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Facile, One-Step Production of Niacin (Vitamin B_3) and Other Nitrogen-Containing Pharmaceutical Chemicals with a Single-Site Heterogeneous Catalyst

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Abstract: Niacin (3-picolinic acid), which is extensively used as vitamin B_3 in foodstuffs and as a cholesterol-lowering agent, along with other oxygenated products of the picolines, 4-methylquinoline, and a variety of pyrimidines and pyridazines, may be produced in a single-step, environmentally benign fashion by combining single-site, open-structure, heterogeneous catalysts with a solid source of active oxygen, namely acetyl peroxyborate (APB), in the absence of an organic solvent. The high activities, selectivities, and the relatively mild conditions employed with this single-site heterogeneous catalyst, coupled with ease of transport, storage, and stability of the solid oxidant, augurs well for the future use of APB in conjunction with other open-structure, single-site catalysts for fine-chemical, pharmaceutical, and agrochemical applications.

Keywords: acetyl peroxyborate · green chemistry · heterogeneous catalysis · mesoporous materials · oxidation

Introduction

Single-site heterogeneous catalysts (SSHCs) are those in which the active centers are spatially isolated from one another, and uniformly distributed over a large three-dimensional (internal) surface of a porous, high-area solid such that each site has the same energy of interaction between it and the incoming reactant.[1] Because of their high porosity, such catalysts facilitate ingress of reactants to, and the egress of products from, the active centers, which are so designed, inter alia, as to liberate intermediate active species that attack a reactant bound within a microcavity in a shape-selective or regioselective manner. This yields a product which, in general, would otherwise be difficult to synthesize. In addition to their regioselectivity, SSHCs possess the advantage of combining the merits of conventional, single-site homogeneous catalysts (and enzymes) and those of heterogeneous ones, in that separation of product from reactant is generally facilitated.

Niacin (3-picolinic acid, also known as Vitamin B_3 or nicotinic acid) and other oxygenated products of the picolines, 4-methyl quinoline, 4-methyl derivatives of pyrimidine and pyridazine, and 2-methyl pyrazine, are of considerable value in pharmaceutical, agrochemical, and fine-chemical applications (see Schemes 1 and 2). Niacin is used extensively as vitamin B_3 in foodstuffs and as a cholesterol-lowering agent; isonicotinic acid (4-picolinic acid) and its derivatives have applications as an antibacterial drug for treating tuberculosis, psoriasis, and arthritis and is also used as a plant growth regulator, as well as a herbicide, pesticide, and as a corrosion regulator. Derivatives of quinoline carboxylic acids are used as biocides, pesticides, anti-bacterial agents, cancer drugs, seed disinfectants, herbicides (e.g. "Quinclorac", "Im-

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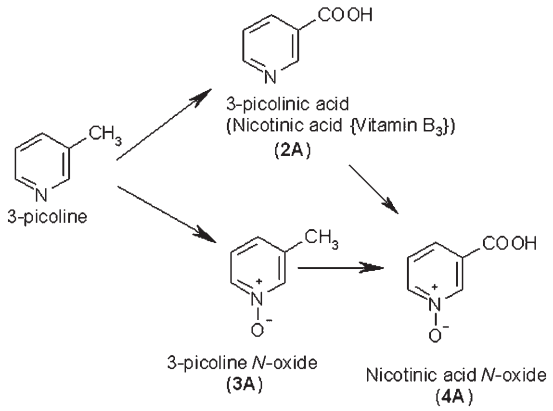
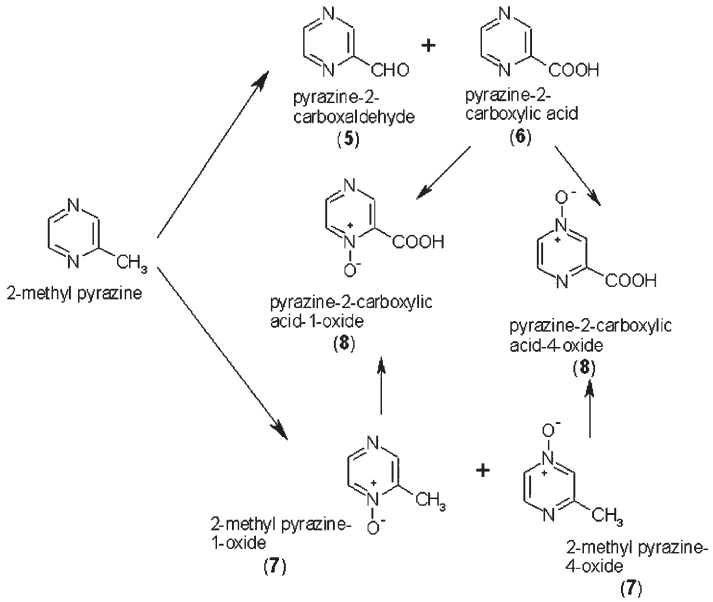


Scheme 1.



Scheme 2.

azaquin"), plant growth regulators, antibiotics, anti-fungal agents for plants, trypsin inhibitor, charge control agent for toners (copiers), and as metal-ion chelators (application in plating baths). Pyridazine carboxylic acids are used widely as plant growth regulators (e.g. "Clofencet MON21200"—Monsanto). Almost all these pharmaceutical and agrochemical intermediates are usually produced from environmentally aggressive oxidizing agents, such as chromic acid, permanganates, selenium dioxide (SeO_2), and *tert*-butylhydroperoxide + O_2 and may involve two (or more) separate steps. More recently, liquid-phase oxidation processes that involve reacting 3-picoline with homogeneous cobalt and manganese acetates with hydrobromic acid at relatively high temperatures (483 K) and high pressures (100 atm) have been reported.[2] The yields and selectivities are, however, quite low (32% conversion with 19% selectivity for nicotinic acid). Notwithstanding the aggressive and environmentally harmful nature of some of these processes, 2.8 tonnes of inorganic waste is produced for every tonne of niacin generated. In terms of environmental pollution, these methods also account for 1.5 tonnes of CO_2 and 0.37 tonnes of NO_x.

As part of a general program[3–6] that entails the design of "green", one-step production of desirable chemicals, both thermally and photochemically,[7] we have evolved efficient, straight-forward methods of producing all the above-named fine-chemical compounds using a combination of a monofunctional, single-site (open-structure) heterogeneous catalyst that operates under mild conditions in association with a dissolved, solid source of active oxygen, acetyl peroxyborate (APB).[8] Earlier, we showed[9] that this stable source of active oxygen—which may be indefinitely stored and transported with impunity, unlike hydrogen peroxide (H_2O_2) or peracetic acid, for which it substitutes (see below)—is an extremely powerful selective oxidation system when dissolved in aqueous solutions in the presence of a single-site microporous catalyst containing redox active centers. Thus dissolved APB, in combination with ferric ions located inside a microporous aluminophosphate (AlPO) catalyst (e.g. Fe^{III}AlPO-31)[10] converts cyclohexane, in a single-step, solvent-free fashion, with unprecedented efficiency (ca. 88%) and exceptionally high selectivity (ca. 81%) to adipic acid (an important precursor in the manufacture of nylon 6,6 and polyurethanes) at 383 K.[9] More importantly, this approach circumvents the need to use corrosive oxidants, such as nitric acid, that are favored industrially, and is consequently environmentally benign, as it does not produce undesirable greenhouse gases such as N_2O that contribute to ozone depletion. This combination of dissolved APB and an open-structure SSHC also readily converts styrene to styrene oxide and α-pinene and (+)-limonene to their corresponding epoxides (that are important intermediates in the fragrance industry).

We have also shown[11–13] that a wide range of primary, secondary, benzylic, and other unsaturated alcohols, substituted olefins as well as phenols, anisoles and other substituted aromatics may also be selectively oxidized to desirable products and specialty organics with APB and an appropriately designed open-structure SSHC. Here, however, we focus on a range of nitrogen-containing heterocyclic compounds that are feedstocks for generating many desirable pharmaceutical, agrochemical, and fine-chemical intermediates.

Results and Discussion

From prior ^{13}C, ^{1}H, and ^{11}B NMR studies (solid and liquid),[9] it has been established that, after dissolution of the APB (which is not totally single-phase in the solid-state) in water, the system establishes the equilibrium, given in Equation (1), with a half-life of approximately 2 h at 65 °C.

$$CH_3COOH + H_2O_2 \rightleftharpoons CH_3COOOH + H_2O \quad (1)$$

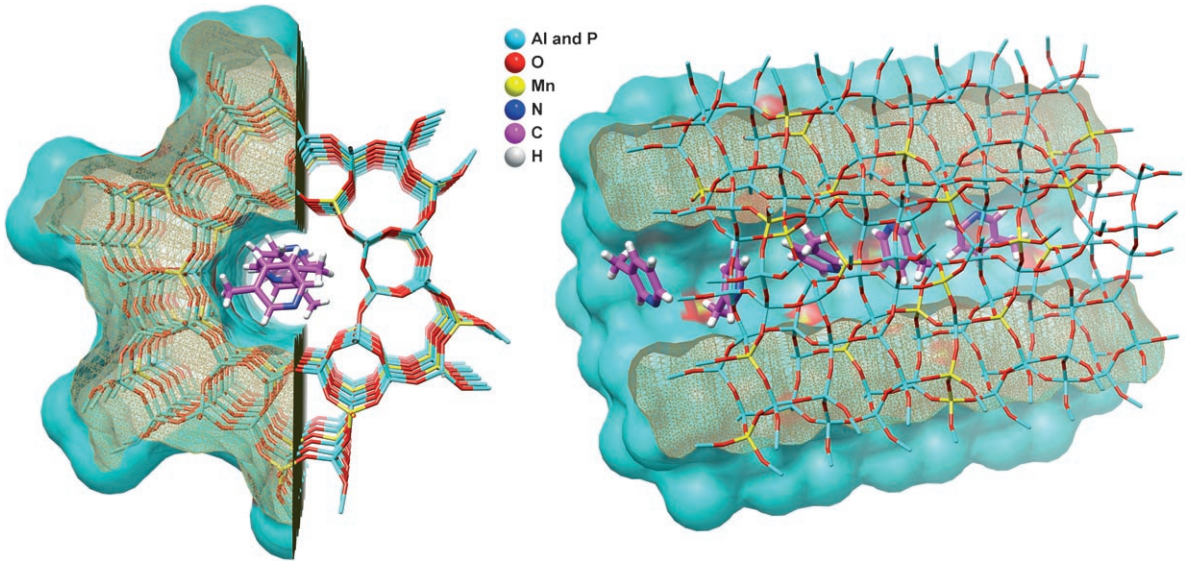


Figure 1. Top (left) and side (right) perspective views showing the accessibility of nitrogen-containing heterocyclic compound (3-picoline represented as example) to the internal, high-area catalytic-active surface of the single-site MnAlPO-5 catalyst (the Mn^{III} active sites are shown in yellow). The structural drawings were performed by using a series of software packages, which include Crystal Impact Diamond,[20] Mercury,[21] BABEL for file conversion,[22] GaussView, Chimera,[23] and POV-Ray[24] in tandem. The computation of zeolitic surfaces has been performed by selecting a probe radius of 1.4 Å.

Moreover, trigonal $B(O)_3$ species are also present in solution, representing the average over an equilibrium involving different species of this type including boric acid $[B(OH)_3]$. Whilst the precise nature of the released "active" oxygen and the critical reaction intermediate that effects the selective oxidations described below, are at present unclear, the key feature of the use of this novel and readily preparable solid oxidant (APB) is that the peroxyacetic acid releases its active oxygen at the locus of the single-site redox active center within an open structure that accommodates the reactant. This facilitates shape-selective and regioselective oxidation in the reactants described herein; for example, the methyl group of the 4-picoline (see Figure 1) is more liable to oxidative attack than the ring nitrogen (which is rapidly oxidized in the absence of the solid single-site catalyst), thereby yielding the desired product with high selectivity.

The single-site, open-structure, solid catalyst used in this work, Mn^{III}AlPO-5, belongs to a large family of microporous aluminophosphates that have been fully characterized in previous studies[14–16] and notably in our single-step synthesis of ε-caprolactam from cyclohexanone.[17] AlPO-5, which is composed of corner-linked, alternating AlO_4^{5-} and PO_4^{3-} tetrahedra, has pores of diameter approximately 7.3 Å, large enough to allow ingress of all the reactant, nitrogen-containing heterocyclic compounds studied here, to reach the isolated, active centers at which Mn^{III} replaces Al^{III} ions tetrahedrally coordinated to oxygen. Figure 1 illustrates the ease with which the reactants may gain access to the interior of the open structure and hence to the active site.

The performance of APB as an oxidant in contact with the open-structure redox SSHC was compared with a number of other known powerful and popular peroxidic oxidants, such as peracetic acid (PAA), as well as conventional aqueous peroxides, such as hydrogen peroxide (H_2O_2). To rule out the possibility that changes in pH might affect the observed activities or selectivities with neat PAA, additional experiments were carried out by adjusting the pH to be the same as that in the experiments with APB.

Selective oxidation of 4-picoline to isonicotinic acid: The results are summarized in Figure 2 and Table 1 which show

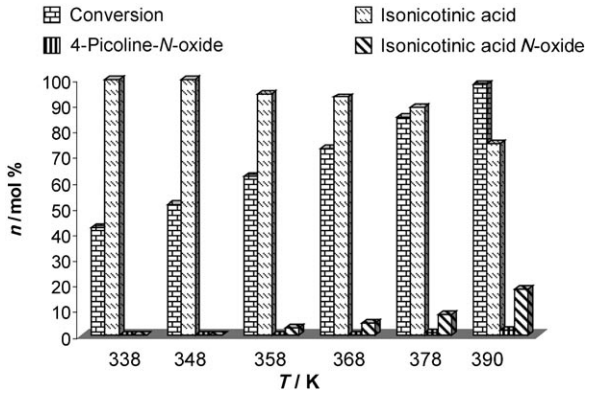


Figure 2. The effect of temperature in the catalytic, solvent-free oxidation of 4-picoline using Mn^{III}AlPO-5 as the catalyst.

the influence of temperature and the nature and effect of the different types of oxidant, respectively. It is clear that the solid APB in conjunction with the Mn^{III}AlPO-5 catalyst affords good conversions, and exceptional selectivities (100% in a few cases, see Figure 2) are achieved in the production of isonicotinic acid (4-picolinic acid). The effect of

Table 1. The influence of oxidant and role of the borate component in the solvent-free, selective oxidation of 4-picoline at 368 K.[a]

Oxidant	Microporous	Conv	Product selectivity [mol%]			
	Catalyst[b]	[mol%]	**2**[c]	**3**[d]	**4**[e]	others
APB (solid)	$Mn_{0.10}Al_{0.90}PO_4$	72.0	92.0	3.0	–	4.8
PAA (neat)	$Mn_{0.10}Al_{0.90}PO_4$	74.5	44.1	20.5	25.9	9.3
PAA + Neobor	$Mn_{0.10}Al_{0.90}PO_4$	66.7	89.5	4.2	1.5	4.7
PAA + NaOAc	$Mn_{0.10}Al_{0.90}PO_4$	81.5	33.7	45.3	15.5	5.4
APB (solid)	TS-1 (2 wt% Ti)	61.9	45.0	35.0	11.3	8.5

[a] Reaction conditions: 1) With APB solid freshly prepared (PAA 22.4%): APB solid (≅3.49 g) dissolved in double-distilled water (20.5 g), 4-picoline (≅2.8 g), catalyst (≅0.30 g); 2) With PAA (neat peracetic acid): peracetic acid (25%) solution in acetic acid (4.2 g), double-distilled water (20.5 g), 4-picoline (≅2.8 g), catalyst (≅0.30 g); 3) With PAA+Neobor®: peracetic acid (25%) solution in acetic acid (4.2 g), double-distilled water (20.5 g), Neobor® (1 g), NaOH (1 g; pH ≅5.1), 4-picoline (≅2.8 g), catalyst (≅0.30 g); 4) With PAA+NaOAc: peracetic acid (25%) solution in acetic acid (4.2 g), double-distilled water (20.5 g), NaOAc (0.934 g), NaOH (1 g, pH ≅5.1), 4-picoline (≅2.8 g), catalyst (≅0.30 g). In all cases adamantane was the internal standard (≅0.5 g); $T \equiv 368$ K; $t = 4$ h. [b] The absolute values of the elemental composition have error limits of $\pm 3 \times 10^{-3}$. [c] **2**: Isonicotinic acid (4-picolinic acid). [d] **3**: 4-Picoline *N*-oxide. [e] **4**: Isonicotinic acid *N*-oxide.

temperature (Figure 2) shows that at lower temperatures (338 and 348 K) virtually no *N*-oxides (4-picoline *N*-oxide or isonicotinic acid *N*-oxide) are formed. Conversion improves significantly on increasing the temperature attaining reasonable yields and selectivities at 368 K, but the selectivity for the isonicotinic acid sharply decreases beyond this temperature.

For the purpose of comparison, the oxidation of 4-picoline was also carried out with the same catalyst (Mn^{III}AlPO-5) with neat peroxyacetic acid (PAA) rather than APB as the oxidant. Although the conversions observed in both cases were comparable, the selectivity for isonicotinic acid is reduced drastically when PAA was used—the propensity for N-oxidation of the ring and of the *para*-methyl group was equally favored with PAA. In one set of experiments, a combination of peroxyacetic acid, sodium acetate trihydrate, and NaOH was used to bring the pH close to that for APB, while in another set, Neobor® borax pentahydrate ($Na_2B_4O_7 \cdot 5H_2O$; ex Borax Europe Limited), an important component that is present in APB, was used. The above sets of experiments were particularly designed to exclude the effects of pH, if any. The addition of Neobor® significantly enhances the selectivity for 4-picolinic acid, whereas in the absence of Neobor®, N-oxidation is simultaneously favored (as with the results for neat PAA). However, this series of experiments shows that the borate component contained in Neobor® is critical for the high activities and selectivities observed when APB is used as the oxidant. Thus, while APB serves as a source of "active" oxygen for these catalytic oxidation processes, the role of key borate-containing species that arise from dissolution of APB also seems necessary for the high performance and high selectivity.

A titanosilicate catalyst, known as TS-1[18,19] and which a popular single-site, open-structure solid catalyst, was also investigated for comparison (Table 1). It is seen that both the conversion and selectivity, even under optimized conditions of temperature and contact time are distinctly inferior to those of Mn^{III}AlPO-5, in part due to the narrower diameter of the pores (ca. 5.5 Å) in TS-1 compared with those of Mn^{III}AlPO-5 (7.3 Å).

With the robotic set-up (see Experimental Section) used to follow the course of the liquid-phase oxidation in contact with Mn^{III}AlPO-5, the kinetics of the process (Figure 3)

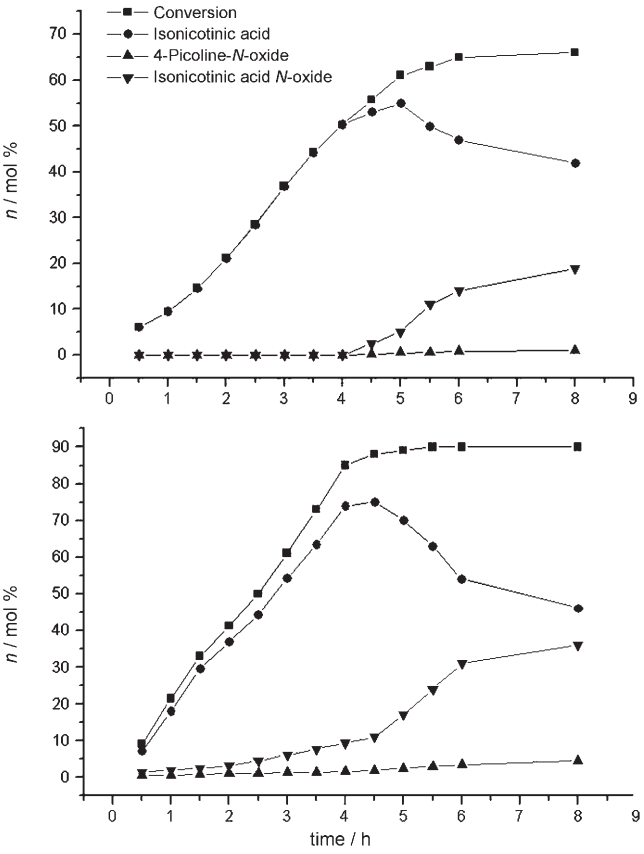


Figure 3. Typical kinetic plots contrasting the performance and selectivity of the Mn^{III}AlPO-5 catalyst at 348 (top) and 378 K (bottom) for the solvent-free oxidation of 4-picoline.

were followed. It is seen that up to 4 h contact time, all the conversion of the 4-picoline is to the desired isonicotinic acid at 348 K (Figure 3, top), and this is further oxidized to the isonicotinic acid *N*-oxide at prolonged contact times. At higher temperatures (378 K), a small amount of isonicotinic acid *N*-oxide is produced right from the outset along with isonicotinic acid (Figure 3, bottom), but there is a steep increase in the concentration of the isonicotinic acid *N*-oxide at prolonged contact times (beyond 4 h). Interestingly, in both cases, 4-picoline *N*-oxide is not generated at lower contact times (up to 4 h), irrespective of the temperature used, and is produced only in small amounts beyond 6 h. The influence of substrate/oxidant mole ratio on the activity and selectivity was also studied (Figure 4). There is an optimal

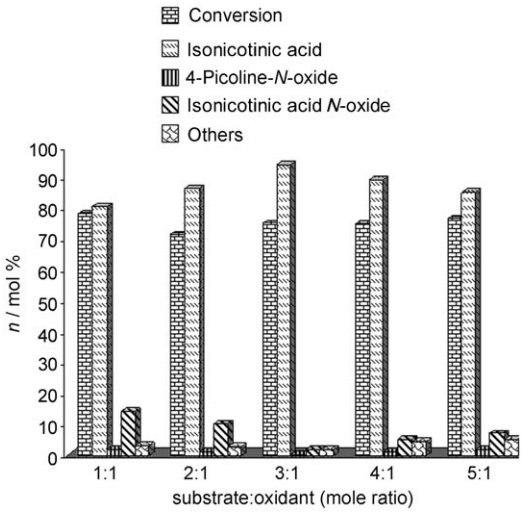


Figure 4. The influence of substrate:oxidant mole ratios, showing that an optimal ratio is required for enhancing the activity and selectivity, in the oxidation of 4-picoline after 4 h at 368 K.

ratio (3:1) for enhanced performance and selectivity for the $Mn^{III}AlPO$-5 catalyst.

Selective oxidation of 3-picoline to nicotinic acid: As with 4-picoline there are good conversions (reaching a maximum of ca. 87% at 378 K) and high selectivities (ca 78% at 348 K); but, interestingly, more of the 3-picoline *N*-oxide is produced in sharp contrast to what was observed with 4-picoline, under comparable conditions of temperature and contact time (Table 2, Scheme 1). Kinetic experiments further confirm that 3-picoline *N*-oxide is produced right at the outset, again, in contrast to the observations in Figure 3. The position of the methyl group, in relation to the nitrogen within the picolines, clearly plays a role in influencing the shape- and regioselectivity of the reaction, when APB is used in combination with $Mn^{III}AlPO$-5.

Table 2. The influence of temperature in the one-step, solvent-free production of nicotinic acid using a single-site $Mn^{III}AlPO$-5 catalyst.[a]

T [K]	Oxidant	Conv [mol%]	Product selectivity [mol%]			
			2A[b]	**3A**[b]	**4A**[b]	others
338	APB	37.0	78.5	21.4	–	–
348	APB	46.8	67.3	25.0	7.5	–
358	APB	58.3	60.0	19.5	20.3	–
368	APB	71.2	45.7	18.0	28.8	7.5
378	APB	86.9	42.6	15.0	27.8	14.5
348	PAA	54.5	40.6	19.3	24.5	15.5

[a] Reaction conditions: 3-picoline (≅2.8 g), catalyst $Mn_{0.10}Al_{0.90}PO_4$ (≅0.30 g), adamantane (internal standard; ≅0.5 g), $t=4$ h; for more details see the footnotes in Table 1. [b] For the products see Scheme 1.

In a competitive experiment, an equimolar mixture of 3- and 4-picoline was oxidized with APB with $Mn^{III}AlPO$-5 as the catalyst. Not surprisingly, in view of its cylindrical symmetry, there is a slight excess (ca. 25%) of conversion of the 4-picoline compared with the 3-picoline (Figure 5), and the total percentage selectivity of the desired acids amounts to a value expected from the non-competitive (separate) experiments. Again, consistent with earlier observation we see that, 3-picoline *N*-oxide is generated in much larger excess (ca. 4.5 times) than the corresponding 4-picoline *N*-oxide derivative.

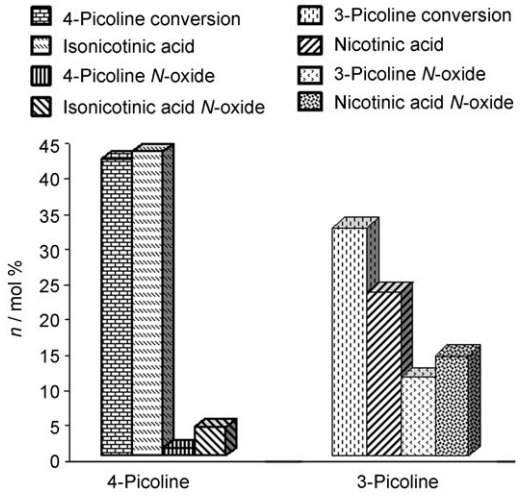


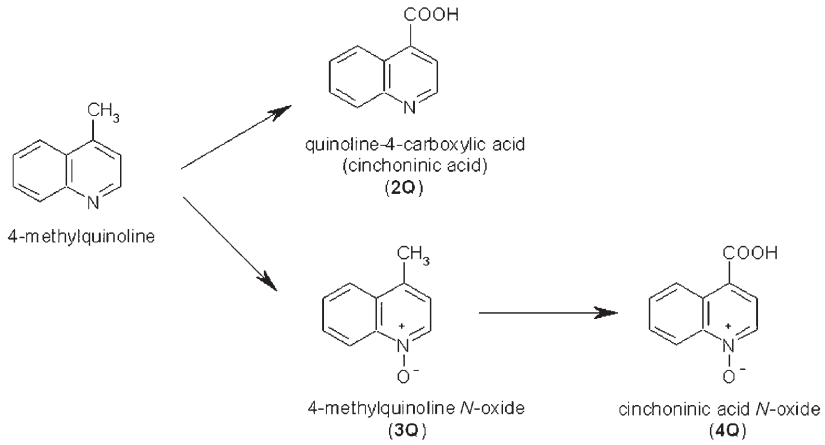
Figure 5. The competitive oxidation of an equimolar mixture of 3- and 4-picoline at 368 K substantiates the fact that, the single-site $Mn^{III}AlPO$-5 catalyst plays a crucial role in influencing the shape- and regioselectivity of the reaction, with respect to the position of the methyl group and that of the nitrogen moiety within the picolines.

Selective oxidation of 4-methylquinoline: From Table 3 (see also Scheme 3) it is seen that significantly higher temperatures are required to achieve reasonable conversions (e.g., 47% at 448 K), but this consequently results in a lower selectivity (ca. 32%) for the desired cinchoninic acid. Much higher selectivities and moderate conversions (88 and 20%,

Table 3. The influence of temperature and comparative performance of other oxidants in the selective oxidation of 4-methylquinoline to cinchoninic acid.[a]

Oxidant	*T* [K]	Conv [mol%]	Product selectivity [mol%]			
			2Q[b]	**3Q**[b]	**4Q**[b]	others
APB	338	2.5	80.2	19.9	–	–
APB	348	3.3	79.8	20.1	–	–
APB	368	7.2	83.5	16.5	–	–
APB	398	19.8	88.5	9.0	2.6	–
APB	423	31.2	65.1	15.9	9.0	10.2
APB	448	46.9	32.1	25.7	15.3	27.0
PAA	398	19.5	35.5	21.2	15.4	28.0
H_2O_2	398	17.6	21.5	45.0	18.0	15.6

[a] Reaction conditions: 4-methylquinoline (≅4.25 g), catalyst $Mn_{0.10}Al_{0.90}PO_4$ (≅0.50 g); H_2O_2 (25% 1.5 g), double-distilled water (20.5 g), adamantane (internal standard, ≅0.5 g), $t=4$ h; for more details see the footnotes in Table 1. [b] For the products see Scheme 3.



Scheme 3.

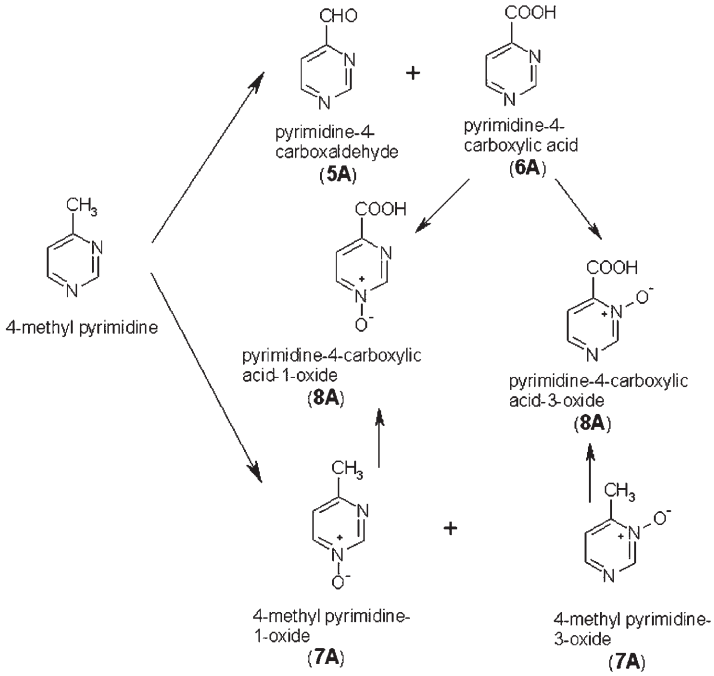
respectively) are obtained at 398 K (Table 3). The relatively large size of the 4-methylquinoline, in comparison to the 3- and 4-picolines, is doubtless responsible for the sluggish performance of this substrate, due to the diffusion limitations presented within the microporous AlPO-5 cavity (Figure 1). However, it is worth noting that the solid APB in conjunction with the microporous Mn^{III}AlPO-5 catalyst displayed a much higher selectivity for the cinchoninic acid compared to peracetic acid (ca. 2.5 times) or H_2O_2 (ca. 4 times) under identical reaction conditions (Table 3).

Selective oxidation of 4-methylpyrimidine, 2-methylpyrazine, and 4-methylpyridazine: Table 4 (see also Schemes 2, 4, and 5) highlights the salient features of these catalyzed conversions and compares the performance of APB oxidant with those of peracetic acid and H_2O_2. We again note that APB is superior not only in overall performance compared with these oxidants, but especially in regard to the desired product selectivity. As in the case of 4-picoline, the use of APB in combination with the Mn^{III}AlPO-5 SSHC did not result in the oxidation of the nitrogen within the ring, both for 4-methylpyrimidine and 4-methylpyridazine, after 5 h at 348 K.

Table 4. Comparative performance of APB, PAA, and H_2O_2 in the solvent-free oxidation of 2-methylpyrazine, 4-methylpyrimidine, and 4-methylpyridazine.

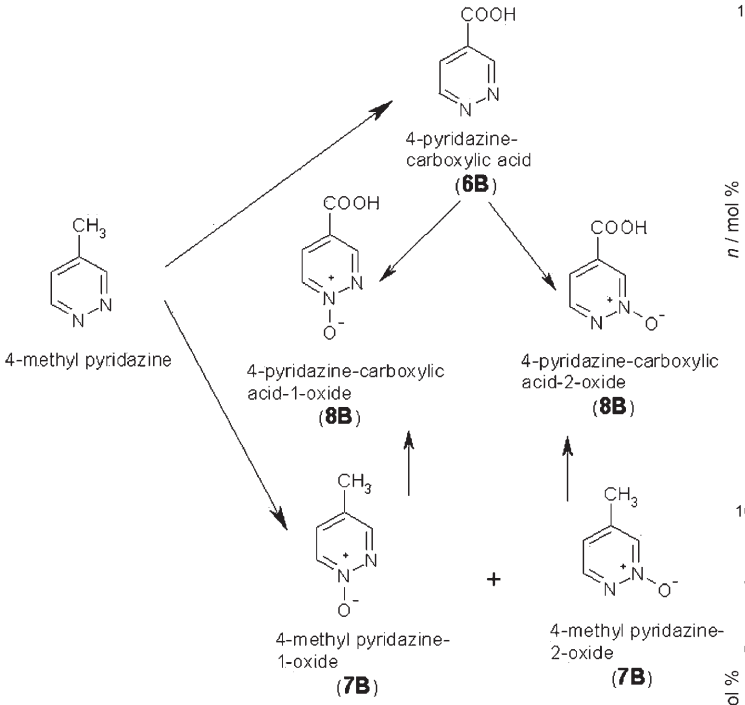
Substrate	Oxidant	T [K]	Conv [mol%]	Product selectivity [mol%]			
				5[b]	**6**[b]	**7**[b]	**8**[b]
2-methyl pyrazine	APB	338	38.9	41.2	28.5	21.5	9.0
	APB	368	67.3	4.5	56.3	23.0	16.2
	PAA	368	61.2	–	19.2	60.6	20.0
	H_2O_2	368	59.8	25.0	16.9	49.5	8.5
				5 A[b]	**6 A**[b]	**7 A**[b]	**8 A**[b]
4-methyl pyrimidine	APB	338	51.5	45.3	54.5	–	–
	APB	368	81.2	–	69.5	–	30.5
	PAA	368	65.4	–	25.3	45.0	29.5
	H_2O_2	368	45.2	34.7	21.2	29.8	14.2
					6 B[b]	**7 B**[b]	**8 B**[b]
4-methyl pyridazine	APB	338	32.5	100	–	–	
	APB	338	78.4[c]	86.6	–	13.5	
	APB	368	77.2	82.3	–	17.9	
	PAA	368	46.5	35.0	49.3	15.4	
	H_2O_2	368	26.3	41.2	48.6	10.3	

[a] Reaction conditions: substrate (≅2.8 g), catalyst $Mn_{0.10}Al_{0.90}PO_4$ (≅0.30 g), adamantane (internal standard, ≅0.5 g), t = 5 h; for more details see the footnotes in Tables 1 and 3. [b] For the products see Schemes 2, 4, and 5. [c] t = 8 h.



Scheme 4.

Kinetic plots (Figure 6) confirm the above observation. In the case of 4-methylpyrimidine, pyrimidine-4-carboxaldehyde and pyrimidine-4-carboxylic acid were the prime products of conversion up to about 5 h of contact time (Figure 6, top). Interestingly, after 5 h, small amounts of pyrimidine-4-carboxylic acid-1-oxide and pyrimidine-4-carboxylic acid-3-oxide started appearing in the product stream. 4-Methylpyrimidine-1-oxide and 4-methylpyrimidine-3-oxide were not generated, in line with the results with 4-picoline. The kinetic plot of 2-methylpyrazine (Figure 6, bottom) was very different though—2-methylpyrazine-1-oxide and 2-methylpyrazine-4-oxide were simultaneously produced along with pyrazine-2-carboxaldehyde and pyrazine-2-carboxylic acid, and products resulting from the oxidation of the nitrogen group



Scheme 5.

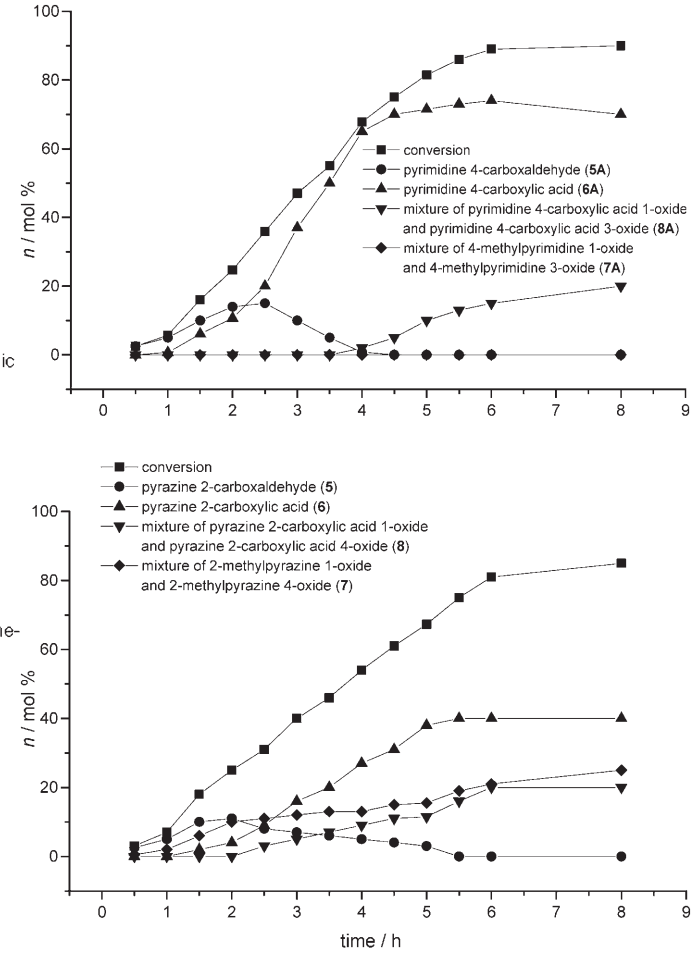


Figure 6. Kinetic plots contrasting the shape- and regioselective behavior of the single-site $Mn^{III}AlPO$-5 catalyst in the solvent-free oxidation of 4-methylpyrimidine (top) and 2-methylpyrazine (bottom) at 368 K.

in the 2-methylpyrazine start to dominate at prolonged contact time (i.e., beyond 5 h). The use of the single-site microporous catalyst, in conjunction with APB, coupled with the position of the methyl group with respect to that of the two nitrogen atoms in these types of substrates, predisposes shape- and regioselective behavior.

Conclusion

Is the open-structure solid host for the catalytically active site essential?: To answer this question we have compared the performance, for a given conversion (in the oxidation of 4- and 3-picoline), using catalysts of identical composition, one being crystalline and the other amorphous so that the porosity of the microcrystalline parent is essentially destroyed. This was achieved by heating the crystalline, phase-pure $Mn^{III}AlPO$-5 catalyst at 1023 K for 24 h in air: the resulting material was X-ray amorphous.

The results for the oxidation of 4- and 3-picoline with these catalysts are shown in Table 5 (Scheme 1). In the case of 4-picoline, the overall conversion falls by an order of magnitude (ca. 2.5 times), but, more significantly, the selectivity for the target (desired) product (isonicotinic acid) was greatly diminished. Interestingly, substantial amounts (almost tenfold) of 4-picoline *N*-oxide and isonicotinic acid

Table 5. The influence of microporosity, crystallinity, and redox-active site on the activity and selectivity, in the oxidation of 3- and 4-picoline using APB.[a]

Oxidant	Substrate	Catalyst	*T* [K]	Conv [mol%]	Product selectivity [mol%]			
					2	**3**	**4**	others
APB (solid)	4-picoline	microporous $Mn_{0.10}Al_{0.90}PO_4$	368	72.0	92.0	3.0	–	4.8
APB (solid)	4-picoline	amorphous $Mn_{0.10}Al_{0.90}PO_4$	368	25.9	16.0	35.8	40.5	7.9
					2A	**3A**	**4A**	others
APB (solid)	3-picoline	microporous $Mn_{0.10}Al_{0.90}PO_4$	338	37.0	78.5	21.4	–	–
APB (solid)	3-picoline	amorphous $Mn_{0.10}Al_{0.90}PO_4$	338	7.4	–	41.5	50.0	8.7

[a] Reaction conditions: 4-picoline (≅2.8 g), 3-picoline (≅2.8 g), catalyst (≅0.30 g), adamantane (internal standard; ≅0.5 g), $t = 4$ h; for more details see the footnotes in Table 1. [b] For products see Table 1 and Scheme 1.

N-oxide were formed, whereas with the open-structure microporous host, containing the redox-active site in high oxidation (Mn^{III}) state (15–17), 92% selectivity for the desired isonicotinic acid was maintained. In the case of 3-picoline, the results were even more pronounced: there was almost a fivefold decrease in the conversion and virtually no nicotinic acid was produced.

In summary, we have demonstrated that niacin (Vitamin B_3), quinoline-, pyridazine-, pyrazine-, and other heterocyclic carboxylic acids can be produced in a single-step, environmentally benign fashion by combining single-site, open-structure, heterogeneous catalysts with a solid source of active oxygen, acetyl peroxyborate (APB), in the absence of an organic solvent. The crystallinity and microporosity of the Mn^{III}-framework-substituted aluminophosphate catalyst plays a major role in influencing the shape-selectivity and regiospecificity of the reaction, when APB is used in combination with this catalyst. The high activities, selectivities and the relatively mild conditions employed with this single-site heterogeneous catalyst, coupled with ease of transport, storage, and stability of the solid oxidant, augurs well for the future use of APB in conjunction with other single-site catalysts for fine-chemical, pharmaceutical, and agrochemical applications.

Experimental Section

APB was freshly prepared according to US 5462692.[8] Briefly, concentrated (24.5%) peracetic acid (40 g) was reacted with of partially dehydrated borax ($Na_2B_4O_7{\cdot}xH_2O$ $0<x<1$; 20 g) for 3 h at 35 °C to form a paste. The resulting paste was washed twice on a suction filter with ethanol (50 mL) and subsequently dried for 2.5 h at 50 °C in a circulating air drying chamber to yield the white powdered product.

The catalytic reactions were carried out in a stainless-steel catalytic reactor (100 mL, Parr) lined with poly ether ether ketone (PEEK). The substrates (4-picoline, 3-picoline, 4-methylquinoline, 4-methylpyrimidine, 4-methylpyridazine, and methylpyrazine), a suitable internal standard (adamantane), and the catalyst (Mn^{III}AlPO-5) were then introduced into the reactor, which was subsequently sealed. The reactor and the inlet and outlet ports were purged thrice with dry nitrogen prior to reaction. The contents were stirred at 1200 rpm and the reactor was heated to the desired temperature under autogeneous pressure (N_2).

The oxidants used in our experiments one of the following:

1) APB (comprising 3.49 g of solid APB, prepared according to US 5462692,[8] and shown by titration studies to liberate 0.701 g of peroxyacetic acid and 0.045 g of hydrogen peroxide immediately upon dissolution).
2) Peroxyacetic acid (comprising 4.2 g of 25% peroxyacetic acid solution in acetic acid).
3) Peroxyacetic acid + Neobor® (comprising 4.2 g of 25% peroxyacetic acid solution in acetic acid + 1 g Neobor® + 1 g NaOH)
4) Peroxyacetic acid + NaOAc (comprising 4.2 g of 25% peroxyacetic acid solution in acetic acid + 0.934 g sodium acetate trihydrate + 1 g NaOH).

In each case, the oxidant was dissolved in double-distilled water (20.5 g) and the resulting solution was fed over the course of the reaction, employing a syringe pump (Harvard "33") to the stirred contents of the reactor. The slow addition of the oxidant to the catalyst/substrate mixture improves the overall selectivity and also helps minimize byproduct formation. It also minimizes the contact time of the oxidant with the catalyst thereby enhancing the "peroxide efficiency" and restricting the rapid decompostion of the peroxide.

At the end of the reaction, the heating was turned off and the contents of the reactor were cooled (quenched). A mass-balance calculation was performed at this stage to check for handling and mass losses. Where kinetic and rate effects were studied, a mini-robot liquid sampling valve was employed to remove small aliquots (0.1 μL) of the sample (aqueous and organic phases) during the course of the reaction. The products were analyzed either online [by using a robotically-controlled unit with an online computer-controlled system which is linked to a gas chromatography (GC) and/or liquid chromatography/mass spectrometry (LCMS) apparatus] or offline (with a suitable internal standard) by GC (Varian, Model 3400 CX) employing a HP-1 capillary column (25 m × 0.32 mm) and flame ionisation detector using a variable-ramp-temperature program (from 65 to 300 °C). The identities of the products were first confirmed by using authenticated standards and their individual response factors were determined from a suitable internal standard (adamantane) by the calibration method. The overall yields were normalized with respect to the (GC) response factors obtained as above and the conversions and selectivities were determined by Equations (2) and (3):

$$\text{Conv.}\,\% = \left[\frac{(\text{mol initial substrate}) - (\text{mol residual substrate})}{\text{mol initial substrate}}\right] \times 100 \quad (2)$$

$$\text{Sel.}\,\% = \left(\frac{\text{mol individual product}}{\text{mol total products}}\right) \times 100 \quad (3)$$

For the internal standard GC method, the response factor (RF) and mol% of individual products were calculated from Equations (4) and (5).

$$\text{RF} = \left(\frac{\text{mol product}}{\text{mol standard}}\right)\left(\frac{\text{area standard}}{\text{area product}}\right) \quad (4)$$

$$\text{mol}\,\%\ \text{product} = \left(\frac{\text{RF} \times \text{mol product}}{\text{mol sample}}\right)\left(\frac{\text{area product}}{\text{area standard}}\right) \times 100 \quad (5)$$

The identity of the products was further confirmed by using LCMS (Shimadzu LCMS-QP8000), which was again employed either online or offline. Hot filtration experiments and inductively coupled plasma (ICP) measurements of the aqueous and organic mixtures were independently (and regularly) carried out to rule out the possibility of leaching. In most cases, the catalysts have been re-used three times without appreciable loss in catalytic activity or selectivity. Further, experiments analogous those reported earlier,[12,13] were carried out to rule out the possibility of leaching, and analysis of the resulting filtrate at the end of reaction by ICP and AAS revealed only trace amounts (< 5 ppb) of dissolved metal ions (Mn, Cr).

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