The effect of substitution on the utility of piperidines and octahydroindoles for reversible hydrogen storage

Yi Cui,[a] Samantha Kwok,[a] Andrew Bucholtz,[a] Boyd Davis,[b] Ralph A. Whitney[a] and Philip G. Jessop*[a]

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Substituted piperidines and octahydroindoles are compared in terms of their usability as reversible organic hydrogen storage liquids for hydrogen-powered fuel cells. Theoretical Gaussian calculations indicate which structural features are likely to lower the enthalpy of dehydrogenation. Experimental results show that attaching electron donating or conjugated substituents to the piperidine ring greatly increases the rate of catalytic dehydrogenation, with the greatest rates being observed with 4-aminopiperidine and piperidine-4-carboxamide. Undesired side reactions were observed with some compounds such as alkyl transfer reactions during the dehydrogenation of 4-dimethylaminopiperidine, C–O and C–N cleavage reactions during hydrogenation and/or subsequent dehydrogenation of 4-alkoxy and 4-amino indoles, and disproportionation during the hydrogenation of 4-aminopyridine.

Introduction

One major factor preventing widespread use of automotive fuel cells is the lack of a viable on-board method for hydrogen storage. While many methods have been proposed, such as compressed hydrogen, metal hydrides, reversibly hydrogenated liquids, and reactive chemical hydrides, each method has its own critical drawbacks.[1–3]

As part of the effort to develop a solution for on-board hydrogen storage, our long term goal is to optimize the structure of reversible organic hydrogen-storage liquids so that they meet the following five requirements: (1) be capable of facile, clean and reversible dehydrogenation; (2) have an enthalpy of dehydrogenation low enough that the dehydrogenation is thermodynamically favored at as low a temperature as possible (at least below 180 °C); (3) be liquid and nonvolatile from −40 °C to the dehydrogenation temperature; (4) have a hydrogen storage capacity >6% by weight and 45 g H_2 per litre of liquid;[4] and (5) be stable against thermal or catalytic decomposition at operating temperatures. This paper describes work towards meeting the first two requirements in this list.

Dehydrogenation enthalpy has been a serious problem preventing the adoption of earlier examples of organic hydrogen storage liquids. The idea of hydrogenating benzene to cyclohexane off-board followed by dehydrogenation in a vehicle was proposed decades ago,[5–8] but the enthalpy of dehydrogenation for cyclohexane is so high that excessively high temperatures were required. In 2004, Pez *et al.* suggested hydrogen storage by reversible dehydrogenation of heterocycles;[9,10] Gaussian calculations showed that incorporation of a heteroatom in the ring can lower the dehydrogenation enthalpy. Interesting work has already been done on the potential hydrogen storage applications of nitrogen heterocycles for automotive uses.[11,12] On the theoretical side, Clot *et al.* have also done significant computational work to determine the enthalpy, entropy, Gibbs energy, and optimal dehydrogenation temperature for a wide range of compounds.[13] They predicted that the incorporation of nitrogen atoms into a ring structure and the addition of electron-donating groups would lower the temperature at which hydrogen can be easily released. Experimentally, Crabtree and coworkers achieved good results using indoline over Pd/C or Rh/C, reporting 100% conversion after 24 h in refluxing toluene, and even 100% conversion after only half an hour under the same conditions when palladium on carbon was chosen as the catalyst.[14] Indoline unfortunately has quite low releasable hydrogen content (1.7 wt%).

The present work was designed to experimentally test combinations of three strategies for the design of hydrogen-storing heterocycles: (a) the addition of electron-donating substituents outside the ring, (b) the addition of conjugated substituents outside the ring, and (c) the design of multicyclic structures so that each ring has roughly equal dehydrogenation enthalpies. These strategies need further elaboration.

The electronic effects of external substituents are certain to have an influence on the dehydrogenation rate and equilibrium. It has been proposed by Lunn that electron-withdrawing groups aid the rate of hydrogenation.[15,16] Experimental dehydrogenation enthalpies for substituted cyclohexanes show that electron-donating groups help at least the thermodynamics of dehydrogenation (Fig. 1). The presence of a conjugated external substituent also has a lowering effect on the dehydrogenation enthalpy; cyclohexanes with conjugated substituents have, on average, an 11 kJ mol^{-1} H_2 lower enthalpy

[a] *Department of Chemistry, Queen's University, Kingston, Ontario, Canada K7L 3N6. E-mail: jessop@chem.queensu.ca; Fax: 1-613-533-6669; Tel: 1-613-533-3212*
[b] *Queen's-RMC Fuel Cell Research Centre, 945 Princess St., 2nd Floor, Kingston, Ontario, Canada K7L 5L9. E-mail: Boyd.Davis@mine.queensu.ca; Fax: 1-613-547-8125; Tel: 1-613-547-0116 x141*

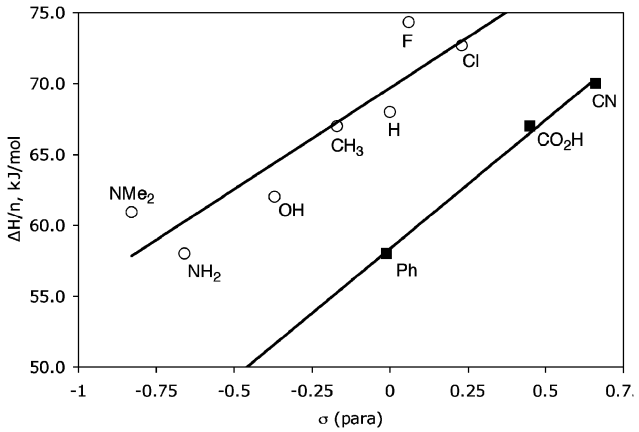
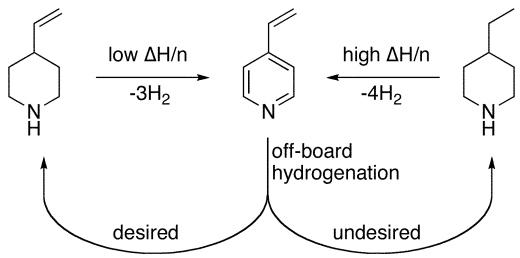


Fig. 1 Dehydrogenation enthalpies per mole of H_2 for mono substituted cyclohexanes as a function of the Hammett σ (*para*) parameter for the unconjugated (○) or conjugated (■) substituent. Enthalpies calculated from the experimental enthalpies of formation of the liquid substituted cyclohexanes and benzenes published by NIST.[17] Solid-phase data were used for cyclohexanecarboxylic acid and its product due to the unavailability of liquid phase data.

of dehydrogenation than those containing nonconjugated substituents. If applied to piperidine rings, this strategy would suggest that 4-vinylpiperidine, for example, would be easily dehydrogenated to 4-vinylpyridine (Scheme 1). Note that the conjugated substituent must not be easily hydrogenated; in the above example, if the subsequent off-board hydrogenation of the 4-vinylpyridine were to generate 4-ethylpiperidine instead of the desired 4-vinylpiperidine, then the piperidine would no longer be readily dehydrogenated. To determine the effect of electron donating/withdrawing and/or conjugated external substituents on the dehydrogenation of saturated heterocycles, we compare in this paper the Hammett parameter of several substituents to the calculated thermodynamic dehydrogenation enthalpy and the rate of dehydrogenation with common catalysts.

Two-ring systems are inherently more complicated than single-ring systems for hydrogen storage. Not only is it necessary to have a low overall $\Delta H/n$, but the $\Delta H/n$ values for each ring should be roughly equal; if the $\Delta H/n$ for one ring is significantly greater than the other, then partial dehydrogenation will be favoured over complete dehydrogenation. This concept will be explored more fully in the results and discussion section.



Scheme 1 A hypothetical example of the advantage of having an unsaturated substituent attached to a hydrogen-storing ring. The thermodynamic advantage is only obtained if the substituent remains unsaturated after the off-board hydrogenation. A vinyl group would be too readily hydrogenated to be a good choice.

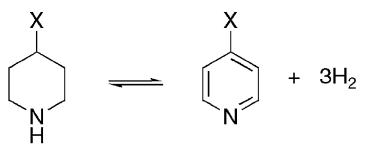
In all of the designed structures, we avoided N–C–N and N–C–O linkages, such as that in *ortho*-aminopiperidine. This is necessary to avoid the thermal hydrolytic and/or hydrogenolytic instability that one would expect for such linkages; even a small amount of decomposition would be unacceptable economically. For simplicity, we also restricted ourselves to substituents in the 4-position for piperidines and indoles, although 3-substituted piperidines are certainly worthy of investigation.

While the literature is extensive for the heterogeneous hydrogenation of pyridines and indoles,[18–27] there is very little literature for the dehydrogenation of piperidines[28–32] and octahydroindoles (Schemes 2 and 3, where X is any substituent and R is H or alkyl).[33] The challenge is in finding the conditions that allow both reactions to be highly selective, so that the hydrogenation/dehydrogenation cycle can be repeated without decomposition of the hydrogen carrier.

Results and discussion

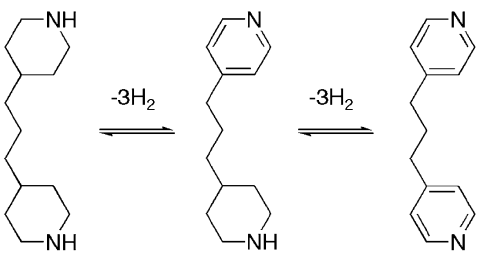
Structure design based upon Gaussian calculations

An optimum hydrogen storage liquid would have an enthalpy of dehydrogenation per mole of H_2 ($\Delta H_{rxn}/n$) close to or below 50 kJ mol^{-1}, so that a reasonable extent of dehydrogenation could be expected thermodynamically at temperatures below 200 °C. While the literature thermodynamic data from which one can calculate $\Delta H_{rxn}/n$ are very limited, reasonably accurate estimations can be made by DFT calculations (experimental section). Such data calculated for monosubstituted cyclohexane derivatives and *para*-substituted piperidines show a nearly linear trend *versus* the Hammett parameter for non-conjugated substituents (σ_p)[34] (Fig. 2), which indicates that (a)



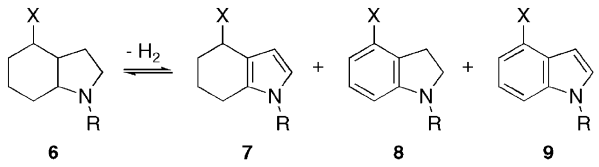
1 **2**

	X	σ_{para}
a	H	0
b	NH_2	-0.66
c	NMe_2	-0.83
d	$C(O)NH_2$	0.36
e	CN	0.66



3 **4** **5**

Scheme 2 The piperidine derivatives investigated as hydrogen storage liquids.



	R	X
a	H	H
b	Me	H
c	Me	OH
d	H	OH
e	Me	OMe
f	Me	NH_2

Scheme 3 The indole derivatives investigated as hydrogen storage liquids.

the enthalpy of dehydrogenation of a substituted piperidine is always significantly lower than that of a substituted cyclohexane, (b) the more electron-donating the substituent the lower the dehydrogenation enthalpy, (c) the more electron-donating the substituent the greater the difference between a cyclohexane and a piperidine, and (d) the lowest enthalpies are obtained for structures that contain *both* a nitrogen in the ring and an electron donating substituent. Thus, among these single-ring substrates, the lowest dehydrogenation enthalpies are those of 4-dimethylaminopiperidine (54.7 kJ mol^{-1}), 4-methylaminopiperidine (54.8 kJ mol^{-1}) and 4-aminopiperidine (55.7 kJ mol^{-1}).

Hydrogenations of pyridine derivatives

The literature on pyridine hydrogenation generally recommends Raney Ni, Pt colloid or black, PtO_2, RuO_2 and Rh/C.[18] We evaluated several catalysts at 70 bar H_2 and at temperatures below the boiling point of the pyridine substrate. Operating at a low temperature in the hydrogenation stage, which would be in a factory rather than a vehicle, is not crucial as long as hydrogenolysis and other unwanted reactions do not occur. Conversion and selectivity data calculated from the ^{1}H NMR spectra (Table 1) indicate that poor selectivity was obtained in most cases, probably due to hydrogenolysis, although the unwanted products were not identified. Pd/C and Pt/C gave poor selectivity for the desired piperidines.

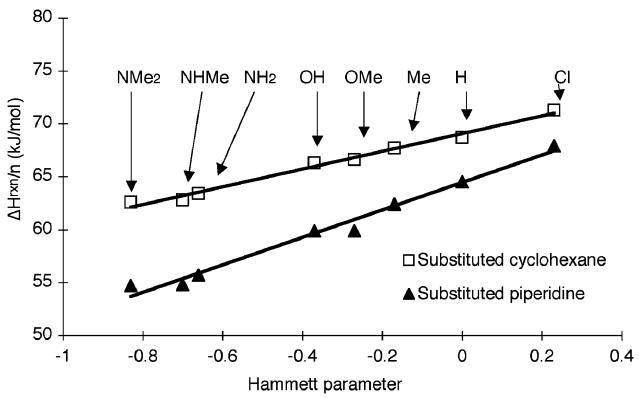
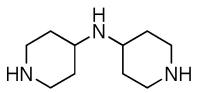


Fig. 2 Calculated dehydrogenation enthalpies ($\Delta H_{rxn}/n$) of monosubstituted cyclohexane and *para*-substituted piperidine derivatives. Electron-donating groups are indicated by a negative Hammett parameter.

Ruthenium oxide (RuO_2)[20] gave the best results for 4-dimethylaminopyridine. Isonicotinamide (**2d**) was readily and cleanly hydrogenated over Rh/C, without reduction of the amide group. 4-Aminopyridine was not hydrogenated cleanly with any of the catalysts tested (Rh/C, RuO_2, Pd/C); while the desired 4-aminopiperidine was observed, very large amounts of a new compound, **10**, were observed. The new compound has the formula $C_{10}H_{21}N_3$ (determined by high resolution MS) and has a ^{1}H NMR spectrum almost exactly matching that of 4-aminopiperidine. These observations are consistent with **10** being the disproportionation product dipiperidin-4-ylamine (structure shown below). Disproportionation of primary alkylamines to secondary amines plus ammonia over precious metal catalysts under reducing conditions has been reported previously,[35] and may be a serious problem for the use of amino-substituted aromatics for hydrogen storage. Methods for avoiding disproportionation are currently being sought.



dipiperidin-4-ylamine **10**

Dehydrogenations of piperidine derivatives

The optimum reaction conditions for dehydrogenation of piperidines were difficult to predetermine due to limited guidance from the available literature. For example, several patents[28–30] recommend 200–500 °C over a Pt or Pd catalyst. Finding an optimum temperature for the reaction involved a fine balance between competing factors: higher temperatures are desired for kinetic and thermodynamic reasons, but lower temperatures are needed to avoid decomposition, to prevent substrates from being too volatile, and to make the system more practical for future automotive applications. We had no expectation that the best catalyst for dehydrogenation would be the same as that for hydrogenation because of the different conditions used for the two reactions.

Testing of the dehydrogenation of piperidines was done first in a closed vessel, so that evolved H_2 would remain in the system and potentially allow a back reaction to take place. Thus, if the reaction time was sufficient, the yield of product would be thermodynamically controlled. High catalyst loading was used in these reactions to ensure that the loading was not the limiting factor for the dehydrogenation reactions.

Several catalysts were tested for 4-aminopiperidine dehydrogenation (Table 2). With Pt/C, no starting material or expected product appeared in the ^{1}H NMR spectrum; however, peaks corresponding to pyridine were observed in the spectrum, which indicated that the C–NH_2 bond was cleaved. Pd/Al_2O_3 provided poor selectivity but Pd/C and Pd/SiO_2 gave good conversion and selectivity to 4-aminopyridine. The first attempt with Pd/C, starting at 160 °C and with the temperature slowly raised over 3 h to 260 °C (Table 2, final entry). This first trial, according to the ^{1}H NMR spectrum, produced 26% of the dehydrogenated product 4-aminopyridine, but the aliphatic region of the spectrum was filled with unidentifiable peaks with little to no starting material remaining. These unwanted products can be avoided by

Table 1 Hydrogenation of *para*-substituted pyridine derivatives[a]

Substituent	Catalyst	T/°C	Loading (%)	Conversion[b] (%)	Selectivity[b] (%)
H	Pt/C	100	1	89	0
H	Pd/C	100	5	100	0
OH	Pd/C	150	5	100	0
NH_2	Pd/C	150	5	69	0
NH_2	Rh/C	160[c]	1.3	95	43
NH_2	Rh/C	160[c]	2	97	42
NMe_2	Pt/C	150	1	0	0
NMe_2	Pd/C	150	5	100	0
NMe_2	Pd/C	125	5	100	0
NMe_2	RuO_2	125[c]	2	78	100
NMe_2	RuO_2	125	3	100	100
$C(O)NH_2$	Rh/C	160[c]	1.8	100	100

[a] At 70 bar H_2 with ~100 mg substrate for 18–24 h. [b] Conversion of the pyridine and selectivity for the piperidine. Calculated from ^{1}H NMR integration assuming that unidentified products have the same number of protons as the piperidine). [c] Reaction duration 3 h.

Table 2 Dehydrogenation of 4-aminopiperidine (**1b**)

Catalyst	T/°C	Loading (%)	Duration/h	Conversion (%)	Selectivity[a] (%)
Pt/C	220	5	6	100	0
Pd/SiO_2	170	10	4	66	100
Pd/SiO_2	190	10	3	77	100
Pd/Al_2O_3	220	5	4	100	15
Pd/C	220	5	4	100	73
Pd/C	260[b]	10	3	100	26

[a] Selectivity for 4-aminopyridine (**2b**). Balance corresponds to unidentified product(s). Selectivity and conversion were calculated from ^{1}H NMR integration assuming that the unidentified products have the same number of protons as the piperidine. [b] Reaction temperature was ramped from 160 to 260 °C during the reaction.

performing the dehydrogenations at lower temperatures, although the conversion begins to drop off. Increasing the reaction time does not result in a noticeable increase in conversion.

Given that a dimethylamino substituent is more electron-donating (σ of −0.83) than an amino substituent (σ of −0.66), one would anticipate that the former would be more effective at promoting dehydrogenation. Not surprisingly, Gaussian calculations for the dehydrogenation of substituted piperidines (Fig. 2) predict dehydrogenation should be slightly more enthalpically favorable for the dimethylamino derivative than the amino derivative. In contrast, the liquid-phase experimental dehydrogenation enthalpies for substituted cyclohexanes (Fig. 1) suggest the reverse, that dehydrogenation should be *less* favorable for the dimethylamino derivative than the dimethylamino derivative. However, very little difference was observed in our experiments with dehydrogenation of piperidines (Tables 2 and 3). Essentially the same conversion is obtained for the dehydrogenation of 4-aminopiperidine (66%) as for 4-dimethylaminopiperidine (67%) under the same reaction conditions (Pd/SiO_2, 170 °C, 3.5 h). However, the selectivity is inferior in the case of 4-dimethylaminopiperidine.

In an open vessel with a continuous flow of N_2 during the dehydrogenation, there is a reduced possibility of back-reaction and therefore the yield is more influenced by kinetics than thermodynamics. Therefore, the predicted dehydrogenation enthalpies do not necessarily have value in predicting which piperidine will be the most readily dehydrogenated. The results under these conditions dramatically show how strongly the dehydrogenation rate is affected by the choice of *para* substituent (Fig. 3). 4-Aminopiperidine (**1b**, Fig. 3a) dehydrogenates rapidly at 170 °C; the reaction nears completion within 30 min and has a half life of 12 min. Dimethylaminopiperidine (**1c**, Fig. 3(b)) starts to dehydrogenate just as quickly but suffers from significant side-reactions, as discussed below. Piperidine-4-carboxamide (**1d**, Fig. 3c), after a short induction period, dehydrogenates to **2d** fairly rapidly with a half life of 16 min.† 4-Cyanopiperidine **1e** shows extremely slow dehydrogenation (2% of **2e** after 3.5 h, not shown in Fig. 3) with significant formation of unidentified byproducts. Thermodynamically, **1e** (predicted ΔH_{rxn} 66.0 kJ mol^{-1} H_2) should be almost as difficult to dehydrogenate as cyclohexane. Finally, a piperidine with an alkyl substituent in the *para* position was tested: 1,3-di(piperidin-4-yl)propane (**3**, Fig. 3(d)). This compound has one piperidine ring at each end of a propane chain, and is electronically identical to a piperidine containing a simple alkyl substituent in the *para* position. This piperidine dehydrogenates relatively slowly, with a $t_{1/2}$ (per ring) of 33 min, and dehydrogenates one ring at a time *via* compound **4**.

Because the poor selectivity observed during the dehydrogenation of 4-dimethylaminopiperidine was unexpected, the nature of the side-reaction was investigated. Three byproducts **11**, **12**, and **13** were observed. Persistent byproduct **11**, having a mass spectrum (M^+ m/z 142, $M^+ - NMe_2$ m/z 97/98)

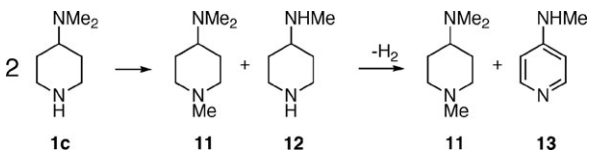
† The plot of log[**1d**] *vs.* time was linear for five half-lives. GC/MS indicates some formation of the undesired dehydration product 4-cyanopiperidine (**1e**) but NMR shows that no **1e** is formed. The dehydration is believed to occur in the GC injection port.

Table 3 Dehydrogenation of 4-dimethylaminopiperidine (**1c**) using Pd/SiO_2 (10 mol% loading)

T/°C	Duration/h	Conversion (%)	Selectivity[a] (%)
100	12	18	100
110	9	22	100
150	6.5	28	100
170	3.5	67	84
190	16	68	82
220[b]	21	100	3

[a] Selectivity for 4-dimethylaminopyridine (**2c**). Balance corresponds to unidentified product(s). Selectivity and conversion were calculated from ^{1}H NMR integration assuming that the unidentified products have the same number of protons as the piperidine. [b] Pd/C 7 mol% loading.

consistent with 4-dimethylamino-1-methylpiperidine, failed to dehydrogenate. Byproduct **12** has a mass of 113, consistent with 4-methylaminopiperidine. **13** was unambiguously identified by NMR and high-resolution MS as 4-methylaminopyridine. We therefore conclude that an undesired methyl group transfer took place between two molecules of starting material (eqn (1)).



(1)

To summarize these open-vessel tests in terms of the electronic properties of the *para* substituents, we note that the five piperidines dehydrogenate at rates almost consistent with the expected trend (Fig. 4). The initial rate of dehydrogenation depends on the choice of *para* substituent in the following sequence (with the Hammett σ_p parameter shown on the line below):

NMe_2	≈	NH_2	>	$C(O)NH_2$	>	alkyl	≫	CN
−0.83		−0.66		+0.36		−0.15		+0.66

The amide substrate **1d** is obviously out of sequence. A plot of $\log_{10}(t_{1/2})$ *vs.* σ_p (Fig. 5) confirms that these two parameters correlate except for **1d**; the interpolated curve predicts a half life of 9 h for **1d**, compared to the observed 16 min. Although the error on that prediction is quite large, it is clear that **1d** dehydrogenates far more readily than expected, evidence that a dramatic improvement can be achieved with the use of a conjugated substituent.

From these dehydrogenation results, **1b** and **1d** are the most promising for further study. Even better performance is expected after catalyst optimization. The two compounds store 6.0 and 4.7 wt% releasable hydrogen by mass.

Hydrogenation of indole derivatives

Octahydroindole derivatives are also promising candidates, as pointed out by the group of Pez.[9,11,36] Our calculations suggest that alkylating the pyrrolidine nitrogen reduces the enthalpy significantly for octahydroindoles and somewhat less so for the dodecahydrocarbazoles (Table 4). External electron-donating substituents on the six-membered ring also lower the

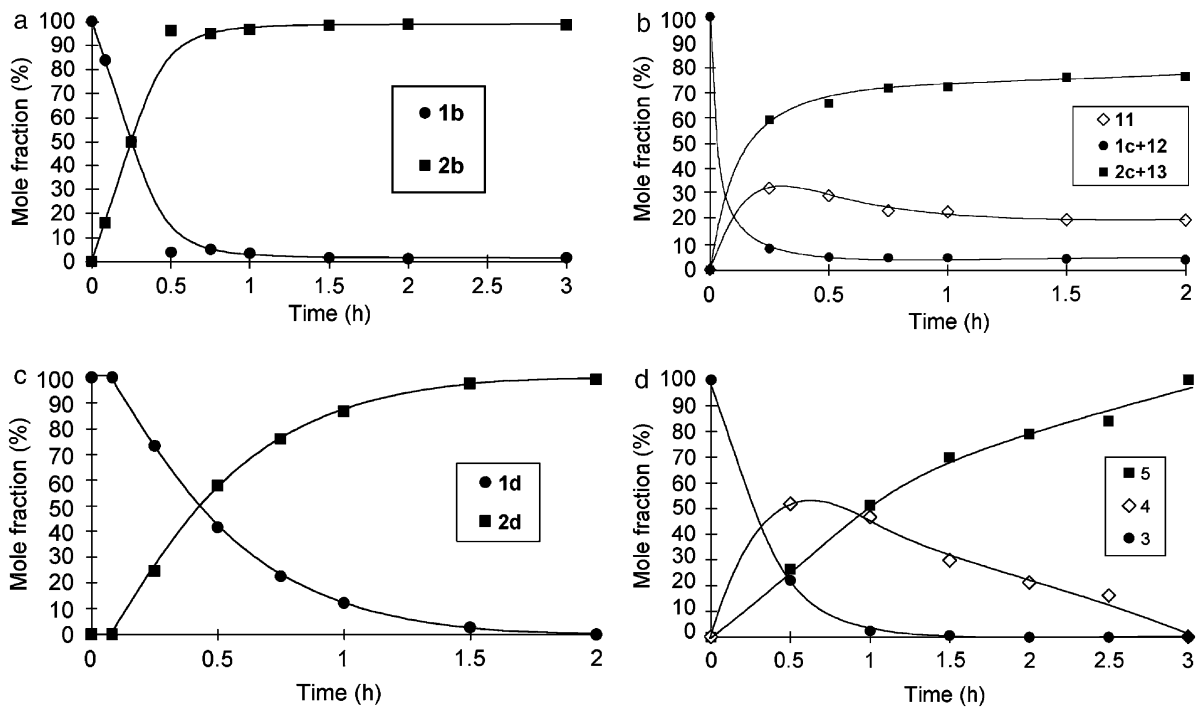


Fig. 3 Time profile for the dehydrogenations of selected piperidine derivatives at 170 °C over 5% Pd/SiO_2 (10 mol% loading) catalyst with constant but slow flow of N_2. (a) 4-Aminopiperidine (**1b**), (b) 4-dimethylaminopiperidine (**1c**), (c) piperidine-4-carboxamide (**1d**), and (d) 1,3-di(piperidin-4-yl)propane (**3**).

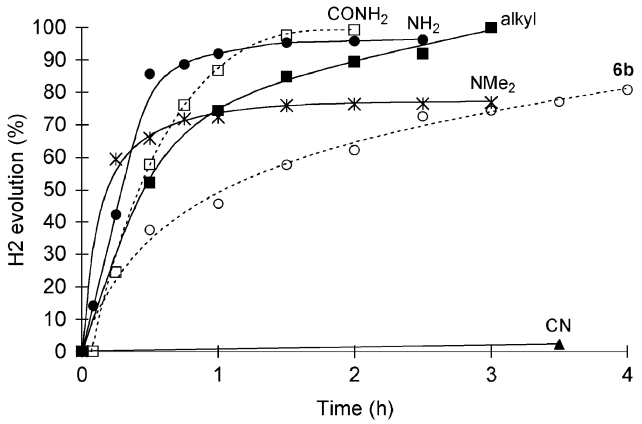


Fig. 4 A comparison of the rates of hydrogen evolution of octahydro-1-methylindole and several piperidines over 5% Pd/SiO_2 (10 mol% loading) catalyst at 170 °C with constant but slow flow of N_2. Evolved H_2 is shown as a fraction of the theoretical maximum and is calculated from the yield of *known* products and intermediates as a function of time. The starting materials were 4-aminopiperidine (**1b**), 4-dimethylaminopiperidine (**1c**), piperidine-4-carboxamide (**1d**), 4-cyanopiperidine (**1e**), 1,3-di(piperidin-4-yl)propane (**3**) and 1-methyloctahydroindole (**6b**).

enthalpy. Both the alkyl group on the pyrrolidine ring and the external substituent lower the wt% releasable hydrogen content of the compound. Placing a heteroatom within both rings is the most powerful technique for lowering the enthalpy of dehydrogenation without lowering the hydrogen content, but this strategy is likely to dramatically increase the cost of synthesizing the compound and was not explored in this study. Our investigations started with the preparation of 1-methyloctahydroindole (**6b**).

The complete hydrogenation of indoles has not been extensively reported in the literature. Raney nickel at 80–300 bar H_2 and 170–230 °C has been reported to be effective for indole and 2-methylindole.[37,38] Teuber and Schmitt recommended RuO_2 at only 105 °C for the hydrogenation of 5-methoxyindole.[39] We experimentally tested the hydrogenation of several indoles. Hydrogenations of 1-methylindole (**9b**) were conducted using various catalysts under 70 bar of H_2 at 125 °C (Table 5). Of the many catalysts tried, RuO_2 and especially Rh/C give the greatest conversion to the fully hydrogenated

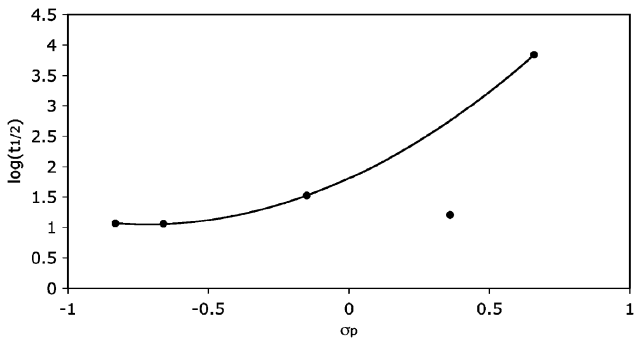
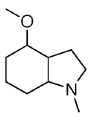
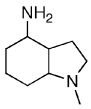
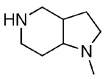
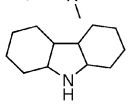
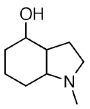
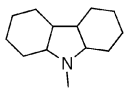


Fig. 5 The correlation of $\log_{10}(t_{1/2})$ with σ_p for the dehydrogenation of substituted piperidines at 170 °C. The error on the $\log(t_{1/2})$ value for the furthest right data point (**1e**) is large. The curve is a quadratic interpolation. The point off the curve represents **1d**.

Table 4 Calculated enthalpies (kJ mol^{-1} H_2) and weight percent releasable hydrogen content of hydrogenated indole derivatives

Structure	$\Delta H_{rxn}/n$	H (wt%)	Structure	$\Delta H_{rxn}/n$	H (wt%)
	57.5	6.4		52.0	4.7
	53.5	5.8		49.2	5.2
	48.6	5.7		52.8	6.7
	50.2	5.7		50.4	6.2

product **6b**. With Rh/C, the reaction can be completed within 1 h with a catalyst loading as low as 0.5 mol%. Decreasing the catalyst loading further or dropping the reaction temperature to 100 °C leads to incomplete hydrogenation.

The major product from the Pd-catalyzed hydrogenation of indole (**9a**) is tetrahydroindole, although a small amount of the fully hydrogenated product (**6a**) is obtained with a high loading of Pd/C (Table 6). The selectivity for the fully hydrogenated product was much greater with Rh/C but the overall conversion was insufficient at 125 °C. At 180 °C, however, complete hydrogenation was achieved with almost complete selectivity; the small amount of byproduct had a molar mass of 127, consistent with a hydrogenative ring opening product.

The incomplete hydrogenation product 4-hydroxyindoline (**8d**) was exclusively obtained from hydrogenation of 4-hydroxyindole (**9d**) with very low conversion using Rh/C as catalyst at 125 °C (Table 7). Using Pd based catalysts with longer reaction times resulted in high yields of the same product. At 180 °C, almost complete hydrogenation was obtained with Rh/C (2 mol% loading, 4 h, 80 bar); the conversion was 100% and the products were the desired 4-hydroxyoctahydroindole **6d** (39%) and undesired C–O cleavage products octahydroindole **6a** (55%) and tetrahydroindole **7a** (6%). Because of the failure of the hydrogenation, the dehydrogenation reaction of the fully hydrogenated 4-hydroxyoctahydroindole was not attempted.

Complete hydrogenation of 4-amino-1-methylindole (**9f**) to **6f** was not observed (Table 8); the main product was determined by GC/MS to be a dihydro-4-amino-1-methylindole, to which we assign the structure **8f**. Increasing the temperature and using Rh/C as catalyst gave a 24% yield of 1-methyloctahydroindole **6b**, showing that complete hydrogenation is possible but is accompanied by undesired cleavage of the C–NH_2 bond.

4-Methoxy-1-methylindole (**9e**) was investigated in the hope that the electron-donating group on the 6-membered ring would facilitate the dehydrogenation of that ring. The unsaturated molecule was prepared in good yield from **9d** using NaH in THF to deprotonate the OH and NH, followed by

Table 5 Hydrogenation of 1-methylindole (**9b**) at 125 °C

Catalyst	Cat. loading (mol%)	Duration/h	Conversion (%)	Selectivity[a] (%)
5% Pd/C	5	20	0	0
5% Pt/C	1	20	0	0
Ru powder	2	4	0	0
PtO_2	2	4	17	24[b]
5% Pd/SiO_2	5	4	81	36[b]
RuO_2	2	4	95	100
5% Rh/C	5	2	100	100
5% Rh/C	1	2	100	100
5% Rh/C	0.5	1	100	100
5% Rh/C[b]	0.5	2	84	81
5% Rh/C	0.25	2	72	75

[a] Selectivity for **6b**. Balance identified by GC/MS to be a tetrahydro-1-methylindole, presumably 4,5,6,7-tetrahydro-1-methylindole **7b**. [b] Reaction at 100 °C.

Table 6 Hydrogenation of indole (**9a**) at 125 °C

Catalyst	Cat. loading (mol%)	Duration/h	Conversion (%)	Selectivity[a] (%)
10% Pd/C	10	7.5	60	11
10% Pd/C	5	7.5	56	0
5% Pd/Al_2O_3	5	7.5	66	0
10% Pd/SiO_2	5	7.5	53	0
5% Rh/C	1	5	41	47
5% Rh/C[b]	3	5	100	98[c]

[a] Selectivity for **6a**. Remainder is known by GC/MS to be a tetrahydroindole, presumably 4,5,6,7-tetrahydroindole **7a**. [b] 180 °C. [c] Balance has a m/z of 127.

Table 7 Hydrogenation of 4-hydroxyindole at 125 °C

Catalyst	Cat. loading (mol%)	Duration/h	Conversion (%)	Selectivity[a] (%)
5% Rh/C	1	5	9	100
10% Pd/C	5	16	86	100
10% Pd/C	10	16	99	100
5% Pd/Al_2O_3	5	16	99	100
5% Pd/SiO_2	5	16	65	100

[a] Selectivity for 4-hydroxyindoline (**8d**), which was identified by the molecular ion peak of the MS.

Table 8 Hydrogenation of 4-amino-1-methylindole (1.3 mol% catalyst loading)

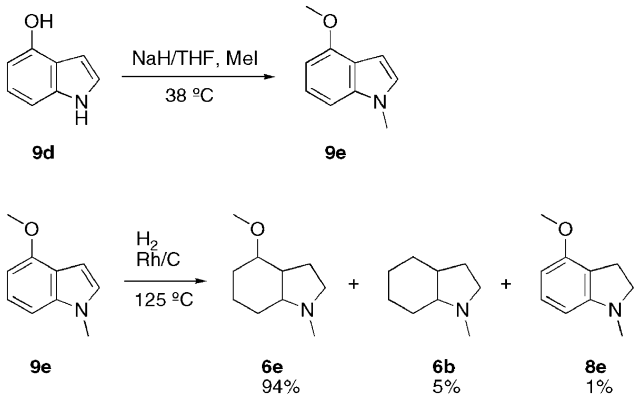
Catalyst	T/°C	Conversion (%)	Selectivity for **8f** (%)	Selectivity for **6b** (%)
5% Rh/C	125[a]	8	100	0
5% Rh/C	180[b]	40	37	59
RuO_2	125[a]	0	—	—
RuO_2	180[b]	13	100	0

[a] 3 h at 125 °C. [b] 3 h at 125 °C followed by 3 h at 180 °C.

reaction with MeI according to the reported procedure (Scheme 4).[40] The ^{1}H NMR spectrum of the isolated **9e** matches the reported spectrum.[40] The synthesized 4-methoxy-1-methylindole was then hydrogenated using the optimized conditions as for 1-methylindole: 5 wt% Rh/C (at 3 mol% loading), 125 °C, 4 h, 70 bar. The conversion (85%) and the selectivity for the complete hydrogenation product **6e** (94%) were greatly enhanced compared to the hydrogenation reaction of 4-hydroxyindole. Product **6e** was not isolated from the mixture but was identified by the molecular ion peak However, small amounts of **6b** and **8e** were detected by GC/MS (Scheme 4). This suggests that the C–OCH_3 bond is cleavable under these conditions, which is likely to be a problem for the use of such compounds in practice. The similar cleavage of the methoxy group from 7-methoxy-1-methylindole during its complete hydrogenation over PtO_2 was reported by Mokotoff.[41]

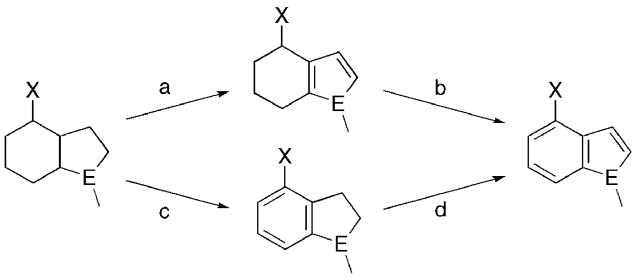
Dehydrogenation of octahydroindole derivatives

As mentioned briefly in the introduction, it is necessary for multi-ring systems to have roughly equal $\Delta H/n$ values for each



Scheme 4 Synthesis and hydrogenation of 4-methoxy-1-methylindole.

ring; if the $\Delta H/n$ for one ring is significantly greater than another, then partial dehydrogenation will be favoured over complete dehydrogenation. With a fused ring hydrocarbon consisting of one six-membered ring and one five-membered ring (*e.g.* 1-methyloctahydro-1*H*-indene, where E = CH and X = H), the dehydrogenation of the 6-ring is greatly favoured over dehydrogenation of the 5-ring (Table 9, path a *vs.* c). One would therefore expect that the dehydrogenation would generate solely the incomplete dehydrogenation product 1-methyl-2,3-dihydro-1*H*-indene. While this is a thermodynamic argument, it is quite likely that the high reaction enthalpy will cause a high activation enthalpy, so that there would also be a kinetic impediment against complete dehydrogenation. Incorporation of a nitrogen in the 5-ring (position E in Scheme 5) greatly lowers the $\Delta H/n$ for the dehydrogenation of that ring. However, the nitrogen raises the enthalpy of dehydrogenation of the 6-ring, so that now we expect dehydrogenation of 1-methyloctahydroindole (**6b**, E = N, X = H) to occur at the 5-ring first (path "a"), giving 1-methyl-4,5,6,7-tetrahydroindole (**7b**); subsequent dehydrogenation of the 6-ring (path "b") will occur more slowly. The enthalpy of the dehydrogenation of the 6-ring can be brought back down again by the addition of an electron-donating substituent in the 4-position (X in Scheme 5). The calculations predict that a methoxy substituent in that position would bring the enthalpies of the two rings to almost equal values,



Scheme 5 Two routes for the dehydrogenation of 1-methyloctahydro-1*H*-indene (E = CH), 1-methyloctahydroindole (E = N) and their derivatives.

Table 9 Enthalpies of dehydrogenation steps in bicyclic [4.3.0] systems as shown in Scheme 5

E	X	$\Delta H/n$ (overall)	$\Delta H/n$ (a)	$\Delta H/n$ (b)	$\Delta H/n$ (c)	$\Delta H/n$ (d)
CH	H	70.7	92.2	48.8	49.9	98.9
N	H	53.5	50.9	56.1	53.9	52.5
N	OMe	52.0	53.0	51.0	51.8	52.7
N	NH_2	49.2	51.6	46.8	48.1	52.4

but an amino group would give the lowest overall enthalpy of dehydrogenation.

Tests of the dehydrogenation of 1-methyloctahydroindole (**6b**, Table 10) in a closed vessel showed that Ru powder, RuO_2, and PtO_2 are poor catalysts for this reaction. Rh/C and Pt/C gave substantial conversion to the partially dehydrogenated compound 1-methyl-4,5,6,7-tetrahydroindole (**7b**), identified by the molecular ion peak in the GC/MS. 1-Methylindole (**9b**, the fully dehydrogenated form) was the major product when the reaction was performed using Pd/C or Pd/SiO_2 as catalyst, the last of these giving 92% conversion to a mixture of **9b** (64%), **7b** (32%), and unknown material (4%). In every test, the N-containing five-membered ring is dehydrogenated rather than the six-membered ring, consistent with the predictions based upon Scheme 5.

Open-vessel tests of the dehydrogenation of 1-methyloctahydroindole (**6b**, Fig. 6) showed that the compound is cleanly but not completely dehydrogenated at 170 °C. A comparison of the rate of H_2 evolution from **6b** with that from piperidines is shown in Fig. 4. A similar test with octahydroindole (**6a**) gave 37% indole plus many unidentified peaks in the GC/MS

Table 10 Dehydrogenations of 1-methyloctahydroindole (**6b**)

Catalyst	*T*/°C	Loading (mol%)	Duration/h	Conversion (%)	Selectivity[a] (%)
Ru powder	165	10	4	0	—
RuO_2	165	5	4	0	—
PtO_2	165	2	4	37	0[b]
5% Pt/C	165	5	5	73	8
5% Pd/Al_2O_3	165	5	16	86	43
5% Pd/Al_2O_3	200	10	4	100	43[b]
10% Pd/C	165	10	4	91	55
5% Pd/SiO_2	150	5	16	89	64
5% Pd/SiO_2	165	5	5	92	64
5% Pd/SiO_2	180	10	5	89	56
5% Rh/C	165	10	4	69	38
5% Rh/C	200	5	6	58	33

[a] Selectivity for **9b**. Remainder is primarily 1-methyl-4,5,6,7-tetrahydroindole (**7b**) with small amounts of unknown material, except as noted. [b] Balance is primarily unknown material.

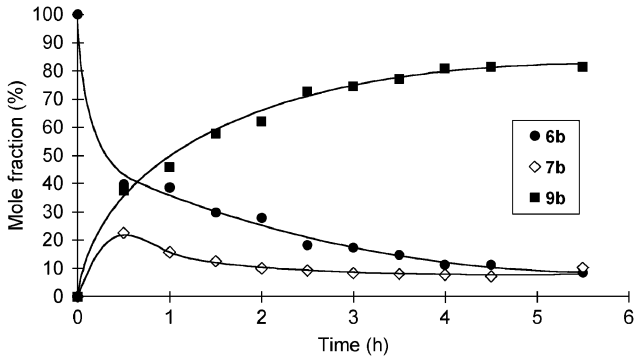


Fig. 6 Time profile for the dehydrogenations of octahydro-1-methylindole (**6b**) over Pd/SiO_2 at 170 °C with constant flow of N_2.

which would require further study before conclusions could be drawn.

An impure sample of 4-methoxy-1-methyloctahydroindole (**6e**) obtained from the hydrogenation of **9e** was used for preliminary dehydrogenation tests. At 130 °C, there is essentially no reaction with Rh/C and a low yield of the dehydrogenated products (**9e** and **9b**) with Pd/SiO_2 and Pd/C. At 150 °C with Pd/C, much of the dehydrogenation occurs but the major product is **9b**, indicating cleavage of the methoxy group from the ring. This reaction was not pursued further.

Conclusions

The work was designed to experimentally test combinations of the three strategies mentioned in the introduction.

(1) The first of these strategies, the addition of electron-donating substituents outside the ring, was shown to be valid in both closed-vessel and open-vessel tests. Gaussian calculations showed that the predicted reaction enthalpies correlated almost linearly with the Hammett σ_p parameter. Experimental results show that the $t_{1/2}$ for dehydrogenation increases monotonically with increasing sigma parameter for non-conjugated substituents.

(2) The addition of conjugated substituents outside the ring was spectacularly successful in the open-vessel tests; the dehydrogenation of compound **1d** was far more rapid than one would expect based solely upon the Hammett parameter of the substituent.

(3) Gaussian calculations showed the thermodynamic benefit of designing multicyclic structures so that each ring has roughly equal dehydrogenation enthalpies, but the structures designed with this strategy in mind, namely 4-methoxy-1-methylindole and 4-amino-1-methylindole showed some instability. The strategy may still be valid but must be evaluated with more stable structures.

Various catalysts were tested for hydrogenations of the substrates studied and it was found that RuO_2 is a clean and efficient catalyst for hydrogenation of 4-dimethylaminopyridine and 1-methylindole. Rh/C was an excellent catalyst for the hydrogenation of piperidine-4-carboxamide, indole and 1-methylindole. Satisfactory conditions for the hydrogenation of 4-aminopyridine were not identified, due to the disproportionation of the product **2b** into a dipiperidylamine. For dehydrogenations, the best performance was obtained with Pd catalysts, especially Pd/SiO_2.

In several cases, undesired side reactions were observed. Methyl group transfer was observed during the dehydrogenation of 4-dimethylaminopiperidine. Disproportionation of product 4-aminopiperidine was observed when 4-aminopyridine was hydrogenated. C–O and C–N bond cleavage leading to loss of substituents in the 4-position of indoles readily occurs, which is an undesired weakness in structures intended for hydrogen storage.

Two substituted piperidines, 4-aminopiperidine and piperidine-4-carboxamide, are the most promising structures among those tested in this study as reversible hydrogen storage compounds. They are both readily and cleanly dehydrogenated at low temperatures and the resulting pyridine, at least in the case of pyridine-4-carboxamide, is readily and cleanly hydrogenated to regenerate the piperidine. These compounds, by the ease of dehydrogenation at low temperatures, demonstrate the validity of the strategies of incorporating electron donating or conjugated unsaturated external subtituents.

Future work will include catalyst optimization, equilibrium measurements, and modification of the hydrogen storage compounds to meet the other requirements listed in the introduction.

Experimental methods

Materials and instruments

THF was freshly collected from an alumina-based solvent drying system. Reactions that required air-free conditions were carried out under an atmosphere of nitrogen in oven-dried glassware using standard Schlenk techniques. ^1H and ^{13}C NMR spectra were recorded on 300 or 400 MHz NMR spectrometers using tetramethylsilane (TMS) as the internal reference at room temperature. GC/MS were acquired with an Inert Mass Selective Detector *via* a HP-5MS capillary column (30 m × 0.25 mm I.D., 0.25 μm film). The temperature was raised from 100 to 275 °C at 25 °C min^{-1} and held for 2 min. The compositions of samples taken from open-vessel dehydrogenations were determined from GC/MS uncorrected peak areas.‡ High-resolution mass spectra were measured using a Waters/Micromass GC–T TOF system equipped with an EI source. Flash chromatography was carried out on silica gel 60, 70–230 mesh. Hydrogen (ultra high purity), palladium on silica (5%, reduced, dry), palladium on alumina powder (5%, reduced), palladium on carbon (10%, dry), ruthenium(IV) oxide (anhydrous), platinum on carbon (5%, dry), aluminium oxide, rhodium on carbon (5%, dry), platinum (IV) oxide, and amines (97–99% purity) were used as received. 4-Methoxy-1-methylindole was synthesized according to literature method.[40]

‡ To determine the amount of error introduced by the use of uncorrected peak areas, test samples containing binary mixtures of **1b** and **2b** having actual compositions of 28, 47 and 63% **2b** were measured by GC/MS, giving uncorrected analyses of 29, 51 and 72%, respectively.

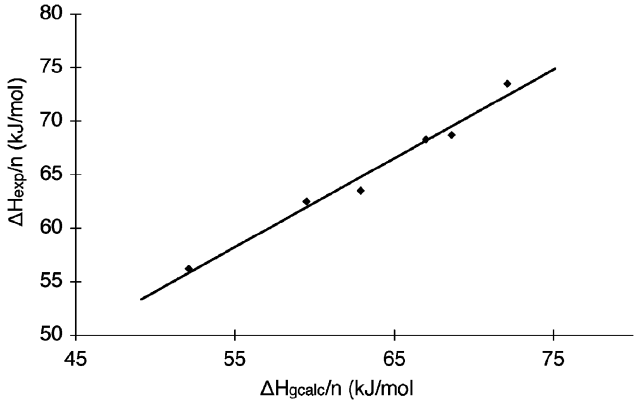


Fig. 7 Linear relationship between raw calculated and literature experimental values of $\Delta H_{rxn}/n$ for the dehydrogenation of selected six-membered ring compounds. The fitted line represents the equation ($\Delta H_{rxn}/n = 0.7653\Delta H_{gcalc}/n + 16.345$). All calculated enthalpies shown in the results have been corrected using this equation.

Gaussian calculations and calibrations

Enthalpies of dehydrogenation per mole of hydrogen gas ($\Delta H_{exp}/n$) were calculated for cyclohexane, chlorocyclohexane, methylcyclohexane, piperidine, cyclohexanol, and piperazine from enthalpies of formation available on the NIST database,[17] using eqn (2) where n is the number of H_2 molecules produced per molecule of starting compound.

$$\Delta H_{exp}/n = \{\Delta H_f(\text{dehydrogenated form}) - \Delta H_f(\text{hydrogenated form})\}/n \quad (2)$$

The enthalpies of dehydrogenation were also calculated from DFT-calculated enthalpies of formation of the same compounds plus their dehydrogenation products (eqn (3)). The density functional theory (DFT) calculations were performed with the B3LYP/6-311G** basis set, employing the Gaussian 03 suit of programs.[42]

$$\Delta H_{gcalc}/n = \{\Delta H_f(\text{dehydrogenated form}) + n\Delta H_f(H_2) - \Delta H_f(\text{hydrogenated form})\}/n \quad (3)$$

A plot of $\Delta H_{exp}/n$ *vs.* $\Delta H_{gcalc}/n$ (Fig. 7) showed a linear dependence; the linear equation thus derived was used to correct all raw DFT-calculated $\Delta H/n$ values for the dehydrogenation of other compounds. Because this equation was derived from data for six-membered single-ring compounds, it is uncertain whether it can be used accurately for the prediction of $\Delta H/n$ values for compounds of fused six- and five-membered rings such as octahydroindole and dodecahydrocarbazole. There is insufficient experimental data to evaluate this properly, but the experimental $\Delta H/n$ value for one such compound, 9-ethyldodecahydro-1*H*-carbazole (51.9 kJ mol^{-1} H_2),[11] is moderately close to the value predicted by the equation from Fig. 2 (49.2 kJ mol^{-1} H_2). The enthalpies calculated for multi-ring systems in the present work are therefore considered to be indicative of trends rather than quantitatively accurate.

General procedure for hydrogenation

A stir bar and the desired quantities of substrate and catalyst were added to a glass vial inside a 31 mL pressure vessel, which was closed, flushed three times with hydrogen and then pressurized to 70 bar with hydrogen. The vessel was heated to the desired temperature using an electric heater and stirred magnetically for the duration of the reaction. The vessel was cooled to room temperature and the pressure was released. The reaction mixture was dissolved in ethyl acetate or methanol and dried with $MgSO_4$. Vacuum filtration through Al_2O_3 was used to remove the drying agent and remaining catalyst. The solvent was removed by rotary evaporation under vacuum.

Compounds **1b**, **1c** and **1d** were identified by comparison of their ^{1}H NMR spectra to those of commercially obtained samples. Compound **6a** was identified by comparison of its ^{13}C, HSQC and mass spectra with the ^{13}C NMR and mass spectra in a database.[43] Compound **6b** was identified by its mass spectrum (MS) and comparison of its ^{1}H NMR spectrum with that in the literature.[44] Compound **7a** was identified as a tetrahydroindole by the GC/MS molecular ion peak; the structure is assumed to be 4,5,6,7-tetrahydroindole. Compounds **8d** and **8f** were identified on the basis of the molecular ion peak in GC/MS. Compound **10** had a high-resolution molecular ion peak of 183.1734 (*cf.* 183.1735 calculated for $C_{10}H_{21}N_3$).

General procedure for dehydrogenation in a closed vessel

A stir bar and the desired quantities of substrate and catalyst were added to a glass vial inside a 31 mL pressure vessel, which was flushed three times with nitrogen. The vessel was heated to the desired temperature using an electric heater and stirred magnetically for the duration of the reaction. The vessel was cooled to room temperature and excess pressure was released. The reaction mixture was washed with ethyl acetate or methanol and filtered through Al_2O_3 under vacuum to remove the remaining catalyst. The solvent was removed by rotary evaporation under reduced pressure.

Identification of **2b** and **2c** was made by comparison of the MS and ^{1}H NMR spectra to those observed with purchased samples. Compound **9b** was identified by comparison of its MS with that of a commercial sample.

General procedure for dehydrogenation in an open vessel

A stir bar and the desired quantities of substrate and 5% Pd/SiO_2 (10 mol% loading) were added to a 25 mL Schlenk tube. The tube was heated to the desired temperature using a high-temperature oil-bath and stirred magnetically under flowing nitrogen for the duration of the reaction. The tube was briefly cooled to room temperature periodically and a portion of the reaction mixture was removed. That sample was extracted with ethyl acetate or methanol and vacuum filtered over Al_2O_3 to remove the remaining catalyst. The filtrate was analyzed by GC/MS.

Products **2b** and **2d** were identified by comparison of the MS and ^{1}H NMR spectra to those observed with purchased samples. Products **2c**, **2e** and **9b** were identified by comparison of the MS to those observed with purchased samples. Compound **2c** was also confirmed by high resolution MS (M − 1 obs. 121.0762, calc. 121.0766). Product **7b** was identified solely on the basis of the molecular ion peak in GC/MS. Compound

13 was identified by high resolution MS (M − 1 obs. 107.0606, calc. 107.0609) and by comparison of its ^{1}H NMR spectrum to that of a commercially available sample in CD_2Cl_2 (–NHCH_3 δ 2.87 ppm, doublet, 5.1 Hz; aromatic C^{3}H δ 6.48 ppm, doublet, 6.3 Hz; aromatic C^{2}H δ 8.17 ppm, doublet, 6.3 Hz).

Although intermediate **4** was never isolated, its formation was evident from the GC/MS of the dehydrogenation samples. The mass spectrum of the peak representing intermediate **4** contains the requisite molecular ion peak (*m*/*z* 204), large peaks (93 and 106, corresponding to pyridine–CH_3 and pyridine–CH_2CH_3) that are in common with the MS of **5** and consistent with an alkylpyridine, and large peaks (98 and 112, corresponding to piperidyl–CH_3 and piperidyl–CH_2CH_3) that are in common with the MS of **3** and consistent with an alkylpiperidine. The final product **5** was identified by comparison of its ^{1}H, ^{13}C and mass spectra to those in a database.[43]

The half-lives for the dehydrogenation of **1b**, **1d** and **3** were calculated from the slopes of the plots of log [**1b**], log[**1d**] and log([**5**] + 0.5[**4**]) *vs*. time. These plots were linear for 5, 5 and 3 half-lives, respectively, although the plot for **1b** had one outlier at 30 min. The half lives for the dehydrogenation of **1c** and **1e** were estimated to be 12 min and ∼100 h, respectively, based upon the first data point for each (59% dehydrogenation after 15 min for **1c** and 2.1% in 3.5 h for **1e**) and assuming first-order behaviour.

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