphorous groups	
$-O-PO_2^{1-}-$ (participating in a ring)	14.8
$-CO-OPO_3^{2-}$	–72.5
$-OPO_3^{2-}$ (primary)	–29.5
$-OPO_3^{2-}$ (secondary)	–30.0
$-OPO_3^{2-}$ (tertiary)	–25.7
$-PO_3^{2-}$	9.5
$-O-PO_2^{1-}-O-$	–29.8
$-O-PO_2^{1-}-$	–5.2
Nitrogen groups	
–N< (participating in two fused rings)	18.9
$>N=^{1+}$ (the double bond and one single bond participating in a ring)	0.4
=N– (participating in a ring)	10.4
>NH (participating in a ring)	9.5
–N< (participating in a ring)	7.6
$-NH_2$	10.3
$-NH_3^{1+}$	4.3
≡N	14.9
$=NH_2^{1+}$	0.4
=NH	13.6
$>NH_2^{1+}$	6.9
>NH	7.6
>N–	6.3
$>NH^{1+}-$	8.6
Oxygen groups	
–O–CO– (participating in a ring)	–54.6
>CO (participating in a ring)	–27.4
–O– (participating in a ring)	–24.3
–CH=O	–17.8
–OH (attached to benzene ring)	–31.8
–OH (primary)	–29.3
–OH (secondary)	–32.0
–OH (tertiary)	–30.5
$-COO^{1-}$	–72.0
–CO–O–	–73.6
>CO	–27.2
–O–	–22.5
Unsaturated carbon/hydrogen groups	
>C= (participating in two fused benzene rings)	2.5
>C= (participating in two fused non-benzene rings)	16.8
>C= (participating in two fused rings: one benzene ring and one non-benzene ring)	6.0~
–CH= (participating in a benzene ring)	8.4
>C= (the formal double bond and a formal single bond participating in a benzene ring)	1.5
>C= (two single bonds participating in a non-benzene ring)	22.8
–CH= (participating in a non-benzene ring)	9.6
>C= (the double bond and one single bond participating in a non-benzene ring)	8.2
≡CH	35.7
≡C–	24.0
–CH=	11.1
=CH2	18.4
=C<	5.0
Saturated carbon/hydrogen groups	
>CH– (participating in two fused non-benzene rings)	–0.9
>C< (participating in two non-benzene rings)	–12.0~
$>CH_2$ (participating in a non-benzene ring)	6.1
>CH– (participating in a non-benzene ring)	–2.2
>C< (participating in a non-benzene ring)	–12.8
$-CH_3$	7.9
$>CH_2$	1.7
>CH–	–4.8
>C<	–12.8

Table II. Estimated standard Gibbs energies of formation of selected acyclic compounds. The compounds for which results are given below are only those acyclic compounds that occurred in the database used in the course of the development of this method. The compounds are grouped under subheadings, based on key heteroatoms. Within each subheading, they are listed in descending order of number of nitrogen atoms, then oxygens, then carbon, and finally hydrogens.

Compound	Molecular Formula	$\Delta G°'$ (kcal/mol)
Sulfur compounds		
cystine	$C_6H_{12}O_4N_2S_2$	−159.4
methionine	$C_5H_{11}O_2NS$	−75.2
homocysteine	$C_4H_9O_2NS$	−79.3
cysteine	$C_3H_7O_2NS$	−81.0
dimethyl-sulfide	C_2H_6S	1.9
ethyl-mercaptan	C_2H_6S	−0.6
Phosphate compounds		
sedoheptulose-1,7-diphosphate	$C_7H_{12}O_{13}P_2^{4-}$	−253.4
3,5-diphosphomevalonate	$C_6H_9O_{10}P_2^{5-}$	−150.6
3-phosphoglyceroyl-phosphate	$C_3H_4O_{10}P_2^{4-}$	−160.6
2,3-diphosphoglycerate	$C_3H_3O_{10}P_2^{5-}$	−158.2
isopentenyl-pyrophosphate	$C_5H_9O_7P_2^{3-}$	−23.5
dimethylallyl-pyrophosphate	$C_5H_9O_7P_2^{3-}$	−24.5
arginine-phosphate	$C_6H_{14}O_5N_4P^{1-}$	−60.9
creatine-phosphate	$C_4H_8O_5N_3P^{2-}$	−57.1
β-aspartyl-phosphate	$C_4H_6O_7NP^{2-}$	−166.9
3-phospho-1-serine	$C_3H_6O_6NP^{2-}$	−123.9
carbamoyl-phosphate	$CH_2O_5NP^{2-}$	−96.1
sedoheptulose-7-phosphate	$C_7H_{13}O_{10}P^{2-}$	−253.2
mannitol-1-phosphate	$C_6H_{13}O_9P^{2-}$	−226.0
6-phospho-2-dehydro-3-deoxy-gluconate	$C_6H_8O_9P^{3-}$	−222.4
xylulose-5-phosphate	$C_5H_9O_8P^{2-}$	−179.6
ribulose-5-phosphate	$C_5H_9O_8P^{2-}$	−179.6
5-phospho-mevalonate	$C_6H_{10}O_7P^{3-}$	−155.3
erythrose-4-phosphate	$C_4H_7O_7P^{2-}$	−142.7
glycerotetrulose-1-phosphate	$C_4H_7O_7P^{2-}$	−142.9
3-phosphoglycerate	$C_3H_4O_7P^{3-}$	−160.1
2-phosphoglycerate	$C_3H_4O_7P^{3-}$	−158.0
3-phospho-hydroxy-pyruvate	$C_3H_2O_7P^{3-}$	−150.6
glycerol-3-phosphate	$C_3H_7O_6P^{2-}$	−114.2
dihydroxyacetone-phosphate	$C_3H_5O_6P^{2-}$	−106.1
glyceraldehyde-3-phosphate	$C_3H_5O_6P^{2-}$	−105.9
phosphoenolpyruvate	$C_3H_2O_6P^{3-}$	−102.2
acetyl-phosphate	$C_2H_3O_5P^{2-}$	−88.1
Nitrogen compounds		
argininosuccinate	$C_{10}H_{17}O_6N_4^{1-}$	−217.5
arginine	$C_6H_{15}O_2N_4^{1+}$	−67.7
citrulline	$C_6H_{13}O_3N_3$	−121.0
creatine	$C_4H_9O_2N_3$	−63.9
guanidino-acetate	$C_3H_7O_2N_3$	−70.6
n-succinyl-α-ε-diaminopimelate	$C_{11}H_{16}O_7N_2^{2-}$	−266.4
saccharopine	$C_{11}H_{19}O_6N_2^{1-}$	−227.8
n-carbamoyl-aspartate	$C_5H_6O_5N_2^{2-}$	−200.7
meso-α-ε-diaminopimelate	$C_7H_{14}O_4N_2$	−163.5
α-ε-diaminopimelate	$C_7H_{14}O_4N_2$	−163.5
n-formimino-glutamate	$C_6H_9O_4N_2^{1-}$	−149.9
carbamoyl-oxamate	$C_3H_3O_4N_2^{1-}$	−152.8
glutamine	$C_5H_{10}O_3N_2$	−120.0
3-ureidopropionate	$C_4H_7O_3N_2^{1-}$	−122.2
lysine	$C_6H_{15}O_2N_2^{1+}$	−85.0
2-4-diaminopentanoate	$C_5H_{13}O_2N_2^{1+}$	−87.0
ornithine	$C_5H_{13}O_2N_2^{1+}$	−86.7
formimino-glycine	$C_3H_5O_2N_2^{1-}$	−61.6
urea	CH_4ON_2	−50.9
1,2-ethane-diamine	$C_2H_{10}N_2^{2+}$	−11.6
n-α-succinyl-α-amino-ε-keto-pimelate	$C_{11}H_{12}O_8N^{3-}$	−293.0
n-acetyl-glutamate	$C_7H_9O_5N^{2-}$	−191.0
formyl-glutamate	$C_6H_7O_5N^{2-}$	−179.2
2-aminoadipate	$C_6H_{10}O_4N^{1-}$	−163.0
glutamate	$C_5H_8O_4N^{1-}$	−164.7
hydroxymethylserine	$C_4H_9O_4N$	−159.3
aspartate	$C_4H_6O_4N^{1-}$	−166.4
α-aminoadipate-δ-semialdehyde	$C_6H_{11}O_3N$	−108.8
glutamate-semialdehyde	$C_5H_9O_3N$	−110.5
2-amino-4-oxo-pentoate	$C_5H_9O_3N$	−113.6
allothreonine	$C_4H_9O_3N$	−124.9
α-methyl-serine	$C_4H_9O_3N$	−123.8
threonine	$C_4H_9O_3N$	−124.9
homoserine	$C_4H_9O_3N$	−122.0
3-keto-threonine	$C_4H_7O_3N$	−115.4
aspartate-β-semialdehyde	$C_4H_7O_3N$	−112.2
serine	$C_3H_7O_3N$	−123.7
oxamate	$C_2H_2O_3N^{1-}$	−122.8
leucine	$C_6H_{13}O_2N$	−83.3
isoleucine	$C_6H_{13}O_2N$	−83.3
valine	$C_5H_{11}O_2N$	−85.0
4-aminobutyrate	$C_4H_9O_2N$	−86.2
alanine	$C_3H_7O_2N$	−88.2
β-alanine	$C_3H_7O_2N$	−87.9
glycine	$C_2H_5O_2N$	−89.6
carbamate	$CH_2O_2N^{1-}$	−95.7
acetamide	C_2H_5ON	−42.9
triethylamine	$C_6H_{16}N^{1+}$	14.0
n-butylamine	$C_4H_{12}N^{1+}$	−6.2
diethylamine	$C_4H_{12}N^{1+}$	2.6
trimethylamine	$C_3H_{10}N^{1+}$	8.9
dimethylamine	$C_2H_8N^{1+}$	−0.8
ethylamine	$C_2H_8N^{1+}$	−9.7
acetonitrile	C_2H_3N	23.3
methylamine	CH_6N^{1+}	−11.4
Oxygen compounds		
heptose	$C_7H_{14}O_7$	−252.7
sedoheptulose	$C_7H_{14}O_7$	−252.9
homoisocitrate	$C_7H_7O_7^{3-}$	−277.8
homocitrate	$C_7H_7O_7^{3-}$	−277.8
gluconate	$C_6H_{11}O_7^{1-}$	−270.2
5-keto-gluconate	$C_6H_9O_7^{1-}$	−260.6
citrate	$C_6H_5O_7^{3-}$	−279.5
isocitrate	$C_6H_5O_7^{3-}$	−278.0
homoaconitate	$C_7H_5O_6^{3-}$	−220.1
sorbitol	$C_6H_{14}O_6$	−225.7
mannitol	$C_6H_{14}O_6$	−225.7
iditol	$C_6H_{14}O_6$	−225.7
2-deoxy-gluconate	$C_6H_{11}O_6^{1-}$	−231.7
2-deoxy-3-keto-gluconate	$C_6H_9O_6^{1-}$	−222.2
aconitate	$C_6H_3O_6^{3-}$	−221.8
2-keto-4-hydroxy-glutarate	$C_5H_4O_6^{2-}$	−229.9
2-keto-adipate	$C_6H_6O_5^{2-}$	−189.7
ribitol	$C_5H_{12}O_5$	−189.0
xylitol	$C_5H_{12}O_5$	−189.0
citramalate	$C_5H_6O_5^{2-}$	−201.2
α-ketoglutarate	$C_5H_4O_5^{2-}$	−191.4
malate	$C_4H_4O_5^{2-}$	−202.7
oxaloacetate	$C_4H_2O_5^{2-}$	−193.1
mevalonate	$C_6H_{11}O_4^{1-}$	−155.1
α,β-dihydroxy-β-methyl-valerate	$C_6H_{11}O_4^{1-}$	−158.0
α-aceto-α-hydroxy-butyrate	$C_6H_9O_4^{1-}$	−148.5
adipate	$C_6H_8O_4^{2-}$	−160.8
2-methylene-3-methyl-succinate	$C_6H_6O_4^{2-}$	−141.0
2-methylene-glutarate	$C_6H_6O_4^{2-}$	−140.8
glutarate	$C_5H_6O_4^{2-}$	−162.5
erythrose	$C_4H_8O_4$	−142.5
erythrulose	$C_4H_8O_4$	−142.6
threose	$C_4H_8O_4$	−142.5
succinate	$C_4H_4O_4^{2-}$	−164.2
fumarate	$C_4H_2O_4^{2-}$	−145.5
glycerate	$C_3H_5O_4^{1-}$	−159.9
hydroxy-pyruvate	$C_3H_3O_4^{1-}$	−150.3
tartonate-semialdehyde	$C_3H_3O_4^{1-}$	−150.2
malonate	$C_3H_2O_4^{2-}$	−165.9
a-keto-β-methylvalerate	$C_6H_9O_3^{1-}$	−110.0
2-oxo-4-methyl-pentanoate	$C_6H_9O_3^{1-}$	−110.0
β-hydroxybutyrate	$C_4H_7O_3^{1-}$	−122.7
3-hydroxyisobutyrate	$C_4H_7O_3^{1-}$	−120.0
4-hydroxybutyrate	$C_4H_7O_3^{1-}$	−119.7
α-keto-butyrate	$C_4H_5O_3^{1-}$	−113.1
methyl-malonate-semialdehyde	$C_4H_5O_3^{1-}$	−110.2
succinate-semialdehyde	$C_4H_5O_3^{1-}$	−110.0
β-ketobutyrate	$C_4H_5O_3^{1-}$	−113.1
glycerol	$C_3H_8O_3$	−114.0
glyceraldehyde	$C_3H_6O_3$	−105.7
dihydroxyacetone	$C_3H_6O_3$	−105.9

ß-hydroxypropionate	$C_3H_5O_3^{1-}$	−121.4
lactate	$C_3H_5O_3^{1-}$	−124.4
malonate-semialdehyde	$C_3H_3O_3^{1-}$	−111.7
ketopyruvate	$C_3H_3O_3^{1-}$	−114.8
glycollate	$C_2H_3O_3^{1-}$	−123.1
glyoxalate	$C_2HO_3^{1-}$	−113.4
palmitate	$C_{16}H_{31}O_2^{1-}$	−63.8
caproate	$C_6H_{11}O_2^{1-}$	−80.8
valerate	$C_5H_9O_2^{1-}$	−82.5
2,3-butanediol	$C_4H_{10}O_2$	−81.2
ethyl-acetate	$C_4H_8O_2$	−79.6
acetoin	$C_4H_8O_2$	−71.6
butyrate	$C_4H_7O_2^{1-}$	−84.2
crotonate	$C_4H_5O_2^{1-}$	−65.5
1,2-propanediol	$C_3H_8O_2$	−79.9
2-methoxy-ethanol	$C_3H_8O_2$	−63.9
methyl-acetate	$C_3H_6O_2$	−81.3
lactaldehyde	$C_3H_6O_2$	−70.2
propionate	$C_3H_5O_2^{1-}$	−85.9
acrylate	$C_3H_3O_2^{1-}$	−66.1
ethylene-glycol	$C_2H_6O_2$	−78.7
2-hydroxy-acetaldehyde	$C_2H_4O_2$	−68.9
acetate	$C_2H_3O_2^{1-}$	−87.6
1-octanol	$C_8H_{18}O$	−32.9
dipropyl-ether	$C_6H_{14}O$	−23.3
hexylaldehyde	$C_6H_{12}O$	−26.6
1-pentanol	$C_5H_{12}O$	−38.1
diethyl-ether	$C_4H_{10}O$	−26.7
1-butanol	$C_4H_{10}O$	−39.8
methyl-ethyl-ketone	C_4H_8O	−33.2
butyraldehyde	C_4H_8O	−30.0
1-propanol	C_3H_8O	−41.5
isopropanol	C_3H_8O	−44.4
dimethyl-ketone	C_3H_6O	−34.9
ethanol	C_2H_6O	−43.2
dimethyl-ether	C_2H_6O	−30.1
acetaldehyde	C_2H_4O	−33.4

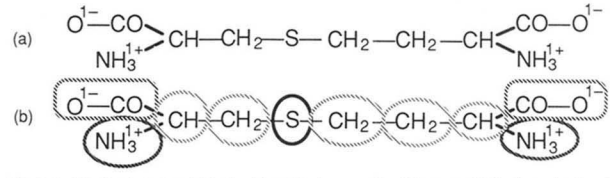

Figure 1. The structure of cystathionine (a) and its decomposition into groups (b) for the estimation of its standard Gibbs energy of formation (Table III).

Table III. Calculation of the Gibbs energy of formation of cystathionine (Figure 1) from contributions of groups.

Group or Correction	Number of Occurrences	Contribution (kcal/mol)	Total Contribution (kcal/mol)
Origin	1	−23.6	−23.6
−S−	1	9.5	9.5
$-NH_3^{1+}$	2	4.3	8.6
$-COO^{1-}$	2	−72.0	−144.0
$>CH_2$	3	1.7	5.1
>CH−	2	−4.8	−9.6
Total Gibbs Energy:			−153.9

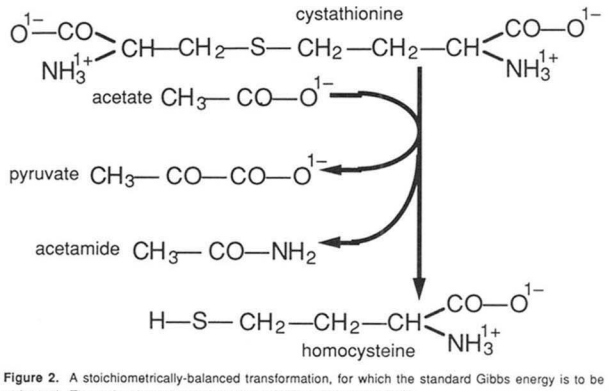

Figure 2. A stoichiometrically-balanced transformation, for which the standard Gibbs energy is to be estimated. The estimation procedure is shown in Figure 3 and Table IV.

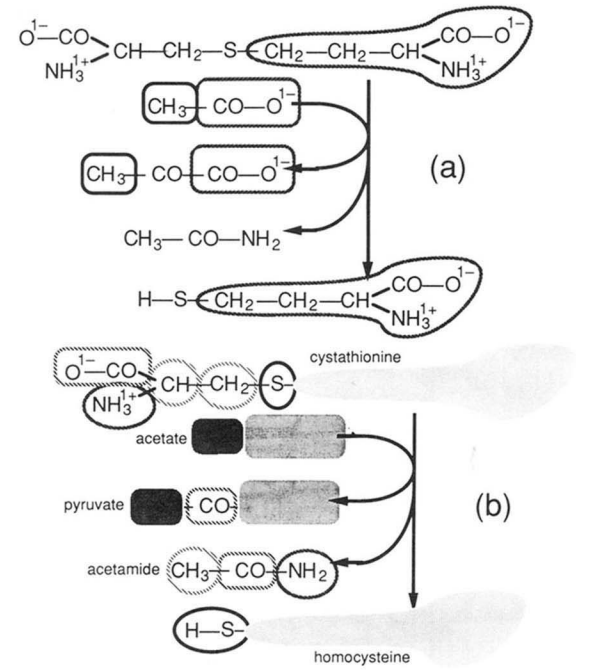

Figure 3. Identification of substructures which are preserved in a transformation (a) and decomposition of the remainders of the structures into groups (b), for the estimation of the Gibbs energy (Table IV).

Table IV. Calculation of the Gibbs energy of the transformation of Figure 3, from contributions of groups.

Group or Correction	Number of Occurrences	Contribution (kcal/mol)	Total Contribution (kcal/mol)
origin	3−2=1	−23.6	−23.6
amide correction	1	−10.4	−10.4
−SH	1	13.4	13.4
$-NH_2$	1	10.3	10.3
>CO	2	−27.2	−54.4
$-CH_3$	1	7.9	7.9
−S−	−1	9.5	−9.5
$-NH_3^{1+}$	−1	4.3	−4.3
$-COO^{1-}$	−1	−72.0	72.0
$>CH_2$	−1	1.7	−1.7
>CH−	−1	−4.8	4.8
Total Gibbs Energy:			4.5

Table V. Comparison between reported standard Gibbs Energies and those estimated from contributions of groups. The deviation (last column) is defined as the absolute value of the difference between the Estimated $\Delta G^{0'}$ and the Reported $\Delta G^{0'}$.

Compound or Transformation	Reported $\Delta G^{0'}$ (kcal/mol)	Estimated $\Delta G^{0'}$ (kcal/mol)	Deviation (kcal/mol)
propionate	−86.3*	−86.0	0.3
glycerol	−114.0*	−115.6	1.6
urea	−48.7*	−51	2.3
phenylalanine	−49.5*	−50.9	1.4
lactate	−123.8*	−124.5¶	0.6
L-allothreonine acetaldehyde lyase or *L-allothreonine aldolase* (EC 4.1.2.6)			
L-allothreonine ⇆ L-glycine + acetaldeyde	2.5†	1.9	0.6
ATP L-arginine phosphotransferase or *L-arginine kinase* (EC 2.7.3.3)			
ATP + L-arginine ⇆ ADP + L-arginine phosphate + H^{1+}	3.2§	2.5	0.7

* Thauer *et al.*, 1977

¶ This value differs from the value of −124.4 kcal/mol computed in Table II. The discrepancy is due to roundoff errors: The results of Table II used the contributions before roundoff to the first decimal, while the results shown here were computed from the rounded contributions of Table I.

† from an equilibrium constant given by Barman (1969b)

§ average of two values, 3.9 kcal/mol and 2.5 kcal/mol, derived from equilibrium constants given by Barman (1969a)