Carbon Neutral Solvents in a Carbon Neutral Future

Part 2: Practical Applications

This is the second part of an article proposing a carbon neutral vision for the future of the chemical industry. This vision prompts for practical steps en route to a zero carbon footprint desiderate by encouraging the strategic adoption of solvents from renewable resources.

In the first part of this article, we showed that the Kyoto Protocol provides for a globally accepted legal mechanism to reduce the carbon footprint of the chemical industry by switching from petroleum-based solvents to solvents from renewable resources[1]. Petroleum-based solvents generate by incineration anthropogenic CO2. Under the provisions of the Kyoto Protocol, anthropogenic CO2 contributes to the national greenhouse gas (GHG) inventories. Solvents from renewable resources are carbon neutral because they generate through incineration biogenic CO2. Biogenic CO2 does not contribute to the national GHG inventories under the Kyoto Protocol. Carbon neutral solvents provide therefore an excellent legal and regulatory hedging strategy for the chemical industry.

These ideas are not mere legal abstract concepts. They find practical support in existing carbon neutral solvents.

In the second part of this article several examples are given of carbon neutral solvents that are competing successfully with fossil-based solvents.

All these solvents are currently available from Pennakem, the leader in furan-based chemicals.

Furfural-based carbon neutral solvents

The chemical community realised a long time ago the potential to derive chemicals from vegetal feedstock as an alternative to oil, gas and coal. One of the pioneering efforts was financed by the US government as part of the WWII effort, and resulted in the industrial development of furfural-based chemicals. Pennakem is the direct descendant of this initiative, and continues to successfully manufacture and distribute chemicals from renewable resources.

All furfural-based products have their origin in naturally occurring pentoses, as shown in Figure 1. The non-edible corncobs are transported, ground and boiled in acidic aqueous solution to generate furfural. From furfural, through reductive and oxidative processes, Pennakem obtains a full range of C5 chemicals that are used in a wide spectrum of industries around the world.

Starting from furfural one can obtain carbon neutral, protic and aprotic solvents such as 2-tetrahydrofurfuryl alcohol (THFA), tetrahydrofuran (THF) and 2-methyltetrahydrofuran (2-MeTHF) (Figure 2). THFA is used in a variety of formulations ranging from agchem, to surface treatment in electronics manufacturing and graffiti removal.

THFA is an excellent replacement for NMP, acetone, glycol ethers and other solvents that carry risk phrases under EU legislation. THFA is easily biodegradable and can be used in water-based formulations.

MeTHF, another solvent available from Pennakem, has risen quickly from the status of an academic curiosity to one of the fastest emerging solvents in the pharmaceutical industry. Today it is poised to become one of the top 10 solvents

Figure 1: Furfural as feedstock chemical

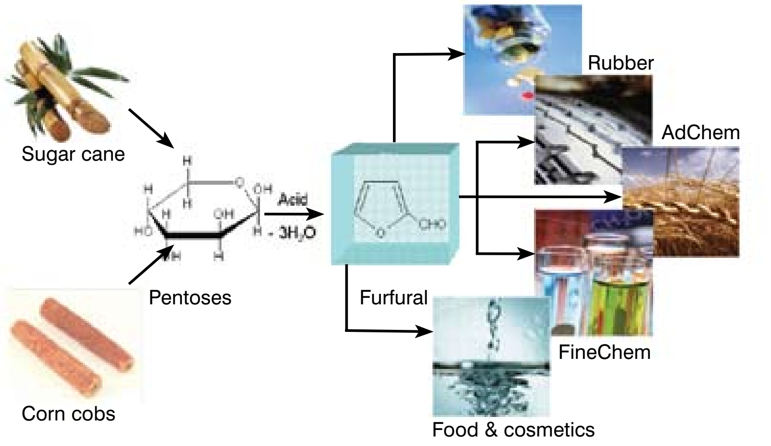
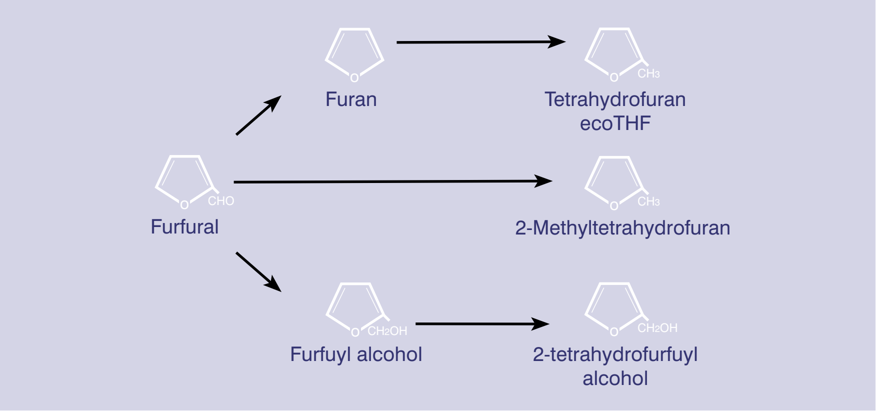


Figure 2: Commercially available carbon neutral solvents from furfural



sometime during the next decade (Figure 3)[1]. The global market demand proves that there is intrinsic technical and economic value in the solvent. The fact that MeTHF is also carbon neutral is simply an added benefit.

Figure 3: 2-MeTHF use as carbon neutral solvent

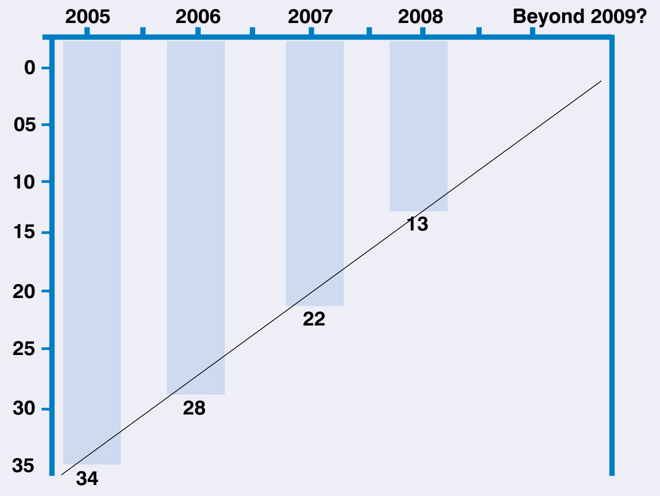
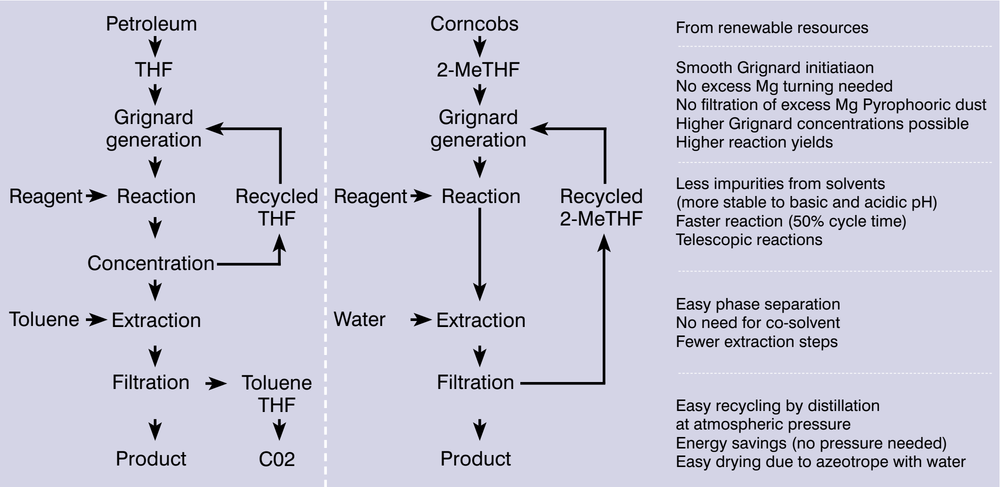


Figure 4: 2-MeTHF versus THF comparison



MeTHF has something to offer to all stakeholders involved in the buying decision process. To R&D it gives the opportunity to create intellectual property while improving processes. From a work safety perspective it is comparable to or better than THF, the industry-accepted norm today. From an environmental perspective MeTHF is a green solvent because it is a carbon neutral solvent and generates biogenic CO2. Moreover, it also allows a dramatic improvement in the process material intensity (less raw materials per kg of product) as well as improvement of the process energy intensity in the recycling step of the solvent. From a purchaser's perspective, introduction of MeTHF contributes to a reduction of the solvent variable cost compared to THF. Last, but not least, due to the fact that MeTHF supply chain is disconnected from the oil feedstock, MeTHF provides a hedging strategy to wild fluctuations in the price of petroleum-based solvents.

Figure 4 shows a head to head comparison of a Grignard reaction step in THF versus 2-MeTHF. The initiation of the reaction is very smooth and reproducible, excluding the potential of having a runaway reaction. Since no excess of Mg turnings is necessary in MeTHF when making allylic and benzylic Grignards, the problem of dealing with the excess pyrophoric Mg dust is eliminated.

Much higher concentration of organometallic reagent is often possible; e.g. in the case of phenylmagnesium bromide the maximum concentration in THF is around 15%, while in 2-MeTHF one can work at around 40% w/w concentration. The dimerisation side-reaction of benzylhalides to dibenzyl is suppressed. As a result, the reaction yield is improved on average by 15% to 20% 1. MeTHF is more stable to highly acidic solutions than THF. It is also more stable to very basic reagents like alkyllithiums than THF. This gives the solvent an extraordinary versatility in a wide range of chemistries. For example, MeLi reactions can be run without decomposition of MeTHF. This stability to acids and bases provides for a better and more reproducible impurity profile when MeTHF is used compared to THF.

MeTHF has a higher boiling point and therefore generates less VOC than THF. It also allows shortening reaction time by 50% in certain applications. Telescopic reactions in MeTHF (that is running several reaction-aqueous work-up cycles without isolating the intermediate from its solution) are common. After every aqueous work-up, the organic phase can be dried easily through azeotropic distillation of a small quantity of MeTHF. This is not possible when using THF.

In the work-up phase, MeTHF phase separates like any other organic solvent. In the THF normal work-up, one needs to add a hydrophobic co-solvent such as toluene in order to obtain phase separation. Moreover, the aqueous phase, which is a mixture of water and THF, needs to be extracted several more times with toluene in order to recover the product.

Last, but not least, MeTHF can be recycled and dried very easily by using simple distillation at atmospheric pressure. This makes recovery of MeTHF possible even for smaller campaigns. By contrast, THF is generally not recoverable for small campaigns and is simply incinerated as a mixture with toluene.

For large volume products, such as blockbuster drugs, THF is recovered in specialised distillation plants, and the product is dried through a process called "swing distillation". This is an energy-intensive process. The simple distillation process used in MeTHF recovery is much more energy efficient. The energy savings when we compare simple distillation for MeTHF with swing distillation for THF are around 60 to 70%.

In conclusion, MeTHF renders the process greener through vast improvements in the process material intensity (PMI) as well as process energy intensity (PEI). This ultimately leads to important cost savings.

Last but not least MeTHF is an extraordinary versatile solvent.

After Pennakem brought MeTHF to the attention of the pharmaceutical R&D community in 2004, there was a flurry of publications and patents highlighting applications in nearly every conceivable field of chemistry.

Discussing the diverse chemistry recently developed in MeTHF is beyond the scope of this article, however Table 1 provides a general feel for the breadth of technical applications along with entry points in the literature.

Pennakem is also producing carbon neutral THF from furfural. Our ecoTHF (to differentiate it from the THF produced from petroleum) is perfectly interchangeable with ordinary THF. Pennakem's ecoTHF has already been qualified and is being used or is about to be introduced as a solvent in a range of industries, such as the pharmaceutical, cosmetics and fragrances industries.

In conclusion, ecoTHF could replace ordinary THF in any existing pharmaceutical process without facing regulatory hurdles. This ecoTHF will bring a considerable reduction in the reported GHG from solvent incineration due to its vegetal origin.

Conclusions

Introducing strategic programs for carbon neutral solvents in the pharmaceutical industry is critical for the rapid reduction of the chemical industry carbon footprint.

CN solvents from renewable resources can reduce GHG emissions because they generate through incineration biogenic CO2; biogenic CO2 is no CO2 for environmental reporting purposes.

For multinational companies active around the world, CN solvents represent a long-term global regulatory risk hedge

This article shows the advantages related to the use of THFA, 2-MeTHF and THF obtained from renewable resources.

In particular, 2-MeTHF is increasingly becoming a universal, carbon neutral solvent; its versatility creates an opportunity to reduce cost and carbon footprint at the same time ■

Table 1: 2-MeTHF applications and literature entry points

Application	Literature entry point
Mg/Cu • Regioselective from 1,2 &1,4 additions • Enantio, diastereoselective reactions	• B. Comanita; D. Aycock, Industrie Pharma Magazine, No.17, 2005, p 54; W. Zhong*, Y. Wu, X. Zhang, J. Chem. Res, 2009, p 370.
Lithiation	• B. Comanita, R. Aul, 2-MeTHF A Green Alternative to THF, Manufacturing Chemist, May 2007, p 34
Hydride based reduction	• U. Lischka, A. Murso, U. Wietelmann, Chemetall, US Patent 2009/0140201
Organopalladium coupling	• E. J. Milton and M. L. Clarke*, Green Chem., 2010, 12, p 381
Organonickel coupling	• C. Werner, F. Platz, A. Kanschick-Conradsen, Honeywell, US 7.205,414 B2, April 2007
Organozinc chemistry	• D. Aycock, Org. Process Res. Dev. 2007,11,156-159
Biphasic reactions; DCM replacement/PTC	• D. H. Brown Ripin, M. Vetelino, SYNLETT 2003, No. 15, p 2353
Enzymatic acylation of nucleosides	• Y. Simeóa, J. V. Sinisterra, and Andrés R. Alcántara*, Green Chem., 2009, 11, p 383
Haloform reaction	• Minakem internal communication
Addition to nitrile	• Minakem internal communication
Peptide coupling	• Allessa Chemie

Dave Aycock is s a senior research chemist at Pennakem, LLC. He has over 30 years experience in industrial product and process development of fine chemicals and polymers. He is the principal contributor that developed the technical data in support of Pennakem's marketing of MeTHF. He holds an undergraduate degree in chemistry from the U. of Florida and a PhD from the U. of S. Florida.
Email: daycock@pennakem.com

Dr. Bogdan Comanita has a broad chemical industry experience spanning chemical engineering, organic synthesis and business development. He is drawing on this vast technical experience in steering the strategic and tactical marketing for various chemical and biotech companies he is involved with. Bogdan is the author of more than 40 publications, including a number of patents in Canada, US and Europe. He holds a MBA from Richard Ivey School of Business at the University of Western Ontario, a PhD degree in Chemistry from University of Ottawa and a degree in Chemical Engineering from Iasi Technical University.
Email: bcomanita@pennakem.com