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ARTICLE

A Virtual Screening Approach to Identifying the Greenest Compound for a Task Reagent: Application to Switchable-Hydrophilicity Solvents

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A virtual or *in-silico* screening approach makes it much easier to identify the molecular structure that best combines efficacy for a specific task with safety and minimum environmental or health impacts. In this approach, software is used to generate a larger number of possible molecular structures and then to use QSARs (quantitative structure-activity relationships) to predict properties related to performance, safety, and health and environmental impact. The structures are are then given scores on criteria (such as flash point or toxicity) and an overall score. The method identifies compounds that have high scores for the 3 performance criteria and 7 health, safety, and environmental criteria. This method allows for larger-scale and faster screening than can be performed using human intellect and a benchtop approach. The success of this approach is demonstrated by its application to the identification of new and possibly greener switchable-hydrophilicity solvents (SHS). Three SHS were identified using this method. This approach to molecular design is entirely modular and can be applied to the design of almost any type of chemical. However, limitations of the method include the fact that it does not take into consideration the health and environmental costs of manufacturing the chemical.

Introduction

Molecular design usually involves designing a molecule to meet a few performance criteria, but *green* molecular design is far more difficult because additional criteria related to health and environmental impacts must also be met. If a molecule must simultaneously meet 3 or 4 performance criteria and perhaps a dozen health, safety and environmental criteria, then the molecular design process can be a long exercise in frustration. No matter how intellectually gifted a researcher is, designing for that many criteria is extremely difficult.

Virtual screening of molecular structures is an alternative strategy that could be more effective in designing to meet many criteria simultaneously. Predicting the physical and chemical properties of small molecules can be done using computer software that incorporates quantitative structure-activity relationships (QSARs). Virtual screening involves generating thousands of potential structures and screening them for those structures that are predicted to have the desired properties. This method is common practice in the pharmaceutical industry for identifying molecules that are likely to display drug-like behaviour.[1–4] However, outside of drug development, virtual screening is not a common practice. Öberg screened 50,000 small molecules for only two criteria (lifetime and baseline (narcosis) toxicity) but not for a specific application.[5] Virtual screening of battery electrolyte solvents was described in recent publications, but only for performance criteria rather than criteria related to health or the environment.[6–9] Studies on ionic liquids, spurred by the proposed use of thinking in Structure-Activity relationships (T-SAR),[10,11] have also been performed to screen specifically for cytotoxicity,[12] or only for applications to chemical separations.[13–15] The structure library to be virtually screened can be either a library of known and available compounds or a library of computer-generated structures, many of which have probably never been made. In the field of green chemistry, a virtual screening approach would be valuable to help researchers identify materials that will not only meet performance criteria but will also be safe for human use and have little environmental impact.

We propose that virtual screening can be used to identify the greenest choice amongst a list of conceivable structures. This should be possible during the design of solvents, reagents, additives, or other species and should be able to identify those compounds that best combine efficacy with safety and minimum health and environmental impact. Large numbers of molecular structures can be generated in-silico and QSARs can be used to predict the physical properties and toxicity values for each structure. By applying filters to the data, it is possible to identify structures with the physical properties (e.g. acidity, nucleophilicity) required for them to display the desired behaviour. Additional filters can be applied to identify the

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structures which not only fit the requirements of the application, but also pose little risk to human safety or the environment. The use of this approach is illustrated here by its application to the task of identifying the greenest switchable-hydrophilicity solvents (SHS). This approach is the first example of a virtual screening method for specific applications focused on the field of green chemistry. It serves as a model that can be used in future studies focused on identifying green solvents, reagents, additives, or other species.

Software design

The software used in this study consists of three components: one for structure generation, one for property prediction, and one for evaluating the structures.

A library of molecular structures was generated using the open source *Script* platform[16] and the OpenChemLib[17,18] library and visualized using the NPellet Visualizer.[19] An online version of this software can be accessed via www.cheminfo.org.[20] Tertiary amine structures were generated by creating a trimethylamine core (Fig. 1) and functionalizing the carbon atoms with 6 additional fragments outlined in Fig. 1. Some fragments could be further substituted with additional groups. Some common functional groups, such as esters, carboxylic acids, and phenols, are not represented in the list because of their incompatibility within SHS structures (discussed below) To prevent an overwhelming number of structures from being generated, the scope of this study was limited to substituents having ≤7 heavy atoms. Furthermore, 2 of the 3 core carbon atoms were always functionalized identically to decrease the synthetic difficulty of the structures being generated. Using this method, 33,856 tertiary amine structures were created.

An initial log K_{ow} (log of the octanol-water partition coefficient) filter was implemented in an effort to decrease the computational time required to predict the properties of these structures. The log K_{ow} value for every structure was predicted using the OpenChemLib library and only structures with $0.9 <$ log $K_{ow} < 2.6$ were kept for further study. An explanation for why a log K_{ow} filter was used is given below. After applying this filter, 5213 tertiary amines remained out of the original

33,856.

Property predictions, apart from log K_{ow} and pK_{aH} (pK_a of the conjugate acid), were performed using the *Toxicity Estimation Software Tool* (TEST) developed at the U.S. EPA.[21] Predicted values include LC$_{50}$ (fathead minnow, 96h; and daphnia magna, 48h), LD$_{50}$ (oral, rat), bioaccumulation factor, boiling point, vapour pressure, melting point, and flash point. More reliable toxicity prediction is available but it is more processor-time intensive and therefore less suitable for the screening of thousands of structures. Log K_{ow} was predicted as described above and pK_{aH} values were predicted using ACD/Percepta software.[22] A list of SMILES from the structure generator was used as input for these calculations. A more complete description of the property prediction methods is present in the supplementary information.

The evaluation component of the software reads the values outputted from the prediction software, applies acceptability functions to the data, and generates acceptability values for each molecular structure. Two overall acceptability values are given: one for properties related to performance and one for properties related to environmental impact, health, and safety (EHS). Larger performance acceptability corresponds to an increased likelihood that the structure works for the desired application. Larger EHS acceptability corresponds to an increased likelihood that the chemical meets the desired EHS requirements. The user can select minima for each acceptability value and be given a list of structures which are predicted to meet or exceed these minima.

Applying the software

A switchable-hydrophilicity solvent (SHS) is a solvent which can reversibly switch between two states: in one state the solvent makes a monophasic mixture with water and in the other state it makes a biphasic mixture with water.[23,24] SHS are hydrophobic organic bases that are poorly miscible with water in their neutral form, creating biphasic liquids when they are mixed with water. These bases can be protonated by hydrated CO_2 to create a bicarbonate salt that dissolves in the water, resulting in a monophasic system. Removing CO_2 from the system reverts the SHS to its neutral form, recreating the biphasic liquid mixture. SHS have advantages over many conventional solvents because SHS do not need to be distilled in order to be separated from product. Therefore, SHS can have very low volatility, which means they are unlikely to be flammable or contribute significantly to smog formation. Due to these favourable properties, SHS have been explored in a variety of uses, including extractions (soybean oil,[24] algal lipids,[25–28] bitumen,[29] and phenols from lignin pyrolysis oil), polystyrene recycling,[23] and forward osmosis.[30–32]

A variety of compounds can display SHS behaviour. The first SHS reported in the literature were alkylated amidine structures,[24] but since then, efforts have shifted toward tertiary amine-based SHS.[23,25,30,33] Secondary amine SHS have also been identified, but they are typically less preferred due to their ability to form carbamate salts.[33] Carbamate formation
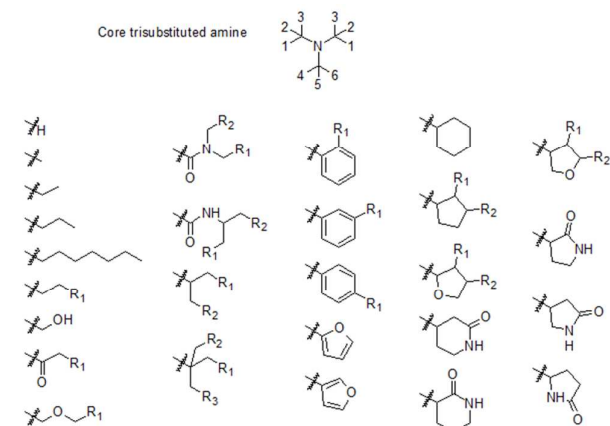

Fig. 1 Fragments used to generate molecular structures, including the core trisubstituted amine centre.

is unfavourable because of the increased energy cost associated with releasing CO_2 and reverting the carbamate back into an amine.[34,35] An amine or amidine functional group must be included in the structure of an SHS to allow the structure to react with hydrated CO_2 in an acid-base reaction. Apart from the core structural requirement of an amine or amidine functional group, a variety of other structural features have been explored including alcohols, acetals, esters, aromatic rings, alkynes, and polyethylene glycol chains.[25,33] These specific structural features do not affect a compound's ability to display SHS behaviour, but they do contribute to properties of the compound which relate to switchable behaviour; amine-based SHS must have a log K_{ow} between 1.2 and 2.5 and a pK_{aH} greater than 9.5 in order to display SHS behaviour, though amines that don't match these requirements may act as SHS under more forcing conditions.[36,37] Additionally, some structural features were avoided for other reasons, such as acidic groups (carboxylic acids, phenols) which can protonate the amine group permanently and prevent switchable behaviour, or esters which are often hydrolytically unstable.[33]

In a hypothetical scenario we used for our study, a company is interested in using an SHS in one of its processes (e.g. the extraction of soybean oil or water purification via forward osmosis), but it wants the SHS to meet certain globally harmonized system (GHS) requirements for aquatic toxicity, acute toxicity, and bioaccumulation so that it will not be considered a significant risk. Additionally, the SHS should have a flash point significantly greater than the operating temperatures (25-70 °C). Finally, the SHS should have a low vapour pressure so that its odour is minimized. The software and procedure described below was designed to identify SHS that are suitable for this process.

Prediction reliability and determination of acceptability functions

Predicted properties are not always accurate, so the reliability of the predictions must be taken into account before the filter can be applied. To determine the accuracy of the predictions, a list of amines with experimentally determined values was collected for each of the properties we studied (See Fig. 2a for an example comparison of experimental and predicted flash points). These experimental values were compared to values predicted by the software and the deviations of the data were calculated.

To account for the errors in the calculations, the filters were designed as acceptability functions which describe the likelihood that a prediction will meet or exceed the desired value. To make an acceptability function for a property, the 10th, 20th, 30th... 90th percentiles of the deviation values were applied to a target value for the property to determine the 10th-90th percentile likelihood that the prediction meets or exceeds the target value. Each adjusted percentile was assigned an acceptability value between 0 and 1, with the 10th and 90th percentiles having acceptabilities of 0 or 1, depending on whether lower values are preferred (e.g. vapour pressure), or higher values are preferred (e.g. LD_{50}). The other percentiles
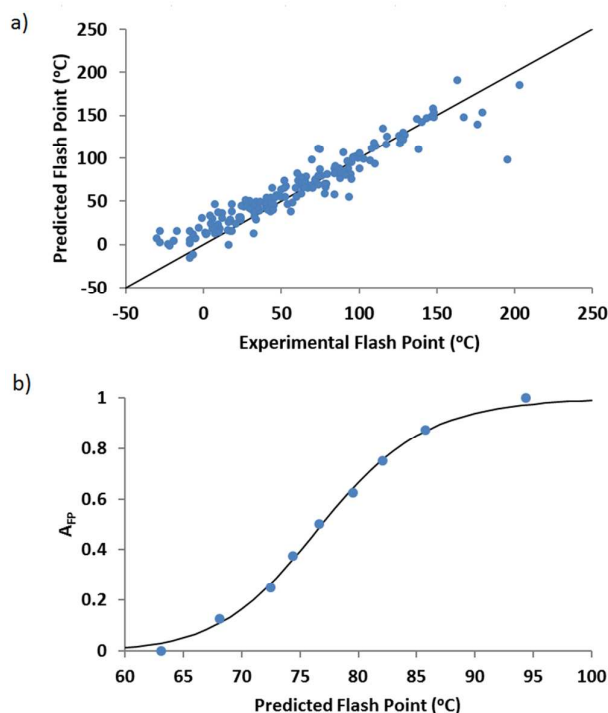

Fig. 2 a) Comparison of predicted and experimental flash points (black line represents a perfect prediction), and b) the sigmoidal acceptability function (black line) fit to the flash point acceptability values (A_{FP}) assigned to every 10th percentile from the 10th to the 90th (blue dots).

were assigned values increasing or decreasing in 1/8th increments (e.g. 0.125 for 20th percentile, 0.25 for 30th, etc.). A sigmoidal function of acceptability vs. predicted value was fit to these data. The sigmoidal functions created from this process describe the likelihood that the predicted value corresponds to an experimental value that will meet the design criteria. Fig. 2b shows a graph of the acceptability function for flash point. Information regarding all acceptability functions can be found in the supplementary information.

These functions account for the reliability of the prediction and were used to calculate the acceptability of the molecular structures. As a result, each molecule was given a score between 0 (completely unacceptable) and 1 (completely acceptable) for each predicted property. In the case of log K_{ow}, both an upper and a lower limit exist, but only the lower limit was given an acceptability function. The acceptability function for the upper limit was found to be unnecessary because the initial log K_{ow} screening was enough to remove compounds that are too hydrophobic to display SHS behaviour.

The overall acceptabilities of each structure were determined by adding together the acceptabilities of the individual properties for that structure. These overall acceptabilities were used to filter compounds for both performance and EHS. Two different overall acceptabilities are needed for filtering because there is not necessarily a relationship between what makes a compound perform the desired function (in this case, acting as an SHS) and being safe to handle. A compound might be very safe, but if it does not perform the task it was designed for it is not useful. For this

reason, two overall acceptabilities were used in this study: one for performance and one for EHS. The performance acceptability was the sum of the three acceptabilities related to performance: log K_{ow}, pK_{aH}, and melting point. A performance acceptability of 3 indicates that the compound is very likely to be an SHS. The EHS acceptability was the sum of the seven acceptabilities related to environmental impact, human health, and safety: oral LD$_{50}$, LC$_{50}$ for fathead minnow (96 h) and daphnia magna (48 h), bioaccumulation factor, flash point, vapour pressure, and boiling point. An EHS acceptability of 7 indicates a compound that is very likely to meet all of the requirements described above.

Only amines with structural similarity to the in-silico generated structures were used for the reliability analysis. By avoiding dissimilar compounds, we hope to have more appropriately characterized the accuracy of the predictions for the types of compounds generated by the software. For this reason, compounds containing heteroatoms apart from nitrogen and oxygen, compounds containing carboxylic acid functional groups, and compounds containing no amine functional group were not included in the reliability analysis.

Performance and EHS design criteria

Identifying the right SHS for this hypothetical application requires knowledge of which compounds act as SHS. Our previous studies of SHS have led to an understanding of the properties that a compound must have if it is to display switchable hydrophilicity.[33,36] As discussed previously, only amines with log K_{ow} values between 1.2 and 2.5 and pK_{aH} above 9.5 act as SHS under our standard conditions (1:1 v/v ratio of water to amine, 1 atm of CO_2). Amines with lower pK_{aH} and higher log K_{ow} can act as SHS under modified conditions (higher pressure of CO_2 and/or larger volume ratio of amine to water), but solvent-solute separations using SHS with higher log K_{ow} will be less complete than more hydrophilic SHS.[37] For this study, we limited our search to only amines with log K_{ow} between 1.2 and 2.5. Amines with pK_{aH} between 9.0 and 9.5 may not function as SHS at 1 atm but can act as SHS at CO_2 pressures up to 10 atm and were considered viable candidates in this study. Also, the amine must be a liquid under operating conditions; it must have a melting point below 25 °C. Therefore log K_{ow}, pK_{aH}, and melting point acceptability functions were applied to the software to identify structures which are likely to meet these criteria.

The EHS requirements for the compound were selected to match various regulatory standards described by the GHS.[38] According to the GHS, a compound is not considered to bioaccumulate significantly if it has a bioconcentration factor less than 500. TEST predicts bioaccumulation factor (BAF) rather than bioconcentration factor, so BAF was used in this study instead of bioconcentration factor, but the target value of <500 was still employed. Compounds with LC$_{50}$ values above 100 mg/L for both fathead minnow (96 h) and daphnia magna (48 h) are not categorized as acutely toxic to aquatic life. Compounds with LD$_{50}$ (oral, rat) higher than 2,000 mg/kg are considered category 5 substances for acute toxicity: relatively

low hazards. An ideal SHS would meet or exceed these values. The SHS should also not be flammable at or near its upper operating temperature, so for our hypothetical application the flash point should be ≥80 °C. Acceptability functions for each of these criteria were applied to screen for compounds that are likely to meet these requirements.

Two other requirements were implemented into the software to account for volatility in an attempt to apply a filter to select only SHS which do not have an odour. A previously identified SHS that has no detectable odour has a vapour pressure of approximately 0.03 torr at 25 °C, estimated using a nomograph.[33] Therefore, to select only SHS which do not have noticeable odours, a filter was applied to screen for amines with vapour pressures below 0.03 torr at 25 °C. However, more volatile amines might have only mild smells which, while not preferred, might be acceptable. Therefore, a linear function for vapour pressure acceptability was used instead of a sigmoidal function, where compounds with a vapour pressures lower than 0.03 torr would be considered completely acceptable and compounds with vapour pressures above 0.5 torr would be considered completely unacceptable as they would likely have a strong odour. The later value was chosen because it is one fifth of the vapour pressure of *N,N*-dimethylcyclohexylamine, an SHS with a strong odour. The acceptability of compounds increases linearly from 0 to 1 between these two values. Boiling point was used as an additional measure of volatility. The software was set to assign a boiling point acceptability value to screen for compounds with boiling points above 180 °C.

Confirming the successful identification of Switchable-Hydrophilicity Solvents

Using the program and the acceptability functions described above, a list of potentially useful structures was generated. The acceptability filters for performance and EHS were adjusted, starting at strict requirements and slowly relaxing the requirements, until synthetically viable structures were identified. Viable structures were identified with performance acceptability values ≥2.5 out of 3 and EHS acceptability values ≥5 out of 7. A select list of structures proposed by the software are shown in Fig. 3. Although some structures identified by the software might have high acceptability, many of them are also difficult to obtain synthetically, making them unviable options.

To confirm that the structures generated from the software are indeed SHS, four easily-prepared amines (compounds **1-4,** Fig. 4) that were proposed by the software were synthesized and tested for their ability to display switchable hydrophilicity. Each amine was added to an equal volume of water (approx. 1 mL amine and 1 mL water). If the mixture was biphasic, CO_2 was bubbled through the mixture using a gas dispersion tube until the mixture became monophasic or for up to 2 h. If the mixture became monophasic, it was heated to 60 °C and sparged with argon to remove the CO_2 to make the mixture biphasic again. If the mixture displayed all of the desired behaviours (biphasic-
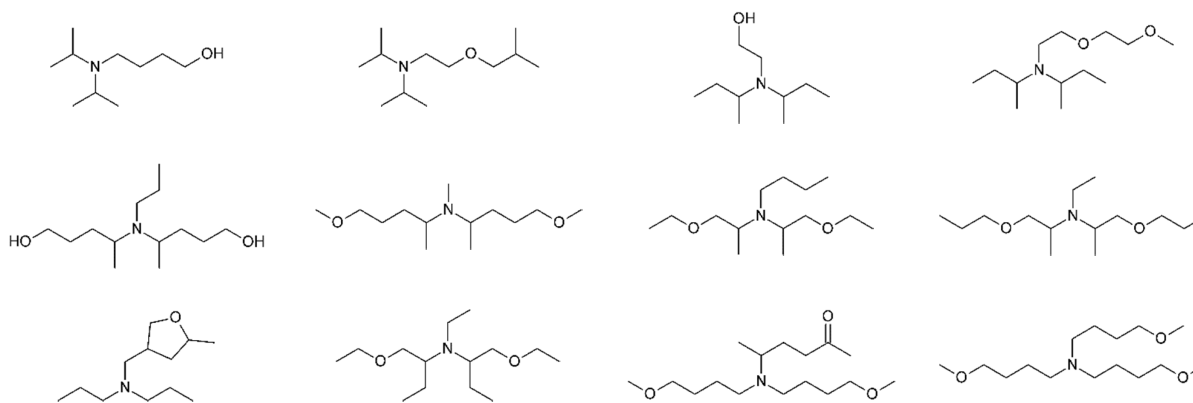
Fig. 3 Examples of molecular structures identified by the software as SHS with a high probability of meeting the design criteria.

monophasic-biphasic), the amine in the mixture is considered an SHS, otherwise it is not an SHS.

Compounds **1**-**3** all displayed the desired behaviour, but compound **4** did not. It was found to be completely miscible with water, even in the absence of CO_2. This false positive is likely due to the fact that log K_{ow} was used as a proxy measurement for solubility in the software. Solubility predictions were not implemented into the software due to their poor performance at predicting complete miscibility for amines (see supplementary information). Despite this false positive, most of the structures identified by the software are likely to be SHS.

Of all the structures identified by the software as good candidates, none of the amines were given a perfect EHS acceptability of 7. In most cases, the predicted LC_{50} values for both fathead minnow, 96 h, and daphnia magna, 48 h, did not meet the requirements for the study. Despite not identifying any compounds which meet every one of the design goals, the SHS identified in this study meet all 3 of our performance criteria and 5 of 7 EHS criteria. These SHS are therefore reasonable candidates for use in the process they were designed for. The predicted properties for the three confirmed SHS (compounds **1**-**3**) are shown in Table 1. Additionally, compounds **1**-**3** have very mild odours. These SHS could be recommended to the hypothetical company for use in their process.

The successful identification of 3 amines with preferable properties demonstrates the efficacy of this type of virtual screening. Although no structures were identified which meet
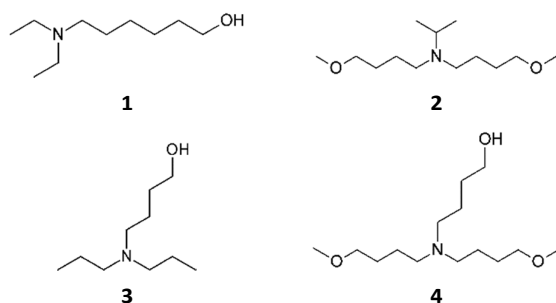
all of the criteria we implemented, the scope of the study did not encompass all possible structures. With a larger scope, the likelihood of finding a structure that meets all of the requirements increases.

In the future, this method will be improved to identify the most desirable compounds. This may include adding additional predictions for other EHS related properties and investigating more structures. Substituents larger than 7 heavy atoms could be added to the study. Secondary amines will also be investigated as potential SHS. With a larger scope, we will be more likely to identify ideal SHS.

Despite the success of this method, it has some disadvantages. The synthetic feasibility of the structures generated by the software is not accounted for, so the chemist using the software must decide which compounds are synthetically viable. The software also does not take into account the environmental and health impacts associated with manufacturing the compounds identified. Finally, some properties, such as solubility in water or the propensity of amines to form nitrosamines, cannot be predicted reliably; new QSAR models must be made before these properties can be incorporated into the screening process.

Fig. 4 Four compounds identified by the screening method that were synthesized for confirmation of the method's success.

Table 1 Acceptability values and predicted properties for SHS identified by the virtual screening method.

Property	Desired Value	Compound		
		1	**2**	**3**
Performance acceptability	-	2.72	2.97	2.76
EHS acceptability	-	5.14	5.31	5.03
Log K_{ow}	1.2 < log K_{ow} < 2.5	1.97	2.26	1.97
pK_{aH}	≥ 9	9.7	9.7	10.6
Melting point (ºC)	< 25	0	-48	-3
LD_{50} (oral, rat) (mg/kg)	> 2000	2600	1600	2400
LC_{50} (fathead minnow, 96h) (mg/L)	> 100	27	97	19
LC_{50} (daphnia magna, 48h) (mg/L)	> 100	46	11	38
BAF	< 500	65	32	31
Flash point (ºC)	≥ 80	97	103	106
Boiling point (ºC)	≥ 180	225	254	227
Vapour pressure (mtorr)	≤ 30	6	1	5

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Conclusions

A general strategy for identifying compounds with desired EHS and performance properties was described. If the properties required for good performance are known, then predictions of those properties can be performed on a large number of molecular structures generated in-silico. Various environmental, human health, and safety (EHS) parameters can also be predicted to describe which of the structures are likely to be the greenest choice. By applying both EHS and performance based filters, compounds combining good performance with minimal risk can be identified. This approach to molecular design has been applied to the identification of SHS properties suitable for a hypothetical application. Three compounds were identified as being good candidates for the application. These compounds were synthesized and found to display the desired switchable hydrophilicity.

Although the identification of an SHS was used as an example of the efficacy of the method, we believe that virtual screening can be used to identify any type of reagent if the chemical or physical properties that are required for performance are known. Additionally, the acceptability functions used in the software are entirely modular, so predicted properties can be added or removed from the software to fit the needs of the user. Therefore, the software can be altered to work for any given application. Using this method for virtual screening of compounds allows for a high throughput, rapid identification of potential compounds which not only function in the manner desired, but also pose little threat to human health and safety or the environment.

Acknowledgements

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