ThermoML†—An XML-Based Approach for Storage and Exchange of Experimental and Critically Evaluated Thermophysical and Thermochemical Property Data. 4. Biomaterials

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ThermoML is an extensible markup language (XML)-based approach for storage and exchange of experimental and critically evaluated thermophysical and thermochemical property data. Extensions to the ThermoML schema for the representation of properties of biomaterials are described. The texts of several data files illustrating the new extensions are provided as Supporting Information together with the complete text of the updated ThermoML schema.

Background

This is the fourth paper in the series describing ThermoML, an extensible markup language (XML)-based approach for storage and exchange of thermophysical and thermochemical property data.[1−3] The principles, scope, and description of the basic structural elements of ThermoML were discussed in the first paper in the series,[1] which covered essentially all experimentally measured thermodynamic and transport property data (more than 120 properties) for pure compounds, multicomponent mixtures, and chemical reactions (including change-of-state and equilibrium) with a primary focus on molecular compounds. Representation of quantities for the expression of uncertainty was discussed in the second paper of the series.[2] In the third paper, we described the expansion of ThermoML for coverage of critically evaluated data, predicted data, and data represented

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† "ThermoML" is the reserved namespace for the XML-based IUPAC standard for experimental and critically evaluated thermodynamic property data storage and capture (http://www.iupac.org/namespaces/ThermoML/).

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as equations.[3] These three papers, in combination, constitute the development of ThermoML as it was authorized by the International Union of Pure and Applied Chemistry (IUPAC) within project 2002-055-3-024, "XML-based IUPAC Standard for Experimental and Critically Evaluated Thermodynamic Property Data Storage and Capture".[4] The meta- and numerical data infrastructure reported in these papers served as the foundation for the IUPAC recommendations establishing ThermoML as the standard for thermophysical property data communications.[5]

ThermoML has proven to be a critical component in the development of one of the first global data delivery processes,[6] now implemented by five major journals in the field.[7] ThermoML is now used extensively by scientists, engineers, and informatics experts worldwide. On the basis of this wide acceptance after the official release of ThermoML as an IUPAC standard, we initiated a new IUPAC project 2007-039-1-024, "Extension of ThermoML - the IUPAC Standard for Thermodynamic Data Communications".[8] The purpose of this project is to broaden the scope of ThermoML to support storage and exchange of thermodynamic property data (1) for biomaterials and (2) for speciation and complex equilibria in aqueous and nonaqueous solvents. The present paper describes extensions of ThermoML for thermodynamic properties of biomaterials developed as part of the new IUPAC project.

The complete ThermoML schema is available on the Internet (http://www.trc.nist.gov/ThermoML.xsd; "xsd" is the file extension for an XML schema).

Scope of Extensions for Biothermodynamic Data

In order for ThermoML to be applicable to biothermodynamic data, extensions were required in three general areas. First, unambiguous identification of biochemical compounds and biological materials (such as proteins and enzymes) posed a major new challenge. This required the addition of new schema elements for specific identification numbers, such as the Enzyme Commission (EC) number[9] and the Protein Data Bank (PTB) identifier.[10] Second, new properties specific to the field of biothermodynamics, such as the *apparent equilibrium constant* for a biochemical reaction, were needed. These can include the effects of dissociation, denaturation, partial unfolding, local dynamic changes, solvent binding, and protonation events that may occur on formation of a biomolecular complex. Also, properties associated with structural changes associated with specific molecules or groups of molecules in a complex solution, such as the denaturation of proteins or phase transitions observed with lipid membrane interactions, required further schema extensions. Finally, solvents for biochemical reactions and properties must be carefully characterized. These are commonly much more complex than the reaction solvents that are presently accommodated in ThermoML. Extensions to represent important variables, such as pH, pMg, buffer composition, cofactors, and so forth, had to be considered for full specification of the biochemical systems.

A key challenge within the current project is the necessity to ensure that clear and consistent data definitions and nomenclature are used throughout and that the definitions and nomenclature are consistent to the fullest extent possible with existing IUPAC recommendations and standards. Extensions to ThermoML involved two distinct types of thermodynamic measurements: those involving properties of reactions (bond making and/or breaking) and those involving physical properties (phase transition properties, heat capacities, etc.). Specifically, the extensions to ThermoML described here are designed for representation of results from four common types of experiments in the field of biothermodynamic property measurements. These are the following:

1. Properties of enzyme-catalyzed reactions,
2. Reaction properties determined with titration calorimetry,
3. Properties determined with differential scanning calorimetry (DSC),
4. Solubilities in complex media.

An extensive database of thermodynamic properties for enzyme-catalyzed reactions has been compiled by Goldberg et al.[11] Full representation of the information in this database was a key goal of this project.

IUPAC recommendations for nomenclature and tables in biochemical thermodynamics were published in 1994.[12] Some aspects of the 1994 recommendations are currently being revised by an IUBMB (International Union of Biochemistry and Molecular Biology)−IUPAC Joint Commission. The new draft recommendations can be found at http://www.chem.qmul.ac.uk/iubmb/thermod2/ (accessed July 26, 2009). The proposed changes and additions in the new recommendations document do not affect the proposed ThermoML extension to biomaterials and biochemical reactions. The recommendations of 1994 revised and extended recommendations published in 1976[13] and 1985[14] and continue today as the foundation for the reporting of reaction data for biothermodynamics. The recommendations of 1994 specifically address biochemical reactions that consist of species in equilibrium with each other and do not balance elements that are assumed fixed, such as hydrogen at constant pH. This approach leads to the specification of *apparent equilibrium constants* written in terms of sums of species and to the calculation of *transformed* thermodynamic functions for reactions. This nomenclature results in the addition of several variables that extend those typically specified in chemical engineering applications (temperature, pressure, density, or composition). For example, the *apparent equilibrium constant* is a function of temperature, pressure, ionic strength, pH, and pMg (various metal ions can be involved, but Mg^{2+} is used here as an example) and can be contrasted with the *thermodynamic equilibrium constant*, which is a function of temperature only.

Data representations for most physical properties of biochemical compounds of defined composition are fully realized in the existing ThermoML schema. An important group of properties that is outside the present scope involves "phase transitions" and conformational changes (e.g., denaturation) in biological systems, such as proteins and nucleic acid sequences. These biochemical properties are typically associated with specific chemical species within a mixture, such as a protein in an aqueous solution. Furthermore, several properties and variables beyond the transition temperature and enthalpy are needed to fully characterize biochemical transitions. Additional properties, such as the zero Gibbs energy temperature, T_G, or the heat capacity change at a transition temperature, are used to characterize the temperature dependence of the heat capacity associated with the biochemical transition. Additional variables are analogous to those required for reactions and include ionic strength and pH. IUPAC recommendations for reporting such experimental data were discussed by the Commission on Biophysical Chemistry in 2001.[15]

Conventions for Names of Elements in the ThermoML Schema

The names (or "*tags*") include special characters related to the type of information to be stored. A name beginning with

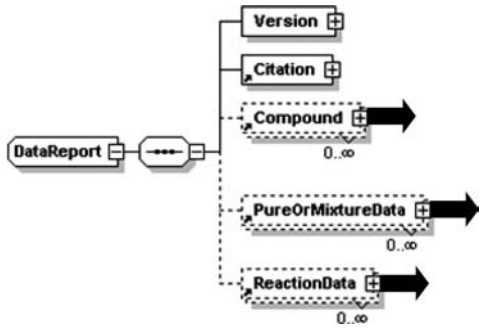

Figure 1. Major components of ThermoML. The arrows indicate the locations of extensions to the schema for representation of biothermodynamic data.

"e" indicates an *enumeration* element (with values selected from a predefined list), and "s" designates *string* elements (text strings). "n" specifies *numerical* elements (integer or floating), and "yr" designates elements characterizing the *year*. "date" specifies *date* elements, and "url" indicates elements specifying addresses on the World Wide Web. Elements shown as dotted boxes in the figures are optional, while those shown as solid-lined boxes are mandatory. A *complex* element is an element that includes subelements. Complex elements illustrated without their internal structure are identified by "+" at the right-hand edge of the box. Multiple elements of the same type are often needed within the schema to specify elements such as multiple authors for a given citation or multiple property values for a given data type. These multiple elements are identified in the figures by lower and upper limits listed below the relevant boxes. The only limits used for repeated elements are "0...∞" for optional elements and "1...∞" for mandatory elements. A switch symbol in a figure indicates that only one of the subelements can be selected. In addition, an element can have associated *attributes* that provide additional information about the contained information. Prior to the extensions described here, *attributes* were not used in ThermoML. Here, they are used for one element to avoid unnecessary duplication.

General Implementation of Structural Elements Related to Biothermodynamic Data in ThermoML

ThermoML consists of four major blocks, which are shown in Figure 1 together with the element **Version** [complex], which specifies the ThermoML version number. All elements of the four major blocks (prior to the present extensions) were fully described previously.[5] The four major blocks are the following:

(1) *Citation* (description of the source of the data),

(2) *Compound* (characterization of the chemical system),

(3) *PureOrMixtureData* (meta- and numerical data for a pure compound or multicomponent mixture),

(4) *ReactionData* (meta- and numerical data for a chemical reaction with a change of state or in chemical equilibrium).

The general locations of extensions described in this paper for predicted and critically evaluated data are indicated with arrows in Figures 1, 2, 3, and 4. Arrows that point to the right indicate that extensions for biothermodynamics are present within the subelements of the complex element. Arrows that point to the left indicate specific schema extensions described in the text. Detailed schema figures and the text of ThermoML were created with the software package XML SPY.[16] (The trade name is provided only to specify the procedure adequately and does not imply endorsement by the National Institute of Standards and Technology. Similar products by other manufacturers may be found to work as well or better.)

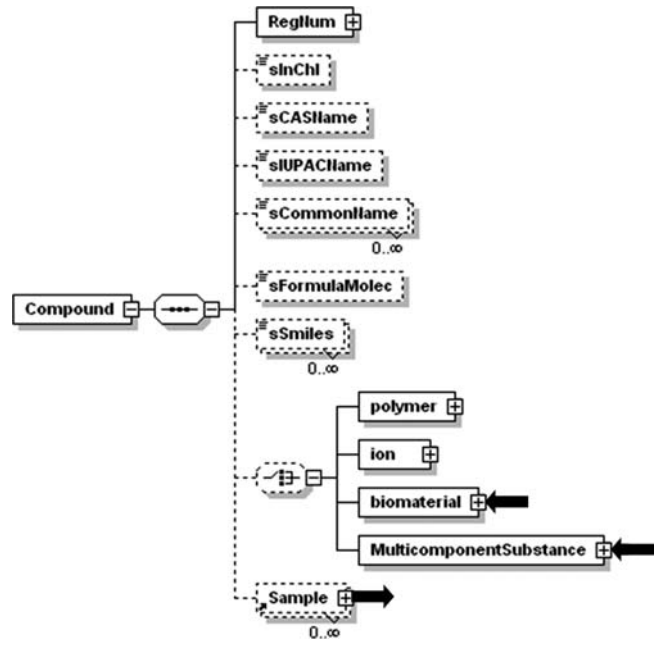

Figure 2. Structure of the *Compound* block. The arrow indicates the extensions to the schema for representation of biothermodynamic data.

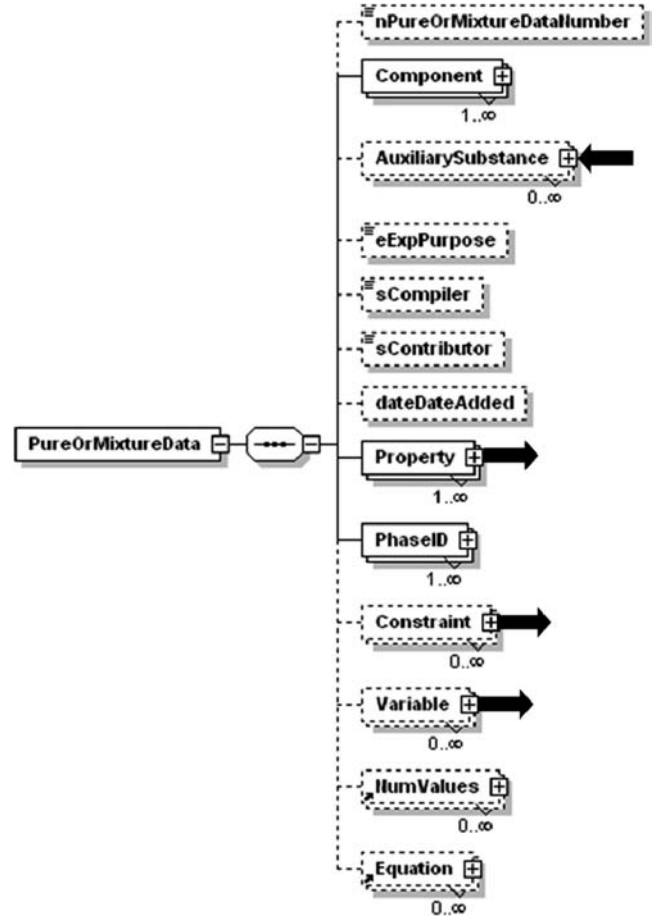

Figure 3. Structure of the *PureOrMixtureData* block. The arrows indicate the location of extensions to the schema for representation of biothermodynamic data.

Structural Elements Related to Biothermodynamic Data in the *Compound* Block

Elements of the *Compound* block are shown in Figure 2. Unique identification of biorelated compounds and materials is

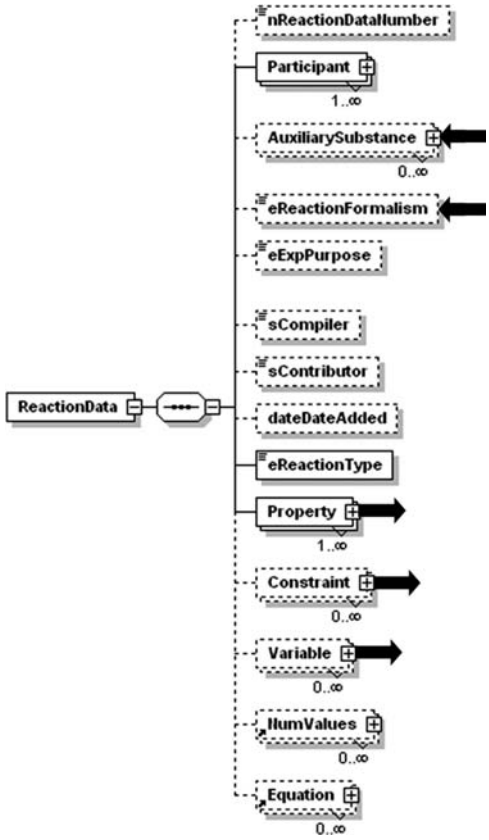

Figure 4. Structure of the *ReactionData* block. The arrows indicate the location of extensions to the schema for representation of biothermodynamic data.

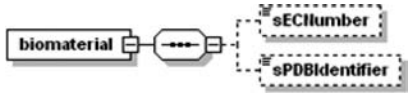

Figure 5. Structure of the **biomaterials** [complex] element in the *Compound* block. Subelements are **sECNumber** [string] (the EC number) and **sPBDIdentifier** [string] (the PDB identifier).

a major challenge. Extensions for specification of biomaterials are contained within the new **biomaterial** [complex] and **MulticomponentSubstance** [complex] elements and within a subelement of the **Sample** [complex] element.

Two identification numbers that are widely used and accepted within the biothermodynamics community are included as the subelements of **biomaterial** [complex], as shown in Figure 5. The subelement **sECNumber** [string] contains the EC number. Enzymes are assigned numerical identification numbers under the auspices of the Nomenclature Committee of the International Union of Biochemistry and Molecular Biology (NC-IUBMB) in consultation with the IUPAC-IUBMB Joint Commission on Biochemical Nomenclature (JCBN). Details are provided on the Web site maintained by the committee.[9] The subelement **sPDBIdentifier** [string] is the Protein Data Bank (PDB) identifier. These numbers are maintained by the Research Collaboratory for Structural Bioinformatics (RCSB), a nonprofit consortium dedicated to a better understanding of the function of biological systems through study of the three-dimensional (3-D) structure of biological macromolecules. RCSB members work cooperatively through joint grants and subsequently provide free public resources and publications to assist others and further the fields of bioinformatics and biology. The PDB is publicly available online.[10]

The structure of the new element **MulticomponentSubstance** [complex] is shown in Figure 6. The element has two attributes:

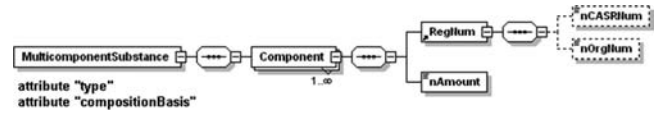

Figure 6. Structure of the **MulticomponentSubstance** [complex] element within the *Compound* block. This element has two attributes: *type* and *composition Basis*.

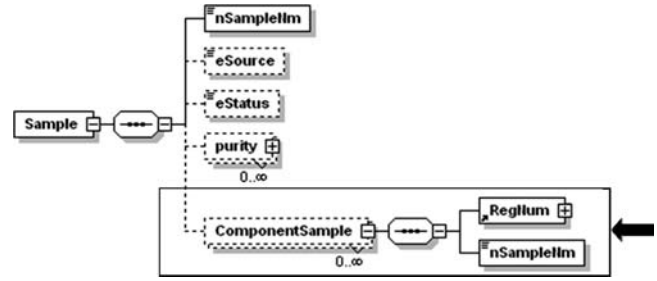

Figure 7. Structure of the **Sample** [complex] element within the *Compound* block. The arrow indicates the three elements that are added to the schema for representation of biothermodynamic data.

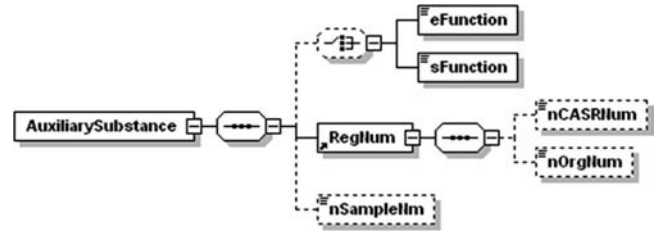

Figure 8. Structure of the **AuxiliarySubstance** [complex] element within the *PureOrMixtureData* block.

type and *compositionBasis*. Only one *type* is defined in the present extensions to ThermoML: *complex*. Addition of the attribute *type* allows for future extensions for multicomponent substances, such as gas hydrates and alloys. The attribute *compositionBasis* has three possible choices: *mass fraction*, *mole fraction*, and *number of molecules*. The composition basis *number of molecules* is used to define the stoichiometry of a complex, such as A_2B, which is composed of two molecules of A and one molecule of B. Numerical values associated with composition bases are stored in the **nAmount** [numerical, floating] element shown in Figure 6. The **RegNum** [complex] associates the particular component of the complex with a compound that is fully specified within the *Compound* block (Figure 2).

The final extensions within the *Compound* block (Figure 2) involves addition of elements for the **Sample** [complex]. Figure 7 shows the structure of the **Sample** [complex] block, including the new subelement **ComponentSample** [complex]. This new element is used to define a particular sample of a component within a multicomponent substance. The subelements of **ComponentSample** [complex] are **RegNum** [complex] and **nSampleNm** [numerical, integer]. As described previously,[5] **RegNum** [complex] contains the subelements that represent the Chemical Abstracts Service (CAS) Registry Number **nCASRNum** [numerical, integer] and an identification number assigned by a user organization **nOrgNum** [numerical, integer].

Structural Elements Related to Biothermodynamic Data in the *PureOrMixtureData* Block

Extensions for biothermodynamic data are added in four locations within the *PureOrMixtureData* block, as shown in Figure 3. **AuxiliarySubstance** [complex] is a new element that

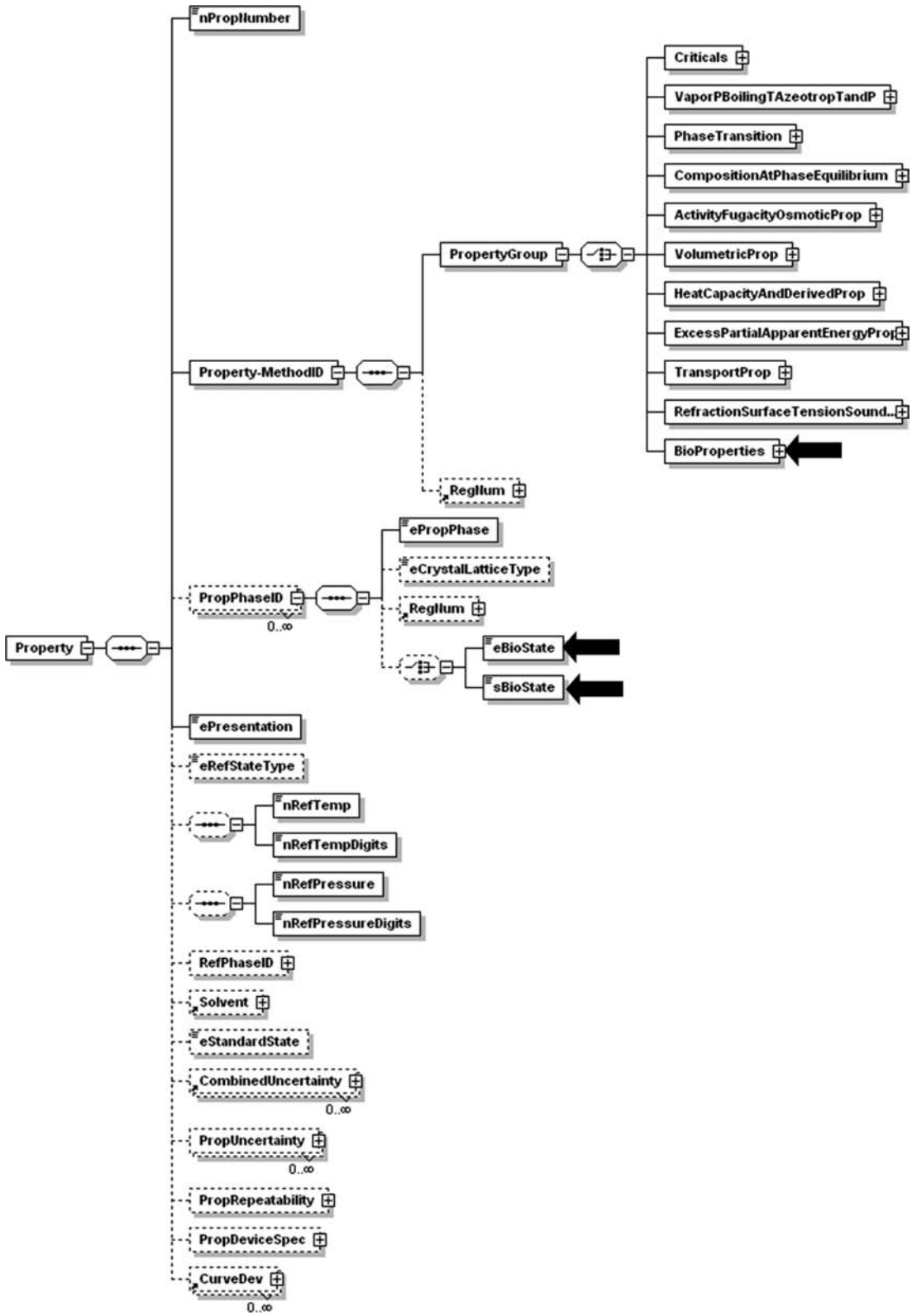

Figure 9. Structure of the **Property** [complex] element within the *PureOrMixtureData* block. The arrows indicate the location of extensions to the schema for representation of biothermodynamic data.

allows identification of substances that are part of the chemical system under consideration but are not directly associated with the particular pure-compound or mixture property. This extension allows, for example, the identification of a buffer used in a denaturation study of a protein by DSC.

The location of the **AuxiliarySubstance** [complex] element in the schema is shown in Figure 3. The **AuxiliarySubstance** [complex] element consists of three subelements, as shown in Figure 8. **RegNum** [complex] is a compound registry number that contains the further subelements **nCASNum** [numerical, integer] for the CAS Registry Number and an identification number assigned by a user organization **nOrgNum** [numerical, integer]. **eFunction** [enumeration] represents the function of the auxiliary substance in the chemical system (buffer, solvent, inert), and

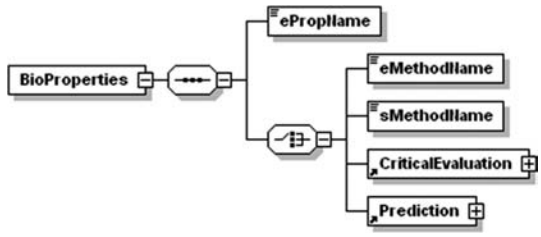

Figure 10. Structure of the **BioProperties** [complex] element within the *PureOrMixtureData* block.

sFunction [string] allows specification of a function not included in the enumeration list; **nSampleNm** [integer] is the sample number for the auxiliary substance. The existence of multiple samples for an auxiliary substance is very unlikely for any given data report; however, this element exists in numerous other analogous locations in ThermoML and is included here for consistency.

The second extension within the *PureOrMixtureData* block is within the **Property** [complex] element. This extension is

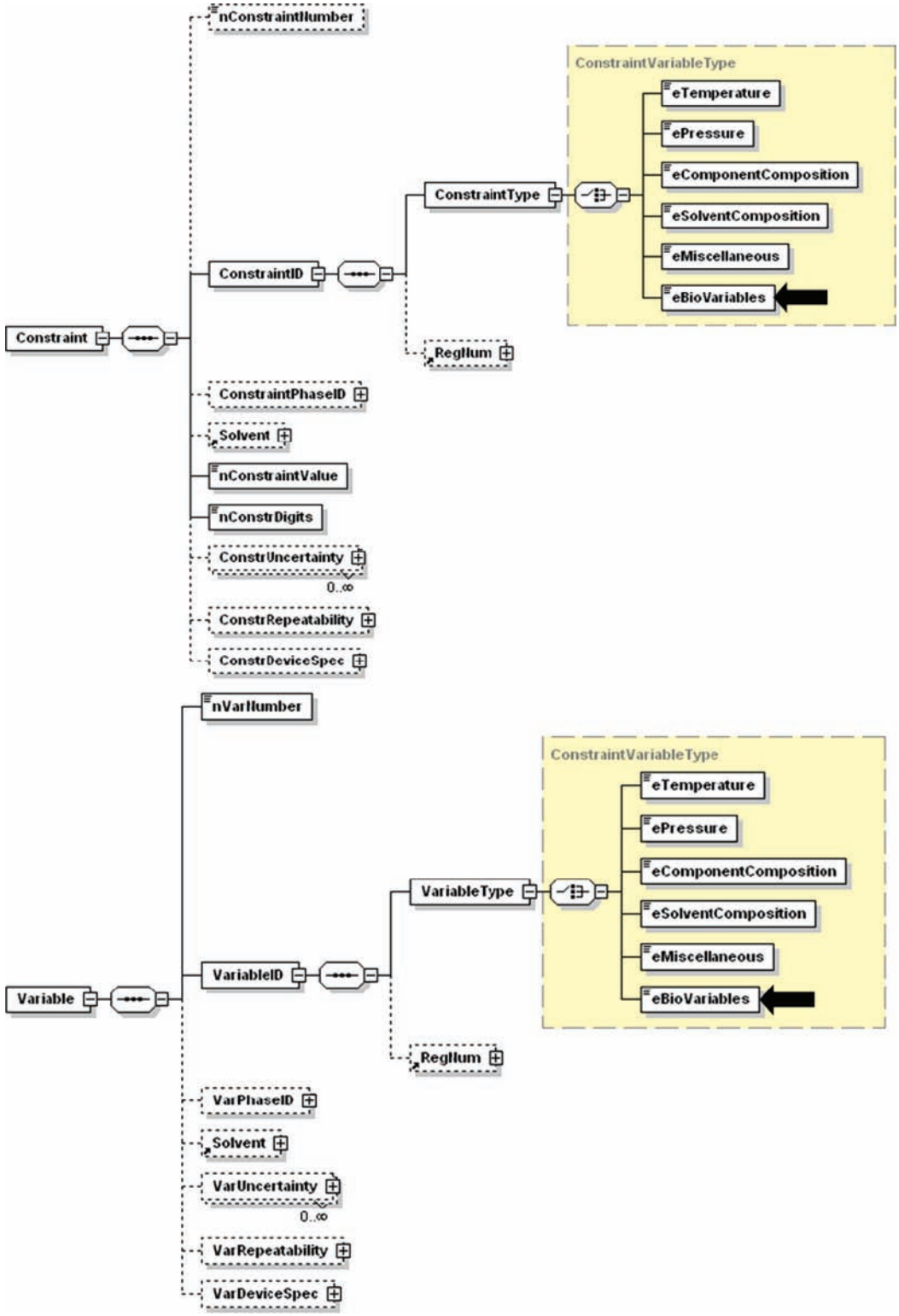

Figure 11. Structures of the **Constraint** [complex] and **Variable** [complex] elements within the *PureOrMixtureData* block. The arrows indicate the location of the extension to the schema for representation of biothermodynamic data.

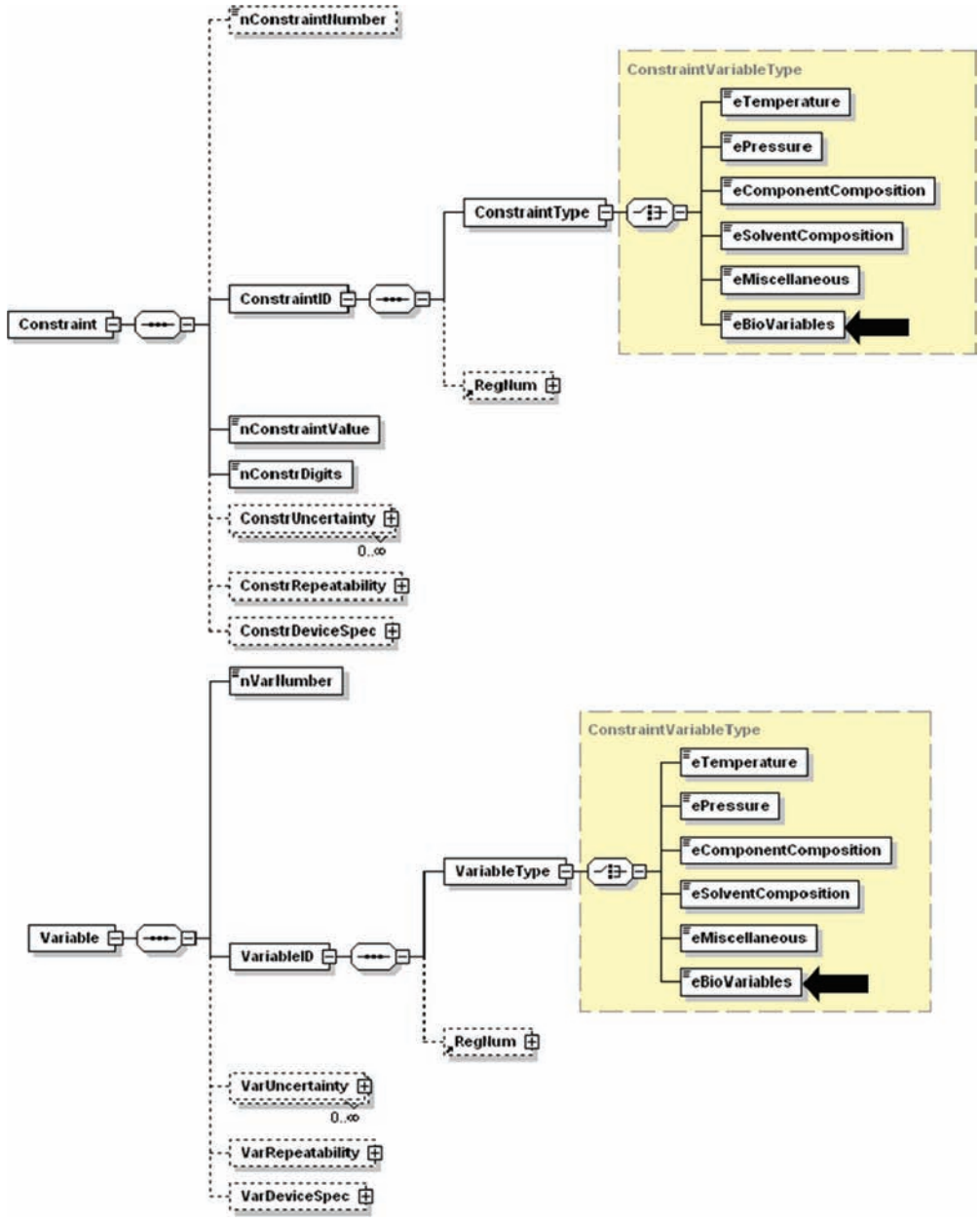

Figure 12. Structures of the **Constraint** [complex] and **Variable** [complex] elements within the *ReactionData* block. The arrows indicate the locations of the extensions to the schema for representation of biothermodynamic data.

used to define new properties within the ThermoML schema that are specific to biothermodynamic studies, as recommended by Hinz and Schwarz[15] for phase transitions in biological systems studied with DSC. These are included as entries in an enumeration list, and further extensions can be added readily, if required. Other properties commonly reported in the biothermodynamic literature are already described within the ThermoML schema.

The **Property** [complex] element is expanded in Figure 9, where the locations of extensions for biothermodynamic properties (**BioProperties** [complex], **eBioState** [enumeration], **sBioState** [string]) are indicated. The structure of **BioProperties** [complex] is shown in Figure 10. The **ePropName** [enumeration] element allows selection of the biothermodynamic property (zero Gibbs energy temperature, K; heat capacity change at transition, $J \cdot K \cdot mol^{-1}$; van't Hoff enthalpy of transition, $kJ \cdot mol^{-1}$). Property names are those recommended by Hinz and Schwarz.[15] Methods enumerated within **eMethodName** are experimental in nature. The enumeration list for **eMethodName** [enumeration] within the **BioProperties** [complex] element is DSC/DTA, which are the common abbreviations for differential scanning calorimetry and differential thermal analysis. **sMethodName** [string] can be used to identify other experimental methods. Methods associated with property prediction (**Prediction** [complex]) and critical evaluation (**CriticalEvaluation** [complex]) are represented separately to distinguish clearly among the three property sources: experiment, critical evaluation, and prediction. Full descriptions of these aspects of the schema were described earlier.[5]

eBioState [enumeration] is a subelement of **PropPhaseID** [complex], as seen in the center of Figure 9, and allows specification of states that are specific to biothermodynamic properties (native, denatured). For a transition from one state to another, a property is associated with two phases, of which the first is the initial state and the second is the final. **sBioState** [string] allows specification of other states not included in the enumeration list. For example, lipid membrane systems have been shown to exhibit a wide variety of states including subgel,

gel, and ripple states.[17] Research in this area is very active currently, and a consensus on specific terminology for the various states has not yet been established.

Structural Elements Related to Biothermodynamic Data in the *ReactionData* Block

Extensions for biothermodynamic data are added in five locations within the *ReactionData* block, as shown in Figure 4. The structure of the **AuxiliarySubstance** [complex] is the same as that within the *PureOrMixtureData* block, which was shown in Figure 8. Within the *ReactionData* block, the enumerations for **eFunction** [enumeration] are specific for reactions (cofactor, buffer, inert). Catalyst and solvent specification are also important for biothermodynamic reaction data, but elements for these already exist elsewhere in the schema.

The **eReactionFormalism** [enumeration] element allows specification of the reaction formalism type (chemical, biochemical). If the *chemical formalism* is used, thermodynamic equilibrium constants depend on temperature only, and apparent equilibrium constants (i.e., those expressed in terms of concentration) further depend on activity coefficients of the species participating in the reaction. In the *biochemical formalism*, thermodynamic equilibrium constants cannot be defined, and apparent equilibrium constants expressed through total concentration of species in various forms of dissociation and complexation depend on many factors, such as pH, pMg, ionic strength, and so forth. The number of these factors is not strictly determined.

New Variable and Constraint Types for Biothermodynamic Data

Several variables that are commonly used in the reporting of biothermodynamic data, but were not present previously in ThermoML, are added now. The new subelement **eBioVariables** [enumeration] {pH; ionic strength (molality basis), $mol \cdot kg^{-1}$; ionic strength (amount concentration basis), $mol \cdot dm^{-3}$; pC (amount concentration basis); solvent pC (amount concentration basis)} is now included within the **Constraint** [complex] and **Variable** [complex] elements of the *PureOrMixtureData* block (Figure 11) and *ReactionData* block (Figure 12).

Use Cases and ThermoML Schema Text (Supporting Information)

Examples of files containing biothermodynamic data were created with the ThermoML formats and are included as Supporting Information. The examples are based upon studies published in the peer-reviewed literature involving lysozyme unfolding in a differential scanning calorimeter (*Example 1*),[18] enthalpy determination for an enzyme-catalyzed reaction (*Example 2*),[19] binding constants determined with isothermal titration calorimetry (*Example 3*),[20] the solubility of some amino acids in salt solutions with various values of pH (*Example 4*),[21] and lipid polymorphism in a complex medium (*Example 5*).[22] The experimental data represented in *Example 5* was taken from the LIPIDAT.2 relational database of thermodynamic and associated information on lipid mesophase and crystal polymorphic transitions (LIPIDAT ID #10698). This database is freely available online.[23]

The complete current text of the ThermoML schema is included here as Supporting Information (in txt format) and is available on the Web (http://www.trc.nist.gov/ThermoML.xsd) or through direct request to the authors. The txt file can be read with any text editor, and the xsd file can be opened with an XML editor, such as XML SPY.[16]

Future Extensions

Future extensions of ThermoML under the current IUPAC project will be related primarily to speciation and complex equilibria in aqueous and nonaqueous solvents. Extensions described in the present paper in combination with those planned will constitute new IUPAC recommendations for the extension of ThermoML.

Supporting Information Available:

Complete current text of the ThermoML schema (in txt format). Five example use-case files containing biothermodynamic data are included. This material is available free of charge via the Internet at http://pubs.acs.org.

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