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Computer-aided molecular design using the Signature molecular descriptor: Application to solvent selection

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ABSTRACT

There is a growing demand to develop more environmentally friendly solvents to reduce costs and comply with regulation. Researchers at GlaxoSmithKline (GSK) have developed a solvent selection guide that ranks 47 frequently used solvents from 1 to 10 in five areas related to environmental compatibility. In this work, we apply a computer-aided molecular design method known as inverse design with the Signature molecular descriptor to identify additional potentially green solvents outside of GSK's list. Applying this approach is much quicker, less expensive and allows for a more comprehensive search for the most suitable candidates than working with experimental data alone. We present results for solvents with optimal predicted properties that span the classes from the 47 compounds in the GSK solvent selection guide and include several which are hybrids that cross-cut amongst classes. Additionally, our technique "rediscovers" the known green solvent ethyl lactate through this method by combining different solvent classes.

1. Introduction

In general, a solvent is a substance that dissolves a solute (solid, liquid or gas) to form a solution. Solvents are needed to produce the goods used during everyday life. The most common solvent encountered is water, which is applied for brewing the morning coffee. Other common examples where solvents are required include dry cleaning, degreasers, paints, adhesives, and textiles (Gani et al., 2006).

For many years, solvents have played an important role in the chemical process and pharmaceutical industries to carry out a reaction or perform a separation. However, there is an ever increasing demand to minimize the use of, or replace, certain solvents due to regulation and rising costs. These expenses can be from environmental, health, and safety (EHS) issues associated with toxicity or waste disposal (Curzons, Constable, & Cunningham, 1999). For example, if it is not feasible to recycle a solvent, then incineration might be necessary accompanied with additional costs because of high energy prices. Utilizing a replacement solvent could be a more viable alternative. For product development, chemical engineers must consider these issues and make the best choice possible.

In order to help chemists and engineers more easily consider the available options, researchers at GlaxoSmithKline (GSK) developed a solvent selection guide (Curzons et al., 1999). It serves as a concise source of information on 35 commonly used solvents, and is intended to supplement existing procedures involved during solvent selection early in the development process. The guide allows one to consider a variety of solvent characteristics other than the standard technical and cost concerns. The following nine categories were deemed important and included as part of the guide: incineration, recycle, biotreatment, volatile organic carbon, environmental impact in water, environmental impact in air, health hazard, exposure potential, and safety hazard (Curzons et al., 1999). For each of the categories given, important properties were listed. For example, properties relevant to the incineration category were heat of combustion and emissions from incineration. All of the properties were judged and ranked on a scale from 1 to 10. For all cases in this study by GSK, the higher scores indicate a superior solvent. A simplification was made in order to make the guide easier to use for those without environmental, health, or safety expertise. The nine original categories were combined and reduced to four new categories (or, as they were termed, areas): waste, impact, health, and safety. Specifically, the categories of incineration, recycle, biotreatment, and volatile organic carbon were combined to create the waste area. The impact area merged the environmental impact in water and air categories, while the health area consisted of the hazard and exposure potential categories. Finally, the safety area involved only the safety hazard category.

The first publication of GSK's solvent selection guide (Curzons et al., 1999) was expanded from the initial 35 solvents to a total of 47 (Jiménez-González, Curzons, Constable, & Cunningham, 2005).

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Table 1
Data from GSK's solvent selection guide (Jiménez-González et al., 2005).

SSG Class	Solvent	CAS #	Env. Waste	Env. Impact	Health	Safety	LCA Ranking
Alcohols	Ethylene Glycol	107-21-1	4	9	8	9	9
	1-Butanol	71-36-3	5	8	8	8	5
	Diethylene Glycol Butyl Ether	112-34-5	5	7	10	9	7
	Isoamyl Alcohol	123-51-3	7	7	7	8	6
	2-Ethylhexanol	104-76-7	9	6	8	7	6
	2-Butanol	78-92-2	4	7	7	7	6
	1-Propanol	71-23-8	3	7	5	8	7
	Ethanol	64-17-5	3	8	10	7	9
	2-Propanol	67-63-0	3	9	9	7	5
	t-Butanol	75-65-0	3	10	7	7	8
	Methanol	67-56-1	3	10	5	8	9
Esters	t-Butyl Acetate	540-88-5	7	10	7	7	7
	Butyl Acetate	123-86-4	7	8	9	8	5
	n-Propyl Acetate	109-60-4	6	7	8	7	5
	Isopropyl Acetate	108-21-4	5	8	8	7	6
	Ethyl Acetate	141-78-6	4	8	8	4	6
	Methyl Acetate	79-20-9	2	10	7	5	7
	Dimethyl Carbonate	616-38-6	3	7	8	7	8
Aromatics	p-Xylene	106-42-3	8	2	7	5	7
	Toluene	108-88-3	7	3	6	4	7
	Fluorobenzene	462-06-6	4	2	4	5	1
Ketones	Methyl Isobutyl Ketone	108-10-1	7	6	6	7	2
	Acetone	67-64-1	2	9	8	5	3
	Methyl Ethyl Ketone	78-93-3	3	6	8	5	3
Polar Aprotics	N-Methyl-2-Pyrrolidone	872-50-4	4	6	8	9	3
	Dimethyl Acetamide	127-19-5	4	7	2	10	3
	Dimethyl Formamide	68-12-2	4	6	2	8	6
	Dimethylpropylene Urea	7226-23-5	4	7	5	9	4
	Dimethylsulphoxide	67-68-5	4	4	8	3	6
	Formamide	75-12-7	3	7	2	10	8
	Acetonitrile	75-05-8	2	6	6	8	4
Acids	Propionic Acid	79-09-4	5	8	4	9	7
	Acetic Acid	64-19-7	3	8	4	8	8
Alkanes	Cyclohexane	110-82-7	5	6	8	2	7
	Methyl Cyclohexane	108-87-2	7	5	8	2	7
	Heptane	142-82-5	6	3	9	1	7
	2-Methylpentane	107-83-5	5	3	5	1	7
	Hexane	110-54-3	5	2	4	1	7
Chlorinated	Dichloromethane	75-09-2	2	5	3	10	7
Ethers	Methyl Tert-Butyl Ether	1634-04-4	4	4	6	2	8
	1-2-Dimethoxyethane	110-71-4	3	5	3	2	7
	Tetrahydrofuran	109-99-9	2	6	7	2	5
	Bis(2-methoxyethyl) Ether	111-96-6	6	5	1	3	6
	Diisopropyl Ether	108-20-3	5	2	9	1	9
Basics	Triethylamine	121-44-8	4	5	2	4	7
	Pyridine	110-86-1	3	4	3	6	2

In addition, a new area was added known as life cycle assessment (LCA) that takes into account the broad impacts of manufacturing, recycling, and disposal during the duration of a solvent. LCA is important because it has previously been shown that solvent use requires a significant amount of energy and treatment for greenhouse gas emissions in the production of an active pharmaceutical ingredient (Jiménez-González, Curzons, Constable, & Cunningham, 2004). The scores for the 47 solvents are provided in Table 1 with both a numerical component (1–10) and color code (green, yellow, or red) as reported by Jiménez-González et al. (2005). Any solvent with a green rating had scores ranging from 8 to 10, a yellow rating was given for scores from 4 to 7, and a red rating was reserved for solvents with scores of 3 or less. For all five areas in Table 1, it is desired to have a green rating. For solvents with a red LCA rating, it is especially important to minimize the amount of fresh solvent required by including recycling techniques into the process. If a solvent is challenging to recover and has a low life cycle score, then a replacement solvent could be the best choice (Jiménez-González et al., 2005).

The solvent selection guide developed by GSK does not state that a particular solvent cannot be used, but instead allows one to effectively consider the potential advantages and disadvantages involved. While the guide is a useful tool, it is not the only option available for finding an alternative. Gani et al. (2006) recently reviewed some current techniques available for identifying potential candidates as part of a general procedure in solvent selection. For certain situations, it could be possible to utilize a solvent from a similar process using a technique known as benchmarking. Additionally, relying on the chemical intuition and previous experience of professionals is another option for solvent selection. Also, if specific properties are needed, a database search could be performed to find solvents readily available that are known to have similar properties. Finally, potential solvents can also be identified using a technique called computer-aided molec-