The total yield of the NAD adducts A–E based on consumed isoniazid is roughly 50% under the conditions shown in Figure 1 (micromolar concentrations of both isoniazid and NAD⁺). The efficient formation of the inhibitor 2 in the absence of InhA is, in our opinion, of great importance for an understanding of the mechanism of action of isoniazid. As the concentration of NAD⁺ inside M. tuberculosis is also in the micromolar range,[3,4] we propose that inside the bacterium 2 is formed by the fast addition of acyl radical 3 to electron-deficient heterocycles such as NAD⁺ and outside the active site of InhA. Considering the low binding affinity of InhA for NAD⁺ (Kᵢ = 4 mM) and the resulting low concentration of InhA-bound NAD⁺[5] the also conceivable addition of 3 to NAD⁺ within the active site of InhA appears rather unlikely. Furthermore, the catalase-peroxidase KatG does not play an active role in the addition of 3 to NAD⁺ (although it is required for oxidation of isoniazid), as the yield of isonicotinoyl–NAD adducts as well as the product composition is about the same after oxidation of isoniazid by KatG or Mn³⁺. The mechanism of action of isoniazid therefore relies on the efficient formation of the isonicotinoyl–NAD adducts by a Minisci reaction as well as the inhibitory potential of the isonicotinoyl–NAD adducts. The proposed reaction mechanism also allows one to reinterpret the observations that a number of isoniazid-resistant mycobacteria appear to possess a higher ratio of reinterpret the observations that a number of isoniazid-resistant mycobacteria appear to possess a higher ratio of NADH/NAD⁺. Furthermore, the catalase-peroxidase KatG does not play an active role in the addition of 3 to NAD⁺ (although it is required for oxidation of isoniazid), as the yield of isonicotinoyl–NAD adducts as well as the product composition is about the same after oxidation of isoniazid by KatG or Mn³⁺. The mechanism of action of isoniazid therefore relies on the efficient formation of the isonicotinoyl–NAD adducts by a Minisci reaction as well as the inhibitory potential of 2 (=B/E), whose Kᵢ value is about 100 nm (see above) and therefore about a factor of 100 below the Kᵢ value of InhA for NADH.[5,12]

The proposed reaction mechanism also allows one to reinterpret the observations that a number of isoniazid-resistant mycobacteria appear to have a higher ratio of NADH/NAD⁺ as the result of defects in NADH-dehydrogenases,[16a] and that overexpression of NAD⁺-binding proteins might contribute to isoniazid-resistance.[16b] A lower intracellular concentration of NAD⁺ should, according to our mechanism, directly lead to a diminished rate of formation of 2 and therefore to an increased resistance towards isoniazid.

In summary, the demonstrated spontaneous formation of the bioactive form of isoniazid significantly simplifies the proposed mechanism of action of the drug and should be helpful in obtaining a better understanding of the molecular events leading to isoniazid-resistance.

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[9] Recombinant InhA was purified by using a N-terminal His-tag.[20] For the incubation experiments, InhA (5.4 μM) was incubated with horse-radish peroxidase (44 μM), isoniazid (250 μM), MnCl₂ (7.5 μM) and either NAD⁺ or NADH (each 47 μM) at pH 7.5 (50 mM Na₂HPO₄) and 25 °C. The InhA activity was monitored by using a NADH-based assay.[20] After the activity dropped below 10% of the value at t₀, the sample was dialyzed for 12 h at 4 °C in a dialysis module (GibcoBRL; Cut-off of the dialysis membrane: 12 – 14 kDa) against 100 mM triethylenediammonium acetate, pH 7. MALDI-TOF spectra were recorded by using a RP Biospectrometry Voyager DE; sinapinic acid, 2,5-di-hydroxybenzoic acid, or 2-amino-5-nitropyridine were used as a matrix.
[11] HPLC analysis was performed on a Merck LiChroCART 250–4 Purospher RP-18e (5 μm) using a linear gradient from NH₄OAc (75 μm) to acetonitrile. UV spectra of the peaks were recorded using a diode-array detector (Kontron 440).
[12] The Kᵢ value of product B/E was determined by using 2-trans-ocenoyl-CoA and NADH as substrates at pH 7.5 (100 mM Na₂HPO₄) and 25 °C. At fixed concentrations of NADH and 2-trans-ocenoyl-CoA the concentration of B/E was varied.

A Microporous Lanthanide – Organic Framework**

Theresa M. Reineke, Mohamed Eddaoudi, M. O’Keeffe, and Omar M. Yaghi*

The recent upsurge of reports on open metal–organic frameworks has provided compelling evidence for the ability to design and produce structures with unusual pore shape, size, composition, and function.[10] To realize the potential of these materials in host–guest recognition, separation, and catalysis, it is essential that their frameworks exhibit perma-
ent microporosity even in the absence of guests, an aspect that is routinely considered for zeolites\cite{2} but has remained largely unexplored for the analogous metal–organic materials\cite{3}. In attempting to address this issue, we aimed at coupling our interest in designing new frameworks with the desire to achieve stable microporous structures. Here we report the synthesis and structure of Tb(bdc)NO$_3$·2DMF (bdc = 1,4-benzenedicarboxylate; DMF = N,N-dimethylformamide) and show that its desolvated derivative Tb(bdc)NO$_3$ has a stable zeolite-like framework that is capable of reversible molecular sorption and of maintaining microporosity in the absence of included guests.

Previous studies on the copolymerization of Zn$^{II}$ with BDC have shown that stable frameworks can be produced\cite{3d, 4}. This was attributed to the bis-bidentate functionality of BDC and its tendency to form large, tightly bound metal carboxylate cluster aggregates that ultimately act as building blocks in the crystal structure. We sought to extend this strategy to the pursuit of lanthanide–organic open frameworks, which remain virtually unknown, despite the established role of lanthanide compounds sensor technology\cite{5}.

Deprotonation of the acid form of BDC (H$_2$BDC) with pyridine followed by its copolymerization with Tb$^{III}$ in methanol/DMF at room temperature gave a crystalline colorless solid, which was formulated as Tb(bdc)NO$_3$·2DMF on the basis of elemental analysis and single-crystal X-ray diffraction\cite{6, 7}. Complete deprotonation of BDC was confirmed by the absence of any strong absorption bands due to protonated carboxyl groups (1715 – 1680 cm$^{-1}$) in the FT-IR spectrum\cite{6}. This material is stable in air and is insoluble in common organic solvents such as methanol, ethanol, acetonitrile, acetone, and DMF.

The single-crystal structure analysis revealed an extended Tb–BDC framework with two crystallographically distinct Tb atoms, BDC units, nitrate ions, and four DMF ligands. The two Tb atoms are each coordinated by eight oxygen atoms: One each from four carboxylate groups of different BDC ligands, two from a nitrate anion, and one from each of two DMF molecules (Figure 1). The framework is composed only of Tb and BDC, whereby each carboxylate moiety bridges two terbium atoms in a bis-monodentate fashion to form chains along the c axis (Figure 2a). These chains are cross-linked by BDC to form a three-dimensional network (Figure 2b) in which the nitrate anions and DMF molecules point into the channels. The topology of the structure is best described in terms of a simple (3,4)-connected net derived from the 4-connected net of the PtS structure (Figure 3a and b). In this case, each of the planar 4-connected vertices (filled circles) are split into pairs of 3-connected vertices that share a common link\cite{8}. As shown in Figure 3c, the 4-connected

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Figure 1. The asymmetric unit of crystalline Tb(bdc)NO$_3$·2DMF; atoms labeled by the letter A are related by symmetry to those without such designation.

Figure 2. a) Tb–BDC chains shown perpendicular to the c axis. b) A projection along the c axis with DMF shown in space-filling (C, shaded; N, cross-hatched; O, open) and the Tb–BDC–NO$_3$ framework as ball-and-stick (Tb, filled; N, cross-hatched; C and O, open) representations. Hydrogen atoms are omitted for clarity.

Figure 3. a) A projection of the Tb–BDC framework viewed perpendicular to the c axis. b) A projection along the c axis with DMF shown in space-filling (C, shaded; N, cross-hatched; O, open) and the Tb–BDC–NO$_3$ framework as ball-and-stick (Tb, filled; N, cross-hatched; C and O, open) representations. Hydrogen atoms are omitted for clarity.
The dissociation and removal of DMF from the channels means that terbium becomes coordinatively unsaturated in the resulting porous solid. Exploring the chemistry of such Lewis acid sites may reveal their potential use in sensors or as catalysts for organic transformations. On studying the solution stability of the porous framework, we observed that immersion of the evacuated solid in water results in its quantitative irreversible conversion to another recently reported porous solid, namely, Tb$_2$(bdc)$_3$·4H$_2$O.[5a] Nevertheless, Tb(bdc)$_3$NO$_3$ appears to be unaffected by organic solvents, and this allowed allowed the study of its inclusion chemistry.

The solution sorption isotherms for methanol, ethanol, and isopropyl alcohol are shown in Figure 5. A known amount of the evacuated solid (30–40 mg) was immersed in a solution in toluene containing a specific amount of a potential guest (0.10–0.90 m). The change in guest concentration was then measured by gas chromatography with a thermal conductivity detector. Each equilibrium point was obtained by monitoring the change in guest concentration with time until no further change was observed.[10] The sorption process was successfully modeled with a 1:1 complex as suggested by the Langmuir isotherm equation (assuming equivalent available sites), and all compounds showed good agreement to the model with high nonlinear regression parameters (typically 0.99). The
Experimental Section

Tb(bdc)NO₃·2DMF: 1,4-benzenedicarboxylic acid (H₂BDC) (0.050 g, 0.30 mmol) and terbium(nitrate)(ii) nitrate pentahydrate (0.131 g, 0.30 mmol) were placed in a small vial and dissolved in a mixture of methanol (3 mL) and DMF (3 mL) with mild heating. The vial was then placed in a larger vial containing pyridine (4 mL), which was sealed and left undisturbed for 5 d at room temperature. The resulting colorless block-shaped crystals were collected by filtration, washed with methanol (3 × 10 mL), and air dried to give Tb(bdc)NO₃·2DMF (0.12 g, 73 % yield). The isostructural europium analogue of this compound was also prepared by an identical procedure and found to have the same composition and structure as the terbium compound. Elemental analysis (%) calcd for C₈H₄O₇NTb: Tb(bdc)(NO₃) C 24.95, H 1.05, N 3.64; found: C 25.37, H 1.31, N 3.95. FT-IR (KBr, 2000 – 500 cm⁻¹): 3452 (w), 2968 (w), 1702 (m), 1663 (vs), 1630 (s), 1512 (w), 1440 (s), 1314 (s), 1255 (w), 1110 (m), 1064 (w), 1031 (w), 900 (w), 821 (m), 761 (s), 682 (m), 511 cm⁻¹ (s). The europium analogue of this compound was also prepared by an identical procedure and found to have the same composition and structure as the terbium compound. Elemental analysis (%) calcd for C₈H₄O₇Neu: Eu(bdc)(NO₃)·2DMF: C 32.07, H 3.46, N 8.01; found: C 32.26, H 3.26, N 8.02.

An X-ray single-crystal analysis was performed on a colorless polyhedral crystal of Tb(bdc)NO₃·2DMF with approximate dimensions of 0.07 × 0.16 × 0.19 mm at 115 ± 1 °C; monoclinic, space group P2₁/c, a = 17.5986(1), b = 19.9964(3), c = 10.5454(2) Å, β = 92.28(3)°, V = 3710.09(7) Å³, Z = 8, μ_{abs} = 1.90 cm⁻¹, μ_{moa} = 38.57 mm⁻¹. All measurements were made on a SMART CCD area detector with graphite-monochromated MoKα radiation. Frames corresponding to an arbitrary hemisphere of data were collected by ω scans of 0.3° counted for a total 10.0 s per frame. Cell constants and an orientation matrix, obtained from a least-square refinement of the measured positions of 7766 reflections in the range 3.00 < θ < 45.00°, corresponded to a primitive monoclinic cell. Data were integrated by the program SAINT[13] to a maximum 0.6 value of 49.5° and corrected for Lorentzian and polarization effects by using XPREP[12]. The data were corrected for absorption by comparison of redundant and equivalent reflections by using SADABS[13] (Tmax = 0.74, Tmin = 0.47). The structure was solved by direct methods. Terbium and oxygen atoms were refined with anisotropic displacement parameters, all carbon atoms with isotropic parameters. Hydrogen atoms of the organic ligands were included but not refined. The final cycle of full-matrix least-squares refinement was based on 3156 observed reflections (I > 3.0σ(I)) and 227 variables and refined to convergence R₁ = 0.058 (unweighted, based on F) and wR₂ = 0.065. The maximum and minimum peaks on the final difference Fourier map corresponded to 5.19 and 1.18 e Å⁻³, respectively. Crystallographic data (excluding structure factors) for the structures reported in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication no. CCDC-119758. Copies of the data can be obtained free of charge on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK (fax: (+44) 1223-336-033; e-mail: deposit@ccdc.cam.ac.uk).


Elemental analysis (%) calcd for C₈H₄O₇Nb: Tb(bdc)(NO₃) C 24.95, H 1.05, N 3.64; found: C 25.37, H 1.31, N 3.95. FT-IR (KBr, 2000–500 cm⁻¹): f = 1630 (m), 1512 (m), 1357 (vs), 1329 (w), 1163 (w), 1117 (w), 1025 (w), 893 (w), 847 (w), 814 (w), 761 (m), 518 cm⁻¹ (m). When this material is exposed to DMF vapor for 1 d, the original product is regenerated. Elemental analysis (%) calcd for the regenerated product C₈H₄O₇Nb: Tb(bdc)(NO₃)·2DMF: C 31.65, H 3.42, N 7.91; found: C 31.40, H 3.44, N 7.88.
Stable Polymer-Bound Iodine Azide**

Andreas Kirschning,* Holger Monenschein, and Carsten Schmeck

Dedicated to Professor Armin de Meijere
on the occasion of his 60th birthday

In addition to numerous methods for the syntheses of organic molecules on polymeric supports, there has been a recent upsurge in the interest in the use of polymer-bound reagents in organic chemistry. The intrinsic advantage of this hybrid solid-/solution-phase technique lies in the simple work-up and isolation of the reaction products combined with the flexibility of solution-phase chemistry. Furthermore, these reagents may be used in excess in order to drive the reaction to completion without making the isolation of the products more difficult. Although stoichiometric polymer-supported reagents have been employed in organic synthesis for many years, their application to the construction of small molecule libraries is a relatively recent phenomenon. This can be ascribed to the fact that the number of readily available reagents of this type is still small. Important developments in this field are polymer-supported reductants, oxidants, solution-phase scavengers, chelating proton donors, carbodimide equivalents, or reagents that are capable of promoting C–C bond-forming reactions. However, polymer-bound reagents for 1,2-cohalogentio- nes[8, 9] of alkynes have not been described so far.[10]

As an extension of our earlier work on ligand-transfer reactions from hypervalent iodine(0) reagents to halides in solution,[11] we initiated a study on the development of the first stable electrophilic polymer-bound reagent that syntheti-}

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3a may also be generated by direct azido transfer from hypervalent iodine(0) reagents to halides in solution.**[11]** we initiated a study on the development of the first stable electrophilic polymer-bound reagent that syntheti-}

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