Integrated solvent and process design exemplified for a Diels-Alder reaction

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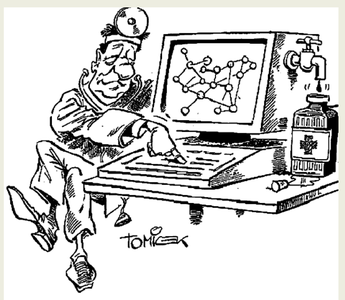
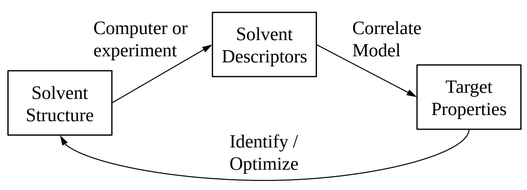
Research Motivation





Computer-Aided Solvent Design **(CASD)**

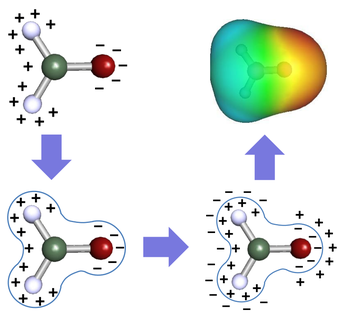
- **CASD:** First relates solvent structure to properties through solvent descriptors, then reversely determines the optimal solvent structure that match target property values based on the established quantitative structure-property relationship (QSPR).
- Conventional QSPR uses empirical or experimentally determined solvent parameters to correlate solvent effects. It can not be directly applied for extensive solvent screening and solvent molecular design.
- Integrated solvent and process design is essential for achieving an optimal chemical process.

<u>Goal</u>: to develop methods for the design of solvents for chemical reactions and integrated reactive processes.

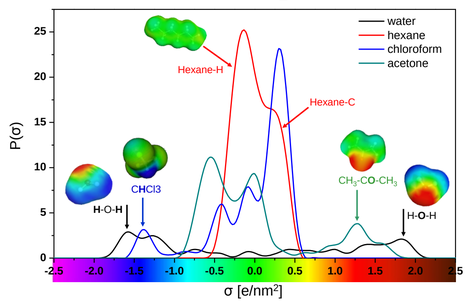
Theoretical Concepts & Methods

Conductor-like Screening Model (COSMO)

Quantum chemical DFT computation

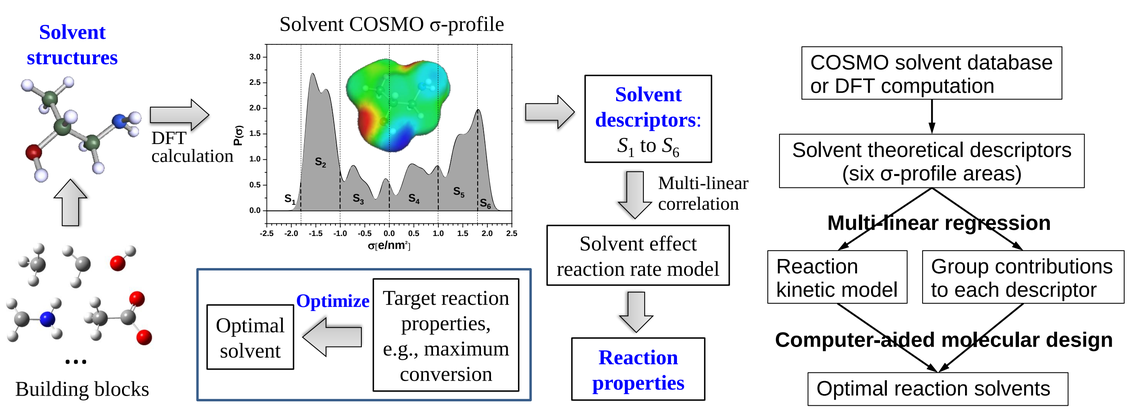


Screening Charge Density distribution, **σ-profile**



σ-profile is **molecule-specific** and intensively **related to atom groups**. This inspires us to develop **new solvent theoretical descriptors** to replace conventional solvent parameters in quantifying their effects on chemical reactions.

Methodology and Framework



Reaction solvent design

Reaction rate regression

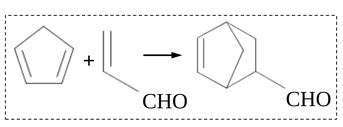
Six σ-profile areas are used to correlate reaction rate constants

$$\log k_{cal} = \log k_0 + \sum_{i=1}^{6} h_i S_i$$

$\log k_0$	-4.0113		
h_1	4.7103	h_4	0.0274
h_2	0.3012	h_5	-0.0292
h_3	0.0050	h_6	3.1087

MAPE = 2.58%
R^2 = 0.923

Solvent	$\log k_{exp}$	$\log k_{cal}$ / Rank
Acetic acid	-2.491	-2.492 / 1
Ethanol	-2.964	-3.179 / 3
1-Propanol	-3.186	-3.202 / 4
1-Butanol	-3.219	-3.210 / 5
Methanol	-3.257	-3.080 / 2
Chloroform	-3.383	-3.540 / 7
dichloroethane	-3.602	-3.677 / 9
DMF	-3.640	-3.615 / 8
CH_2Cl_2	-3.699	-3.501 / 6
Toluene	-3.745	-3.786 / 11
Acetonitrile	-3.757	-3.881 / 13
1,4-Dioxane	-3.827	-3.873 / 12
CCl_4	-3.873	-3.755 / 10
Acetone	-3.983	-3.933 / 14
Ethyl acetate	-4.036	-3.938 / 15



Cyclopentadiene (Cyclo) and Acrolein (Acro) to 5-Norbornane-2-carboxaldehyde (Norbo)

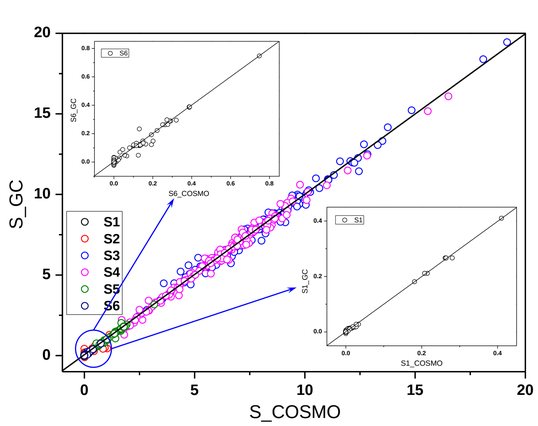
GC method development

Group Contributions (GC) are regressed from σ-profile areas of 168 solvents

$$S_i = s_{i0} + \sum_{j=1}^{N} n_j s_{ij} \quad (i = 1, 2, \ldots 6)$$

(s_{ij} is the j-th group's contribution to the i-th area)

	s_{1j}	s_{2j}	…	s_{6j}
CH_3	0.0009	0.0207	…	-0.0267
CH_2	0.0000	0.0074	…	-0.0013
CH	-0.0021	0.0122	…	0.0215
C	-0.0044	0.0161	…	0.0736
OH	0.0148	0.7146	…	0.0815
CH_3OH	0.0210	0.8769	…	0.1197
H_2O	0.0295	1.7598	…	0.3157
CH_3CO	0.0012	0.1104	…	-0.0294
CH_2CO	0.0006	0.0736	…	-0.0101
CHO	0.0012	0.1153	…	-0.0432
CH_3COO	0.0012	0.1153	…	-0.0430
…	…	…	…	…
COOH	0.2679	0.7073	…	-0.0436



GC predictions on S1 ~ S6
(168 solvents, *MAPE* = 7.28%)

Reaction solvent design

Computer-Aided Molecular Design: $\max_{n_j (j \in G)} (\log k)$

<u>Rate constant *V.S.* Groups</u>

$$\log k = \log k_0 + \sum_{i=1}^{6} h_i S_i$$

$$S_i = s_{i0} + \sum_{j=1}^{N} n_j s_{ij}$$

<u>Chemical Feasibility:</u>

$$\sum_{j=1}^{N} (2 - v_j)\, n_j - 2m = 0$$

$$n_j (v_j - 1) + 2m - \sum_{k=1}^{N} n_k \le 0$$

<u>Chemical Complexity:</u>

$$0 \le \text{integer } n_j \le N_{\max}(j)$$

$$\sum_{j \in G_F} n_j \le 1 \quad if \quad \sum_{j=1}^{N} n_j = 2 \qquad 2 - \sum_{j=1}^{N} n_j \le 0$$

$$\sum_{j \in G_F} n_j \le 2 \quad else \qquad \sum_{j=1}^{N} n_j \le 5$$

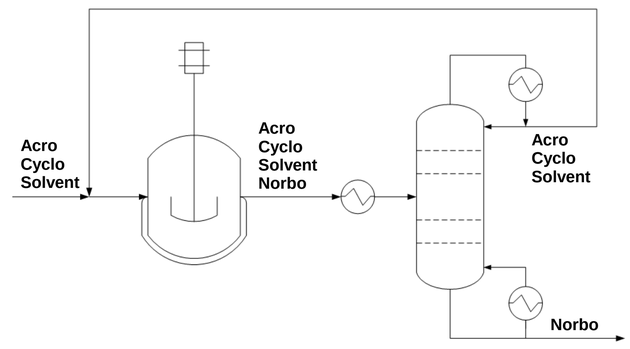
Top 10 solvents from deterministic CAMD optimization:

Group combination	Solvent	$\log k_{pred}$
2 CH_3, 1 C, 1 OH, 1 COOH	$(CH_3)_2C(OH)COOH$	−1.875
3 CH_2, 1 OH, 1 COOH	$OHCH_2CH_2CH_2COOH$	−1.934
1 CH_3, 1 CH_2, 1 CH, 1 OH, 1 COOH	$CH_3CH(OH)CH_2COOH$	−1.942
2 CH_2, 1 OH, 1 COOH	$OHCH_2CH_2COOH$	−1.962
1 CH_3, 1 CH, 1 OH, 1 COOH	$CH_3CH(OH)COOH$	−1.971
1 CH_2, 1 OH, 1 COOH	$OHCH_2COOH$	−1.991
3 CH_3, 1 C, 1 COOH	$(CH_3)_3CCOOH$	−2.406
2 CH_3, 1 C, 1 CH_3CO, 1 COOH	$CH_3COC(CH_3)_2COOH$	−2.455
2 CH_3, 1 C, 1 HCOO, 1 COOH	$HCOOC(CH_3)_2COOH$	−2.462
1 CH_3, 3 CH_2, 1 COOH	$CH_3(CH_2)_3COOH$	−2.465

Best solvent found experimentally: acetic acid ($\log k = -2.491$)

Integrated solvent and process design

✓ The identification of optimal reaction solvent is far away from the final object of engineers.
✓ The integration of solvent design and process optimization based on a process-wide approach is a prerequisite for achieving an optimal chemical process.



- **COSMO σ-profile areas (our GC method)**
- T_b, T_c, P_c, ΔH_{vap}
- liquid molar volume
- heat capacity

Properties are estimated from different group contribution methods

	Integrated design	Reference case
Optimal solvent	Isopropanol	Acetic acid (Fixed)
Reaction conversion	0.755	0.872
Product recovery	99.45%	97.77%
Total profit ($/year)	**27918.1**	**22776.4**
EP ($/year)	65319.7	74118.8
CI_R ($/year)	10145.0	5750.3
CI_{column} ($/year)	7662.7	17133.2
UC_{reb} ($/year)	13399.3	20816.1
log *k*	**-3.294**	**-2.551**

It is essential to investigate trade-offs among different solvent properties in order to achieve an overall highest process performance.

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Publications

1. Zhou, T., Qi, Z., Sundmacher, K. Model-based method for the screening of solvents for chemical reactions. *Chemical Engineering Science* 2014, 115: 177-185.
2. Zhou, T., McBride, K., Zhang, X., Qi, Z., Sundmacher, K. Integrated solvent and process design exemplified for a Diels-Alder reaction. *AIChE J*. 2014, doi: 10.1002/aic.14630.
3. Zhou, T., Sundmacher, K. Robust design of optimal solvents for chemical reactions - a combined experimental and computer-aided strategy (to be submitted).