Innovation in the Japanese Chemical Industry

August 9-12, 2003

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Chief Technology Officer
Mitsubishi Chemical Corporation
Outline of Presentation

• Session-1: The Japanese Government’s Plans
• Session-2: The Reformation, Renovation and Topics in Mitsubishi Chemical Corporation
• Session-3: Examples of computer simulation for R&D speed up in MCC
Session-1

The Japanese Government’s Plans
## Science and Technology Policy

### [ Main Issues ]

<table>
<thead>
<tr>
<th>A. R&amp;D doesn’t lead directly to strengthening of competitiveness</th>
</tr>
</thead>
<tbody>
<tr>
<td>B. Lack of human resources (managers) with MOT sense and skills</td>
</tr>
<tr>
<td>C. Hoarding of “R&amp;D fruits”</td>
</tr>
<tr>
<td>D. Indispensability of activation of fundamental R&amp;D institutes such as universities</td>
</tr>
<tr>
<td>E. Necessity of government budget execution in accordance with R&amp;D characteristics</td>
</tr>
<tr>
<td>F. Lack of industry’s MOT innovation model responding to a new age</td>
</tr>
</tbody>
</table>

### [ Countermeasures ]

<table>
<thead>
<tr>
<th>Economy Activation Project</th>
</tr>
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<tbody>
<tr>
<td>Nurturing of human resources (managers) with MOT sense and skills</td>
</tr>
<tr>
<td>Promotion of spin-off venture businesses</td>
</tr>
<tr>
<td>Reformation of competitive fund system and academia</td>
</tr>
<tr>
<td>Through performance-related evaluation agile and flexible budget execution</td>
</tr>
<tr>
<td>Presentation of MOT innovation model</td>
</tr>
</tbody>
</table>

Ref: Report of Hiramura Minister in April 4, 2003
Nurturing of human resources with MOT sense and skills

[Main Issues]
* Lack of technology management systems in industries
* Necessity of good technology judge and industrialization strategy
  * Over 200 MOT courses and about 10 thousand graduates of MOT per year in US
  * MOT Programs started by some institutes in Japan

[Action Plans]
* Nurturing of about 10 thousand managers with MOT sense and skills

In METI
Support of 39 institutes such as universities being intended to establish MOT courses from FY 2002 supplementary budget

Ref: Report of Hiramura Minister in April 4, 2003
Reform of Competitive Fund System and Academia

[ Main Issues ]
Penetration of competition principle and activation of creative power

In METI
Introduction of Program directors in competitive fund execution etc.

[ Action Plans ]
* Reformation of competitive fund system which maximize researchers’ creativity
* Academia reformation
  * Complete liberalization of establishment of universities, departments and student capacity
  * Consolidation of outside evaluation organization

Ref: Report of Hiramura Minister in April 4, 2003
Prioritization of Science and Technology

Establishment of economy activation project directly linked with commercialization (Focus 21) Total 36.7 billion \ in FY 2003 budget

| Life science: 8.8 billion \ |
|---------------|---------------------|
| * Sugar chain engineering PJ |
| * Bio-IT fused instrument development PJ |

| Environment: 4.4 billion \ |
|-----------------|----------------|
| * Next generation energy saving PDP PJ |
| * High functional materials applied to houses utilizing photocatalysis PJ |

| Information and telecommunication: 17.3 billion \ |
|-------------------|----------------|
| * IT based advanced software development PJ |
| * Chips for semiconductor application PJ |

| Nanotechnology and materials: 6.1 billion \ |
|-----------------|----------------|
| * Carbon nanotube FED PJ |
| * Ultimate function of Diamond PJ |

Ref: METI Report of Focus 21
Session-2

The Reformation, Renovation and Topics in Mitsubishi Chemical Corporation (MCC)
# Corporate Profile of MCC

<table>
<thead>
<tr>
<th>Company Name</th>
<th>Mitsubishi Chemical Corporation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Head Office</td>
<td>5-2, Marunouchi 2-chome, Chiyoda-ku, Tokyo 100-0005</td>
</tr>
<tr>
<td>Capital</td>
<td>145.1 Billions of yen on March 31, 2003</td>
</tr>
</tbody>
</table>
| Representives| Chairman of the Board: Kanji Shono  
President & CEO: Ryuichi Tomizawa |
| Number of Employees | 7,853 members on March 31, 2002 |
| Net sales Consolidated | 1,887.5 Billions of yen  
Non-consolidated | 674.6 Billions of yen |
| For the Year Ended March 31, 2003 | |
Aligning R&TD with Business Strategy

Management Committee: (CEO)

Strategic Planning and Business Development Group

Corporate Business Strategy-Plan

MCC-Group Science & Technology Office (STO)

* R&TD Directors of the five MCC Group Business-Segments

Corporate Technology Council *: (CTO)

Corporate R&TD Strategy-Plan

MCC-Group Science & Technology RC (MCRC)

Technologies from outside MCC Industry-Academia-Government Alliance Program
Stage Gate System and Corporate R&TD Pipeline

Exploratory Research
Outsourcing

Prioritized Product Development Projects

Business Development Projects

Commercialization

Technology Platform

Pipeline Examples

<table>
<thead>
<tr>
<th>Business Development Projects</th>
<th>Prioritized Product Development Projects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nano-Carbons</td>
<td>High Functional Polymers</td>
</tr>
<tr>
<td>Photoelectronics/Display Components</td>
<td>Energy related Inorganic Materials</td>
</tr>
<tr>
<td>Environmental Benign Plastics</td>
<td>Bio-Chemicals</td>
</tr>
<tr>
<td>Designed Chemicals</td>
<td></td>
</tr>
</tbody>
</table>
The project team is composed of several researchers who belong to technology laboratories and have necessary technologies.

The mission of Project teams is to create new products and processes and improve existing products, processes and technology platforms etc.
Academia and Outer Institute Alliances in Information-electronics and Biotechnology

Development of new materials and devices

Cross organizational “Virtual” research institutes
Session-3:

Examples of computer simulation for R&D speed up in MCC
Model-Based Solvent Selection and Protein Crystallization


MCC-Group Science & Technology Research Center

S. Sugio

ZOEGENE Corporation

Objective:
Minimization of HT screening experiments using modeling techniques

Examples:
1. Solvent selection - Resolution of diastereomers
2. Model-based protein crystallization
Solubility Prediction Methods

1. Group contributions
   - UNIFAC
   - New functional groups

2. Molecular simulations
   - Discrete
   - Continuum
   - MC equilibration
   - COSMO-RS
   - Solvation

P - profiles
α-profile

VLE
LLE
SLE
**Example - Resolution of Diastereomer Salts**

- Reactive crystallization:

  \[
  \text{A} + \text{B} \rightarrow \text{R}(-).\text{B} \quad \text{(R-S)} \\
  \text{S}(+)\text{.B} \quad \text{(S-S)}
  \]

  **High solubility**

  **Low solubility**

  (Desired product)

**Similar solubilities**

**Task:** Find a solvent which maximizes R-S / S-S solubility difference

**COSMO-RS prediction method**
### COSMO-RS Prediction of Selectivity

#### Paraffines

<table>
<thead>
<tr>
<th>Solvent</th>
<th>S-S (γ)</th>
<th>R-S (γ)</th>
<th>S&lt;sub&gt;ij&lt;/sub&gt; (S/R)</th>
</tr>
</thead>
<tbody>
<tr>
<td>trans-decalin</td>
<td>690.4</td>
<td>33.7</td>
<td>20.48</td>
</tr>
<tr>
<td>cycloheptane</td>
<td>618.5</td>
<td>30.3</td>
<td>20.42</td>
</tr>
<tr>
<td>cis-decalin</td>
<td>590.9</td>
<td>29.1</td>
<td>20.32</td>
</tr>
<tr>
<td>cyclooctane</td>
<td>615.9</td>
<td>30.4</td>
<td>20.24</td>
</tr>
<tr>
<td>tetradecane</td>
<td>937.2</td>
<td>46.4</td>
<td>20.20</td>
</tr>
<tr>
<td>etcyclohexane</td>
<td>471.1</td>
<td>23.3</td>
<td>20.18</td>
</tr>
<tr>
<td>dodecane</td>
<td>869.2</td>
<td>43.1</td>
<td>20.17</td>
</tr>
<tr>
<td>n-heptane</td>
<td>424.3</td>
<td>21.1</td>
<td>20.12</td>
</tr>
<tr>
<td>octane</td>
<td>774.4</td>
<td>38.5</td>
<td>20.12</td>
</tr>
<tr>
<td>p-xylene</td>
<td>711.5</td>
<td>35.4</td>
<td>20.08</td>
</tr>
<tr>
<td>m-xylene</td>
<td>563.1</td>
<td>28.2</td>
<td>19.99</td>
</tr>
<tr>
<td>o-xylene</td>
<td>637.6</td>
<td>31.9</td>
<td>19.96</td>
</tr>
<tr>
<td>toluene</td>
<td>690.4</td>
<td>33.7</td>
<td>20.48</td>
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</tbody>
</table>

#### Aromatics

<table>
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<tr>
<th>Solvent</th>
<th>S-S (γ)</th>
<th>R-S (γ)</th>
<th>S&lt;sub&gt;ij&lt;/sub&gt; (S/R)</th>
</tr>
</thead>
<tbody>
<tr>
<td>mecn</td>
<td>0.3</td>
<td>0.2</td>
<td>1.51</td>
</tr>
<tr>
<td>t-butanol</td>
<td>0.8</td>
<td>0.7</td>
<td>1.22</td>
</tr>
<tr>
<td>dme</td>
<td>1.4</td>
<td>2.0</td>
<td>0.71</td>
</tr>
</tbody>
</table>

#### Alcohols

<table>
<thead>
<tr>
<th>Solvent</th>
<th>S-S (γ)</th>
<th>R-S (γ)</th>
<th>S&lt;sub&gt;ij&lt;/sub&gt; (S/R)</th>
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<tbody>
<tr>
<td>0.3</td>
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<td>0.71</td>
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</table>

#### Separation selectivity:

\[
S_{ij} (S/R) = \frac{\gamma_{S-S}}{\gamma_{R-S}}
\]

- Higher S/R difference
- Lower S-S solubility

### Paraffins vs. Aromatics

- Higher S/R difference
- Lower S-S solubility
Experimental Validation

a) Solubility of S-S

- Lower S-S solubility

b) Solubility of R-S

- Toluene
  - 80 90 100 110 120 130 140
  - Solubility, mass%: 0.1 1 10 100

- Paraffins C\(_n\) = 7-10
  - 80 90 100 110 120 130 140
  - Solubility, mass%: 0.1 1 10 100

MITSUBISHI CHEMICAL

Good "Chemistry" for Tomorrow
From Biology to Chemical Engineering

Biology
- Central Dogma (DNA --> Proteins)
- Protein functions

Chemistry
- Genome Science (Sequencing)
- Product design

Chemical Engineering
- Process development
- Modeling and simulation
Example: Protein Crystallization

Protein Synthesis → Purification → Protein Crystallization → Crystal → Protein 3D structure determination

(Cell-free) protein expression → Protein single crystal (> 0.1 - 0.3 mm) → X-ray diffraction → Synchrotron → Protein structure

(Bottleneck in proteomic pipeline)
Model-Based Protein Crystallization

- Synthesized protein
- Theory / Know-how
- Crystallization Modeling
- Experiment (HTS)
- Design of experiments (DOE)
- Protein crystals
- Protein 3D structure determination

IN → Model-Based Protein Crystallization → OUT
Reaction Analysis Example of Pharmaceutical Intermediate

Background:
- Low yield
- Unknown byproduct
- Low conversion

Objective:
To increase product yield

Work Flow:
1) Reaction Experiments
2) Determination of Reaction Mechanism
3) Kinetic Estimation
4) Reactor Optimization

Micro Flow Reactor
Reaction analysis tool for rapid reaction (1 sec~)

In-situ IR & Chemometrics
Combination of chemistry and mathematics

Reaction Analysis Studio (RAS)
Software tool developed by MCC Optimization group in collaboration with CAPEC group in Denmark Technical University.
Determination of Reaction Mechanism

Reaction data (by In-situ IR)

With extracted pure component spectrum, unknown byproduct is identified to Sodium Calboxylate

Identified Byproduct

Identification of Key Byproduct

? Determination of Reaction path (R1~R7)?

Byproduct - 1

Byproduct - 2

intermediate

R1

R2

R3

R4

R6

R5

R7

Substrate

COOEt

COONa

CN

CN

COOEt

COOEt
Kinetic Estimation

\[ R_1 = -k_1 \cdot f([\text{Sub}], [\text{NaCN}], [\text{Cat}]) \]

\[ k_1 = A \cdot \exp\left(-\frac{E_a}{R \cdot T}\right) \]

Parameter estimation

Dynamic optimization of control variables (temp, conc, etc.)

Conclusion

Micro flow reactor
In-situ measurement & Chemometrics
Reaction analysis tool (RAS)

Developed an Effective Approach for R&T&D Speed Up
Summary

1. Japanese Government is now going to improve the science and technology policy.
2. Mitsubishi Chemical Corporation is now going to improve R&D policy.
3. Mitsubishi Chemical Corporation has been successfully utilizing many kinds of computer simulation technology for promoting R&D speed up.
Appendix
Good "Chemistry" for Tomorrow

Target Image of Future Society and New Bioindustry
-- Improvement of "Living", "Eating", "Inhabiting" --

Limitations of 20th century technologies

Transformation of
1. Health & Longevity
2. Food Supply
3. Environment & Energy

Future Society

Living: Health & Longevity
* BT diagnostics, medical care promotion
* Realization of both longevity & medical cost prevention

Eating: Safety & Functionality
* BT food industry promotion
* Simultaneous achievement of safety, high functionality & supply

Inhabiting: Sustainable safe and secure society
* Overcome environment & energy limitations
* Realization of profitable environmental industry

Strategy 1
Enhancement of R&D

Strategy 2
Fundamental strengthening of industrialization process

Strategy 3
Intensive understanding by citizen

New Bioindustry (2010)
Over 1 million employees

Medical Care
8,400 billion

Food
6,300 billion

Environment & Process
4,200 billion

Biological Tool & Information Industry
Fusion of BT, IT, NT
5,300 billion

Future Society

Medical Care
8,400 billion

Food
6,300 billion

Environment & Process
4,200 billion

Biological Tool & Information Industry
Fusion of BT, IT, NT
5,300 billion

Over 1 million employees
Middle term Strategy of Mitsubishi Chemical Group

Maintaining the three pillars

2002

1,860 billion 

2007

2,240 billion

180 billion

Performance Products

Health Care

Petrochemicals

Sales

Profit
Strategic Alliance with Outer Institutes

Interdisciplinary collaboration

Exploratory research: Comprehensive alliances with leading universities and outer institutes such as UCSB, Kyoto Univ., AIST and Imperial College etc.

Promoted Alliance Strategy
* Promote comprehensive alliances in specific fields
* Establish alliance department in research institute and send responsible officials from MCC
* Accept individual themes under comprehensive theme (from the public)
* Bring research collaborators from MCC

Collaboration in strong and specific fields from early stage

Business development research: Alliance with business partners
Realization in integrated alliance with Kyoto Univ. and 5 companies
Technology Programs and Pipeline of Future Products

• Areas of Focus
  – Chemicals and Materials: “Product-Innovation”
    • Specialty Chemicals, Materials, and Components for the Information and Electronics Industry
    • Biochemicals and Biomaterials
    • “Specialty” Commodities: Organic and Inorganic
  – Services: “Solution-Partnerships”
    • Genomic Drug Discovery
    • “Designed” Chemicals
    • “Designed” Materials

• The Pipeline of Future Products and their Economic Impact
Technology Programs

“Green” Sustainable Plastics

Become the world-leader in a variety of elastomeric (soft) biodegradable polymers, produced from renewable resources

- Technology Platforms
  - Metabolic Engineering for the low-cost production of monomers from renewable resources
  - Polymer design with desired properties
  - Unique

- Products
  - A broad variety for different applications
Bio-production of ‘GS Pla’ monomers

Fossil resources

- n-Butane
  (Maleic anhydride) → Succinic acid
- 1,3-Butadiene → 1,4-Butanediol

Post fossil resources

Plant resources
  ex. Corn, potatoes, etc.

- Glucose → Lactic acid
  Fermentation

- CO2 → Succinic acid
  Fermentation
  Hydrogenation

1,4-Butanediol

Appl Microbiol Biotechnol 1999
Succinic acid production - Metabolic Engineering -

Enhance product formation and cut by-product with molecular breeding etc.