

Supporting Model Reuse in Organic Reaction Simulation: Towards the Compositional Modelling Approach

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ABSTRACT

Model formulation and model reuse are among the challenges in the field of qualitative reasoning research. In organic reactions, there are many task-level chemical processes. Identifying the generic ones can help promote model reuse in a qualitative simulation environment. This paper describes an approach to automate qualitative models and reuse them for the simulation of a group of organic reactions for learning purposes. In particular, this paper describes how the generic processes are identified and used for the simulation of task-level processes. The generic processes were identified as “make-bond” and “break-bond”. In this work, chemical processes are represented as model fragments using the Qualitative Process Theory (QPT) ontology. The work applied compositional modelling technique to chain model fragments when predicting the final products of organic chemical reactions.

Keywords: *Compositional Modelling, Model Reuse, Organic Reaction, Qualitative Simulation.*

1. INTRODUCTION

Qualitative Reasoning (QR) is an area of research combining Artificial Intelligence (AI) and cognitive science. Qualitative simulation produces predictions directly from the qualitative characteristics of behaviour expressed in conceptual terms which are suitable for students [1]. In QR research, however, several challenges remain. Two of the challenges are: (1) How to formulate a model? (2) How to promote model reuse? This paper describes how the formulation and reusability of models are achieved for the simulation of a group of organic chemical reactions. The findings and results of these two activities formed the basis for the development of a qualitative simulator called Qualitative Reasoning in Organic Mechanism (QRiOM).

The formalization of automated modelling techniques has been one of the hallmarks of QR where a model for a scenario is automatically constructed from a structural description and task constraints. Most QR systems adopt a reductionist view of the world and aimed at building libraries of elementary model fragments. In compositional modelling [2], model fragments are chained. Chaining model fragments provides the basis for reusing models, a highly desirable feature for industrial applications [3]. CyclePad [4] and Garp3 [5] used compositional modelling in assembling qualitative models for process simulation. More recent work done by Horiguchi and Hirashima [6] also applied compositional modelling technique to provide intelligent support for authoring graph of microworld. Our work uses a kind of model composition technique to construct models using qualitative process theory [7] based on the recognition of suitable pairs of views. A “view pair”

is defined as having two individual views, in the form of $\langle \textit{Individual-View-1}, \textit{Individual-View-2} \rangle$. An individual view can be a nucleophile or an electrophile. A “view pair” is also used as the means to select a chemical process (or covalent bonding) in this work. The main contribution of this work is the adaptation of an existing technology (compositional modelling) to a specific area (organic chemical reactions) through a domain analysis.

2. BACKGROUND

This section provides the necessary knowledge on the application domain and the modelling technique. Section 2.1 defines a few terms related to organic chemical reactions and the problems faced by the chemistry students when learning the subject. Section 2.2 provides an overview of the ontology used in modelling the domain knowledge.

2.1 ORGANIC REACTIONS

An organic reaction is a chemical reaction involving organic compounds, usually between an electrophilic centre and a nucleophilic centre. Electrophiles are electron-deficient molecules and can react with nucleophiles. An electrophile will accept electrons in order to fill up their valence shell. In any chemical reaction, some bonds are broken and new bonds are made. A covalent bond is what links two atoms together within a structure. It is formed by the sharing of a pair of electrons between two atoms. Atoms can form bonds by sharing unpaired electrons (also called “lone pair electrons”). Usually, an organic reaction may involve a series of small changes one after the other. A reaction mechanism

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describes this series of changes. This work tested two types of mechanisms, namely S_N1 (unimolecular nucleophilic substitution) and S_N2 (bimolecular nucleophilic substitution). S_N stands for substitution nucleophilic and the “1” shows that the reaction is first order or unimolecular, that is only one of the reactants affects the reaction rate. S_N2 reaction is second order since the rate is dependent on both the organic substrate (e.g. alkyl halide) and the incoming nucleophile. The “2” signifies that the rate of reaction is second order or bimolecular and depends on both the concentration of the nucleophile and the concentration of the alkyl halide.

There are many cognitive steps leading from a chemical reaction to chemical solution. Understanding the cognitive steps is among the many difficulties chemistry students are facing such as lacking the skills to analyze the steps and translate the reactions into the forms that can be used to predict the final product in reasonable and justifiable ways. When students were asked whether they find learning organic chemical reaction difficult, most of them claimed it is so. Students get confused mainly due to the abstract nature of the problem. As such, most of the students learn organic reaction by memorizing the steps involved in a reaction, and the formulas taught in classes. In science education, it is believed that students should understand the qualitative principles that govern the subject including the cause-effect relationships in processes before they are immersed in complex problem solving. When these fundamental skills are acquired, the entire learning activity can be made more effective. The nature of the chemistry domain described in this work is very qualitative and understanding the subject would require application of chemical insight and good use of chemical commonsense [8]. Thus, this problem domain is a suitable field for applying the QR technology.

2.2 QUALITATIVE PROCESS THEORY (QPT)

Among the prominent QR ontologies are process-centred [7], component-based [9], and constraint-based [10]. QPT is a type of process-centred ontology. The ontology is suitable for testing our reaction cases since in this formalism, changes are caused by continuous physical processes (e.g., the series of covalent bonding), which provide the notion of causality. Thus, it is useful as a language to express the intuitive ideas (the cognitive aspects) of organic reactions. In QPT, a “process” model supports changes in system behaviour. One of the important modelling constructs for describing the relationships between *quantities* (chemical parameters) is the *qualitative proportionalities* (the P+/P-). These constructs propagate the effects of processes between two *quantities* (e.g., charge, covalent bond, lone pair electrons, and electro-negativity). The QPT’s *qualitative proportionalities* are especially powerful primitives for building chains of causality to describe and explain a simulation result. This type of causal theories makes QPT a suitable ontology for modelling dynamic physical system such as chemical systems. Apart from this, the ontology

also allows representation of chemical process elements at the finest level of granularity (see Section 3).

3. TOWARDS AUTOMATING QPT MODEL FOR COVALENT BONDING

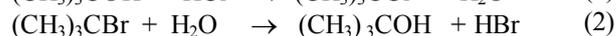
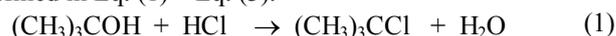
This research began by reviewing 44 chemical reactions involving alcohols and alkyl halides as the organic compounds (also called “substrates”). From the study, “make-bond” and “break-bond” were identified as the generic processes in the simulation of organic reactions involving the two groups of substrates. The two processes are the reusable models in the framework to support the simulation of multiple organic reactions occurring under S_N1 and S_N2 mechanisms. From analysis of various chemical reactions, the common set of chemical theories and behaviour have been identified for the two processes from which the model automation procedures are formulated. To tackle the former issue, we proposed an approach for automating the formulation of QPT models. In particular, the representation of chemical theories and general behaviour of the organic processes via the modelling constructs of QPT are discussed. The latter issue is addressed by proposing a classification scheme for chemical processes based on the movement of electrons resulted in the two bonding processes (“make-bond” and “break-bond”). Representation of the conceptual knowledge and chemical theories of organic chemical reactions at the finest level of granularity allows explanation at deeper level to be achieved.

3.1 GENERIC PROCESSES

It is ascertained that only two chemical processes (“make-bond” and “break-bond”) are required for reproducing the behaviour of the organic chemical reactions that involve alcohols and alkyl halides [8]. Section 3.2 discusses the model formulation procedures that aimed to assemble common chemical properties and behaviour patterns for the identified organic processes. This is the technique used for automating the construction of QPT processes in our simulation environment.

3.2 MODEL FORMULATION PROCEDURES

The chemical data presented in Table 1 – Table 4 provide us the basis for deducing and extracting the qualitative behaviour from the three chemical equations as defined in Eq. (1) – Eq. (3).



We will show how the establishment of the set of functional dependencies for the “make-bond” process is accomplished. When the numerical data in Table 1 – Table 4 are examined, the following cause-effect propagation can be established (refer to (a) – (h)).

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Note that “ $Y \propto X$ ” means “increasing X followed by decreasing Y ”. The symbol “ \propto ” means “proportionality”. The numerical data in Table 1, Table 3 and Table 4 allow us to define the following qualitative proportionalities:

$$\text{lone-pair-electron}(O) \propto \text{no-of-bond}(O) \quad \dots(a)$$

$$\text{charge}(O) \propto \text{lone-pair-electron}(O) \quad \dots(b)$$

$$\text{lone-pair-electron}(H^+) \propto \text{no-of-bond}(H^+) \quad \dots(c)$$

$$\text{charge}(H^+) \propto \text{no-of-bond}(H^+) \quad \dots(d)$$

Likewise, the numerical values from Table 2, Table 3 and Table 4 enable us to define the following relationships:

$$\text{lone-pair-electron}(Cl) \propto \text{no-of-bond}(Cl) \quad \dots(e)$$

$$\text{charge}(Cl) \propto \text{lone-pair-electron}(Cl) \quad \dots(f)$$

$$\text{lone-pair-electron}(C^+) \propto \text{no-of-bond}(C^+) \quad \dots(g)$$

$$\text{charge}(C^+) \propto \text{no-of-bond}(C^+) \quad \dots(h)$$

Table 1: Reacting species and their chemical change in the “protonation” process (“make-bond”) of Eq. (1).

Nucleophile (O)	Before	After	Remarks	Electrophile (H ⁺)	Before	After	Remarks
Charge	Neutral	Positive	Unstable	Charge	Positive	Neutral	Stable
No. of covalent bond	2	3	More than what it should have	No. of covalent bond	0	1	Not informative
Lone pair electrons	2	1	Have not reached maximum pair	Lone pair electrons	0	0	No change and not informative

Table 2: Reacting species and their chemical change in the “capturing of halide anion by carbocation” process (“make-bond”) of Eq. (1).

Nucleophile (Cl ⁻)	Before	After	Remarks	Electrophile (C ⁺)	Before	After	Remarks
Charge	Negative	Neutral	Stable	Charge	Positive	Neutral	Stable
No. of covalent bond	0	1	Not informative	No. of covalent bond	3	4	Stable
Lone pair electrons	4	3	Stable	Lone pair electrons	0	0	No change

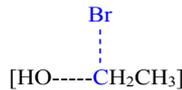
Table 3: Reacting species and their chemical change in the “reacts with water” process (“make-bond”) of Eq. (2) for the formation of alcohol.

Nucleophile (the “O” in OH ₂)	Before	After	Remarks	Electrophile (C ⁺)	Before	After	Remarks
Charge	Neutral	Positive	Unstable	Charge	Positive	Neutral	Stable
No. of covalent bond	2	3	More than what it should have	No. of covalent bond	3	4	Stable
Lone pair electrons	2	1	Have not reached maximum pair	Lone pair electrons	0	0	No change

Table 4: Reacting species and their chemical change in the “nucleophile attacks” process (“make-bond”) of Eq. (3) for the formation of ethanol.

Nucleophile (HO ⁻)	Before	After	Remarks	Electrophile (the “C” that bond to the bromine)	Before	After	Remarks
Charge	Negative	Neutral	Stable	Charge	Positive	Neutral	Stable
No. of covalent bond	1	2	Stable	No. of covalent bond	3	4	Stable
Lone pair electrons	3	2	Not informative	Lone pair electrons	0	0	No change

Table 5: Reuse of generic processes to accomplish the simulation of the three chemical equations presented in Section 3.2.

	Eq. (1)	Eq. (2)	Eq. (3)
Step 1	“make-bond” (CH ₃) ₃ COH + H ⁺	“break-bond” (CH ₃) ₃ C-Br	“break-bond” 
Step 2	“break-bond” (CH ₃) ₃ C-OH ₂ ⁺	“make-bond” (CH ₃) ₃ C ⁺ + H ₂ O	“make-bond” (HO ⁻ ---CH ₂ CH ₃ ----Br)
Step 3	“make-bond” (CH ₃) ₃ C ⁺ + Cl ⁻	“make-bond” (CH ₃) ₃ COH ₂ ⁺ + H ₂ O	--

In all the above cases, an increase in no-of-bond of the nucleophile (e.g., O and Cl⁻) will cause a decrease in its lone-pair-electron ((a) and (e)). This in turn will increase the charge of the affecting species either from neutral to positive (increasing) or from negative to neutral (also increasing). The charge on electrophile is neutral after the “make-bond” process in each case (shown in (d) and (h)). The chemical properties and behaviour of the nucleophile in Table 1 and the nucleophiles in Table 3 and Table 4 are the same while the electrophiles in Table 2 and Table 4 share similar behaviour of that in Table 1. In other words, provided that it is an electrophile then it will demonstrate the same chemical properties change. When these behaviour characteristics are obtained, algorithm that enables model automation can be developed.

4. MODEL REUSE MANIFESTATION

Chemical behaviour generalization requires the study of the processes in each chemical equation. The series of small reaction steps for the three chemical equations will first be presented. The task-level processes for the simulation of Eq. (1) – Eq. (3) are depicted in Figure 1 – Figure 3 respectively. The symbol “δ⁺” (delta-plus) in Figure 3 refers to a partial positive charge species (or neutral electrophile) while “δ⁻” (delta-minus) symbolizes partial negative charge species (neutral nucleophile) that

has a tendency to pull electrons towards it. Even though the names of the chemical processes are different, they can be grouped under either one of the two bonding activities. Based on the information in Table 5, the QPT process models constructed for Eq. (1) can be used by the other two chemical equations. For example, the QPT model constructed for breaking the (CH₃)₃C-OH₂⁺ bond in Eq. (1) is reused by Step 1 in Eq. (2) and Eq. (3). Also, the QPT model constructed for making a bond between the alcohol oxygen of (CH₃)₃COH and a proton (H⁺) can be used by Step 2 in Eq. (2) and Eq. (3). This is the simple scheme used to support the reusability of QPT models.

Task-level processes	View-Pair	
	Reactant 1	Reactant 2
Protonation (“make-bond”)	(CH ₃) ₃ COH (nucleophile)	H ⁺ (electrophile)
Dissociation (“break-bond”)	(CH ₃) ₃ C-OH ₂ ⁺ (electrophile)	(nucleophile)
Capturing of anion by carbocation (“make-bond”)	(CH ₃) ₃ C ⁺ (electrophile)	Cl ⁻ (nucleophile)

Figure 1: Reactants and their associated task-level processes for the conversion of a tertiary alcohol ((CH₃)₃COH) to yield the alkyl chloride ((CH₃)₃CCl).

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Task-level processes	View-Pair	
	Reactant 1	Reactant 2
Dissociation (“break-bond”)	(CH₃)₃C–Br (electrophile)	Br (nucleophile)
Reaction with water (“make-bond”)	(CH₃)₃C⁺ (electrophile)	H₂O (nucleophile)
Fast acid-base reaction (“make-bond”)	(CH₃)₃COH₂⁺ (electrophile)	H₂O (nucleophile)

Figure 2: Reactants and their associated task-level processes for the conversion of the alkyl chloride to yield a tertiary alcohol “(CH₃)₃CBr + H₂O → (CH₃)₃COH + HBr”.

Task-level processes	View-Pair	
	Reactant 1	Reactant 2
Dissociation (“break-bond”)	Br–CH₂CH₃ Where Br is δ- and C is δ+	
Reaction with water (“make-bond”)	C⁺ H₂ CH₃ (electrophile)	HO⁻ (nucleophile)

Figure 3: Reactants and their associated task-level processes for the concerted steps (“dissociation” and “reaction with HO⁻”).

In QPT, *individual views* are used to model the behaviour of individuals (objects) and to provide explanation about their general characteristics. Automatic construction of individual views is made possible through recognizing the reacting species as either a nucleophile or an electrophile. The work suggests that a chemical process is activated based on the recognition of the reacting units, which is called “view-pair”. Note that those symbols printed in boldface in Figure 1 – Figure 3 are the pairs of views used for activating a chemical process during simulation. The set of possible view pairs for this work is given in Table 6. The result is obtained through a detailed analysis performed on numerous reaction cases. The first row in Table 6 says: “a bond will be made (or formed) when the view-pair of <neutral nucleophile, charged electrophile> exists”. Likewise, a bond will be deleted when one of these view pairs exists: <neutral electrophile, neutral nucleophile> or <neutral electrophile, charged nucleophile>.

Table 6: Relationship between view pairs and covalent bonding.

No.	Individual-View1	Individual-View2	Covalent Bonding
1	neutral nucleophile	charged electrophile	make bond
2	charged electrophile	charged nucleophile	make bond
3	neutral electrophile	charged nucleophile	make bond

4	neutral electrophile	charged nucleophile	break bond
5	neutral nucleophile	neutral electrophile	make bond
6	neutral nucleophile	neutral electrophile	break bond

In Table 6, individual views in No. 3 and No. 4 are the same, but the covalent bonding that will take place is different. So, which one would the software advise to occur? The solution is to use the *Ontology for Reaction Mechanism (OntoRM)* to disambiguate the situation [11]. OntoRM is designed specifically for validating the use of chemical data in the QRiom qualitative simulator (implementation of the reasoning framework). The OntoRM ontology will serve as a validation module *during* (to ensure the right data is passed to the reasoning engine) and *after* a simulation is completed (to ensure the results are predicted correctly). With OntoRM, QRiom is able to reduce the simulation possibilities (branches in a state graph) by only returning the most promising one.

Figure 4 depicts the scenario of QPT model reuse in the simulation of organic chemical reactions. The automated QPT models can be used to reproduce the behaviour of reactions such as “A₁ + B₁”, “A₂ + B₂”, ..., “A_n + B_n”. No matter what A’s (e.g., C⁺) and B’s (e.g., Br⁻) are, provided that they belong to the same class of nucleophiles and electrophiles then the same make/break bond processes can be used.

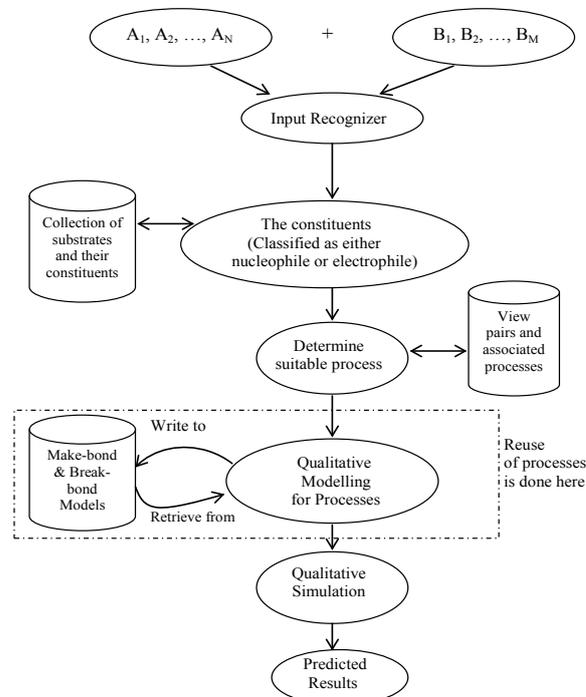


Figure 4: An example of QPT model reuse. The eight task-level processes shown in Figure 1 – Figure 3 will call upon either one of the two generic processes represented as QPT models.

In Section 5, we will demonstrate an example of how model fragments are chained in order to predict the outcome of an organic chemical reaction.

5. QUALITATIVE REASONING WORKFLOW

The QRiOM simulator consists of a number of software components. Figure 5 gives its main components. The main components are: input recognizer, model constructor, reasoning engine, explanation generator, knowledge validation module, OntoRM and the chemical knowledge base. Other subcomponents are the Quantity Space Analyzer (QSA) and the Molecule Update Routine (MUR). The inputs are represented as basic facts in the format of predicate logic (Prolog). The top level design of the process model automation steps is outlined in Figure 6.

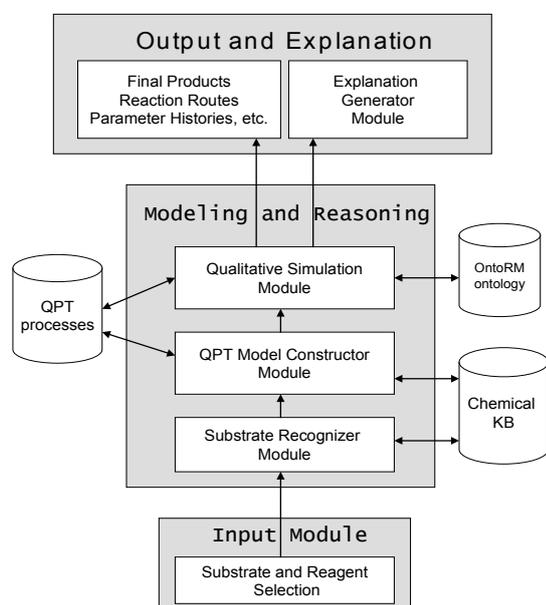


Figure 5: A schematic view of the qualitative reasoning framework described in terms of the input, process, output and the knowledge bases.

INDIVIDUAL VIEWS AND PROCESSES MODELLING ALGORITHM

Qualitative_Modelling(substrate, reagent, QPT_MODEL)

1. Examine user inputs
 - 1.1 Retrieve constituent parts of the substrate from chemical KB
2. Recognize structural units in substrates
 - 2.1 Assign units as either nucleophile or electrophile
 - 2.2 Store them in View Instance Structure (VIS)
3. Retrieve chemical facts and chemical properties of the reacting units
 - 3.1 Compose the four slots of a QPT view
4. Suggest a chemical process based on the view pair
5. Retrieve chemical theories of the suggested organic process
 - 5.1 Assign process quantity to the direct-influence slot of the QPT model
 - 5.2 Compose the other three slots: [Individuals, Quantity-Cond, Relations]

Figure 6: The main steps in the model constructor module.

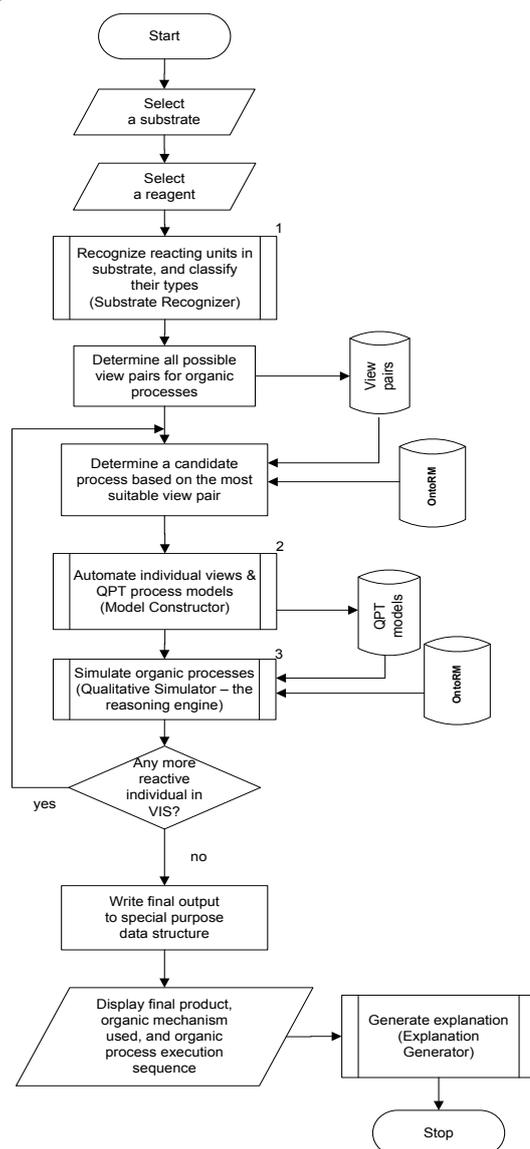


Figure 7: Workflow of the QPT-based reasoning.

Figure 7 depicts the workflow of the QPT-based reasoning for reproducing the behaviour of organic reactions as well as the explanation and justification of the simulation results. The approach presented in Section 3 is implemented in Module 2 of Figure 7. This work treats input pairs as the “structure” for representation, and the set of current states for the organic substrate as the “initial situation”. When a substrate (A) reacts to a reagent (B), some changes are observed. These changes will become the “behaviour” of the reaction between A and B, and they are represented using the modelling constructs of QPT. The behaviour of organic reactions can then be reproduced when simulation algorithms are run. In predicting the final products, all qualitative states and values of affected parameters together with their causality chain are recorded in special purpose data structures. The contents of these structures will be used for generating multiple forms of explanation on-the-fly.

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5.1 REPRODUCING THE BEHAVIOR OF “MAKE-BOND” VIA QPT REASONING

Figure 8 gives the QPT model that represents the chemical theories of “make-bond” for the task-level process called “protonation”.

Process Slots	Modelling constructs in QPT	
Individuals	1. H ⁺ ;represents hydrogen 2. O ⁻ ;represents the alcohol oxygen	A
Quantity-Conditions	3. A _m [lone-pair-electron(O)] >= ONE 4. charges(H, positive) 5. electrophile(H, charged) 6. nucleophile(O, neutral) 7. charges(O, neutral)	B
Direct Influences	8. I ⁺ (no-of-bond(O), A _m [bond-activity]) 9. I ⁺ (no-of-bond(H), A _m [bond-activity])	C
Relations	10. D _s [charges(H)] = -1 ;decreasing sign 11. D _s [charges(O)] = 1 ;increasing sign 12. lone-pair-electron(O) P ⁺ no-of-bond(O) 13. charges(O) P ⁻ lone-pair-electron(O) 14. lone-pair-electron(H) P no-of-bond(H) 15. charges(H) P ⁺ no-of-bond(H)	D

Figure 8: The “protonation” process instantiated from the generic “make-bond” model.

Basically, the behavior of a chemistry system can be described as a sequence of qualitative states occurring over a particular span of time. The following description is an example of how the generic model for “make-bond” is used to support a task-level problem. Given the QPT model in Figure 8, you may read the right column as “If (A and B) Then (C and D)”. In this case, C and D are qualitatively reasoned. This process occurs when the individuals (a nucleophile and an electrophile) are available. It is the candidate process because the statements in quantity-conditions are satisfied (Lines 3 – 7), which speak for “the process needs a proton and alcohol oxygen with at least one lone pair electrons to be donated to the proton in order to make a bond”. We represent chemical changes as starting from direct influence which then propagates via indirect influences. Influences contain statements that specify what can cause a quantity to change, through direct influence imposed by the process (label C). As the process occurs, bond-activity is a direct influence’s process quantity and it has a positive influence (I⁺) on the no-of-bond; which is defined as two direct influence statements using the “I⁺/I⁻” notation of the QPT; as shown in Line 8 and Line 9. Other propagation of effect is defined in Relation-slot (label D). It is propagated via a set of qualitative proportionalities defined in the QPT process model. The QSA module will update the initial values of the affected quantities. If the entry conditions (as defined in label B) are violated, then this process will stop. The new quantity created by this “make-bond” process is the oxonium ion (–OH₂⁺) and it will be placed into the View Instance Structure (VIS). The simulation continues by switching to the second reaction step. When the VIS is left with one species then the entire reaction is claimed

completed. These reaction steps (will become the reaction route) can be used to explain the overall chemical change that occurred.

The QPT model presented in Figure 8 can be used again to simulate the reaction between the <(CH₃)₃C⁺, H₂O> view-pair. Note that this is the second reaction step in Eq. (2). In this pair of views, only the individual views are different. It is also the No. 1 case in Table 6. Similarly, the same model can be used to support the simulation of the third reaction step (between the <C⁺, Br⁻> pair) of Eq. (1) and the second reaction step (between <CH₃, HO⁻>) of Eq. (3). Refer to Table 5 for all the cognitive steps stated above. As far as the simulation results are concerned, the results (produced by the software) matched those written in textbooks. All the simulation results have also been validated by the chemistry lecturers from Malaya University and University of Tenaga Nasional.

6. CONCLUSION

An approach for automating the construction of QPT models has been discussed. The QPT ontology allows representation of chemical process elements at the finest level of granularity. The generic processes are determined based on the movement of electrons such that explanation at deeper level can be achieved. Since there are numerous task-level processes in organic chemical reactions, identifying the generic ones can help promote model reuse in a qualitative simulation environment. The reusability of models in supporting the reproduction of the behaviour of covalent bonding has also been demonstrated. The model automation module has been implemented in a learning tool called QRiOM. Though the tool employed an existing qualitative reasoning technology, its contribution lies on showing how to adapt existing technology to a specific area. The ultimate aim of the tool is to provide explanations to the chemistry students at undergraduate level so as to allow them to gain an intuition of the underlying reactions. Evaluation results show that the tool has enhanced student knowledge in organic chemical reactions [12].

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