PERSPECTIVES

cultures of mammalian cells as well as bacteria expressing other ABC transporters—have led most researchers to believe that P-gp operates by directly binding and transporting multiple types of substrate molecules out of cells (6) (see the figure, panel A). Nevertheless, controversy remains. Alternative models have been proposed in which P-gp alters a single cellular feature, such as intracellular pH and/or membrane fluidity, which then alters the permeability of cell membranes to multiple drugs (7), or a common enzymatic modification of multiple drugs provides a core feature recognized by the transporter (8) (see the figure, panel B).

The direct transport model is supported by transport assays using purified P-gp reconstituted into artificial lipid membrane systems. These assays suggested that P-gp can extract its substrates directly from the inner lipid leaflet of the membrane bilayer (9), that the transporter can bind at least two substrate molecules simultaneously, and that substrates can interact with one another while bound to the transporter (10), thus modulating one another's binding kinetics.

The new crystal structures confirm several features of the direct transport model, for example, showing that the substrate-binding pocket of P-gp is open at its sides to the inner leaflet of the membrane. One of the substratebound crystals shows two molecules of SSS-OZ59 (the SSS isomer of OZ59, a cyclic hexapeptide) bound simultaneously and asymmetrically to the protein, whereas co-crystals of the protein with RRR-OZ59 show a single molecule binding in a position that partially overlaps both of its isomer's binding sites. By offering physical confirmation of multiple drug recognition, this work moves us closer to a resolution of this debate. In so doing, it marks the culmination of an epoch in the multidrug-resistance field.

The finding of multiple substrate binding, and especially of two substrate molecules binding simultaneously to the P-gp structure, opens the door to detailed explanations of the wealth of previous biochemical findings in this system. For instance, crystallization of P-gps with additional substrates should permit a mechanistic explanation for the observed cooperativity between substrates bound at different sites. Future prospects for rational drug design based on these crystal structures are not limited to the discovery of new drugs targeting P-gp. They also include prediction of interactions between pairs of drugs that are P-gp substrates. Given that P-gp is expressed in the blood-brain barrier as well as major organs of drug elimination such as the liver and kidneys, this work is relevant to the pharmacology of many drugs, well beyond the cancer treatment context in which P-gp first became known.

References

- 1. S. G. Aller et al., Science 323, 1718 (2009).
- 2. M. M. Gottesman, V. Ling, FEBS Lett. 580, 998 (2006).
- M. Dean, A. Rzhetsky, R. Allikmets, Genome Res. 11, 1156 (2001).
- 4. R. J. Dawson, K. P. Locher, Nature 443, 180 (2006).
- 5. R. J. Dawson, K. P. Locher, *FEBS Lett.* **581**, 935 (2007).
- H. W. van Veen, C. F. Higgins, W. N. Konings, *Res. Microbiol.* **152**, 365 (2001).
- 7. C. Rauch, A. Pluen, Eur. Biophys. J. 36, 121 (2007).
- 8. B. T. Zhu, Mol. Carcinog. 25, 1 (1999).
- 9. A. B. Shapiro, V. Ling, Eur. J. Biochem. 250, 122 (1997).
- 10. A. B. Shapiro, V. Ling, Eur. J. Biochem. 250, 130 (1997).

10.1126/science.1172428

CHEMISTRY

Producing Transportation Fuels with Less Work

Diane Hildebrandt,¹ David Glasser,¹ Brendon Hausberger,¹ Bilal Patel,¹ Benjamin J. Glasser²

The long-term strategy for reducing emissions of carbon dioxide (CO₂) and other greenhouse gases is to replace fossil fuels with renewable resources. In the short term, liquids derived from fossil resources will be used to power transportation, in part because liquid fuels have an established production and delivery infrastructure as well as high energy density. Liquid fuels are overwhelmingly derived from increasingly scarce crude oil, and it would thus be beneficial to make liquid fuels from other sources, such as coal and biomass (1, 2).

One reason why liquid transportation fuels are derived from petroleum instead of coal is that converting coal into liquids is much more energy-intensive. Thus, substantially less CO_2 is released in the production of a gallon of gasoline derived from petroleum than in the production of fuel from coal-to-liquids (CTL) processes (1). The carbon atoms in coal are largely bonded to one another in graphitic networks, and breaking these bonds requires a large energy input. Energy is also needed to supply hydrogen to the process. We outline reaction chemistry and processing designs that could dramatically reduce these energy inputs and minimize the amount of CO_2 emissions that would be emitted or mitigated by other costly strategies, such as carbon capture and sequestration (3).

There are many methods that convert carbon-rich sources into liquid fuels, including pyrolysis, direct liquefaction, and indirect liquefaction, which proceeds through gasification such as the Fischer-Tropsch (FT) and methanol-to-olefins (MTO) processes (2, 4). Of these, the FT process

$$3C + 4H_2O \rightarrow 2CO + 4H_2 + CO_2 \rightarrow$$
$$2(-CH_2-) + 2H_2O + CO \qquad (1)$$

(where CO is carbon monoxide and -CH₂-

New reaction chemistry may reduce the energy input and carbon dioxide emissions from processes that convert coal into liquid fuels.

represents the alkane products) has been successfully implemented on the largest scale industrially (2, 5) but is very inefficient in that a large part of the carbon fed into the process ends up as CO₂, either directly or indirectly from fuel consumption for heating the reaction (5). However, FT technology gasifies the coal so that unwanted ash, heavy metals, and sulfur can be removed (2).

To identify more efficient ways to run chemical processes, theoretical tools have been developed that can look at the industrial plant as a whole (6-9), even at the level of rethinking the reaction chemistry. These tools assess what would happen if we could operate the plant as efficiently as possible (that is, near thermodynamic reversibility).

For example, thermodynamic principles have been applied to examine the production of molecular hydrogen (H_2) by thermochemical cycles (δ). By analyzing reversible processes, limits can be placed on the best performance that can be achieved for a given cycle. For example, H_2 could be produced through chemical reactions powered directly Downloaded from www.sciencemag.org on March 31, 2009

¹Centre of Material and Process Synthesis, Department of Chemical and Metallurgical Engineering, University of the Witwatersrand, Johannesburg 2050, South Africa. ²Department of Chemical and Biochemical Engineering, Rutgers University, Piscataway, NJ 08854, USA. E-mail: diane.hildebrandt@wits.ac.za

by the heat from a nuclear reactor, such as zinc reacting with water to produce zinc oxide and H_2 . The zinc is recovered by heat-driven decomposition of zinc oxide. A thermodynamic analysis has shown that the currently proposed thermochemical cycles for producing H_2 cannot compete with electrolysis of water through direct use of electricity (6).

Thermodynamic analysis of reversible processes can be coupled with theoretical efficiencies to allow comparison of real processes. Such an analysis was performed for direct H_2 use for transportation, and the findings were compared with other strategies for reducing greenhouse emissions and U.S. oil imports (*6*, *10*). This work has brought to light serious concerns about the feasibility of an H_2 economy.

However, recent work suggests a path forward for the sustainable production of liquid hydrocarbon fuel for transportation that would make use of H_2 produced from carbon-free energy, such as solar or wind (1, 11). These processes add H_2 to the syngas (CO and H_2) produced from gasification of biomass, and convert this mixture to liquid fuels via the FT process. If H_2 is coupled with coal as the carbon source to produce liquid hydrocarbons via FT, then there is potentially no additional CO₂ release to the atmosphere in replacing crude oil with coal (1).

A disadvantage of these approaches is that they borrow inputs from alternative energy sources. A different strategy is to improve the energy use in the FT process, and a thermodynamic analysis has revealed a somewhat paradoxical route that pushes the initial steps toward a more oxidized initial product, CO_2 , rather than CO, and then feeds CO_2 and H_2 into the hydrocarbon synthesis part of the process (9).

To understand how this improvement works, consider that steps that require large inputs of work and heat are potential sources of inefficiency (12-14). For example, if the CTL process produces alkanes from a feed of coal and water (see the figure), the overall process requires 58 kJ/mol of heat per $-CH_2-$ unit to be added. In addition, the reversible process requires about 41 kJ/mol of work to be added, which, in a facility that produces 80,000 barrels per day, amounts to at least 350 MW of work that must be added (9).

The two steps of the CTL process can be viewed as a heat engine (see the figure). The first step is a high-temperature endothermic reaction that converts the solid coal into gases. This heat input, by virtue of its temperature, carries work W_{in} that must be equal to or

HUEY/SCIENCE

≧

ADAPTED

CREDIT:

greater than the Gibbs free energy change of this process. The second step, the FT synthesis reaction, is a low-temperature exothermic process that emits heat and carries work W_{out} out with it. Again, W_{out} should be equal to the Gibbs free energy of this reaction for this step to be reversible. The net work for the overall process is the difference between W_{in} and W_{out} and is equal to the change in the Gibbs free energy of the overall reaction. recovered from the heat rejected from the synthesis reactors, the net work required by the overall process in an 80,000 barrels per day facility is 820 MW—nearer the optimum (350 MW) than the conventional route (1000 MW). This process would produce 0.5 MT less CO_2 per year than the conventional route (15% reduction) (9).

Note that the second part of the new process also represents a direct way of using



Reducing the work. Improvements in efficiency of the Fischer-Tropsch process can be achieved with a carbon dioxide and hydrogen route, rather than the traditional carbon monoxide and hydrogen route. The processes shown would produce 80,000 barrels of liquid fuel per day and have a theoretical minimum work of 350 MW; the work (via heat) inputs for each stage and for the overall processes are shown as red and green arrows.

The conventional FT process is inefficient because it requires too much work to be put in the gasifier and emits too much work from the FT reactor. The gasification process adds more than four times as much work as is needed to run the plant reversibly. Even if electricity is generated from the steam produced in the FT process, the net work added is still nearly three times the minimum amount needed.

More efficient operation requires decreasing both W_{in} and W_{out} . A way to run both reactions to achieve this goal is for the gasifier not to produce CO and H₂ but rather CO₂ and H₂, which is a less endothermic process (9, 15). Furthermore, making fuel from CO₂ and H₂ is less exothermic (see the figure). The synthesis reaction may not go directly via the new gas mixture, but when combined with the reverse water-gas shift reaction, which converts CO₂ and H₂ to CO and H₂O, the process

$$3C + 6H_2O \rightarrow 3CO_2 + 6H_2 \rightarrow$$
$$2(-CH_2-) + 4H_2O + CO_2 \qquad (2)$$

is feasible. Water can be recycled in both cases, and in the second process, can pump heat back into the gasification section. The CO_2 gasification process requires adding about 20% less work to the gasifier than would be required by the CO route. If work is

 CO_2 . If H_2 is produced via nuclear, wind, or solar energy, this process becomes a method for consuming CO_2 and may bypass the difficulties in the direct use of H_2 as a fuel (1). Technological advances developed for CTL readily transfer to processes for converting natural gas to liquids, and eventually could be adapted to biomass sources.

References

- R. Agrawal et al., Proc. Natl. Acad. Sci. U.S.A. 104, 4828 (2007).
- S. Lee, J. G. Speight, S. K. Loyalka, Handbook of Alternative Fuel Technologies (CRC Press, Boca Raton, FL, 2007).
- 3. M. C. Sheppard, R. H. Socolow, AIChE J. 53, 3022 (2007).
- 4. O. Levenspiel, Ind. Eng. Chem. Res. 44, 5073 (2005).
- P. Mukoma, D. Glasser, D. Hildebrandt, *Ind. Eng. Chem. Res.* 45, 5928 (2006).
- 6. R. Shinnar, F. Citro, Chem. Eng. Prog. 103, 10 (2007).
- B. Patel, D. Hildebrandt, D. Glasser, B. Hausberger, Ind. Eng. Chem. Res. 46, 8756 (2007).
- M. Yamamoto, M. Ishida, *Energy Convers. Manage*. 43, 1271 (2002).
- D. Hildebrandt, D. Glasser, B. Hausberger, B. Patel, paper presented at the 1st World CTL Conference, Paris, 3 to 4 April 2008.
- 10. R. Shinnar, F. Citro, Science 313, 1243 (2006).
- 11. R. Agrawal, M. Offutt, M. P. Ramage, *AlChE J.* **51**, 1582 (2005).
- 12. I. L. Leites, D. A. Sama, N. Lior, Energy 28, 55 (2003).
- 13. H. Oaki, M. Ishida, J. Chem. Eng. Jpn. 15, 52 (1982).
- B. Patel, D. Hildebrandt, D. Glasser, Ind. Eng. Chem. Res. 44, 3529 (2005).
- 15. D. Hildebrandt, D. Glasser, B. Hausberger, international patent application WO/2007/122498 (2007).

10.1126/science.1168455