The Synthesis and Characterization of Bicyclooxacalixarenes

Kevin J. Selby
Colby College

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The Synthesis and Characterization of Bicyclooxacalixarenes

By Kevin J. Selby

Approved:

(Jeffrey L. Katz, Assistant Professor of Chemistry)

(5/19/05)

(Bradford P. Mundy, Professor Emeritus of Chemistry)

(5/18/05)
Vitae

Kevin Selby grew up in Winnipeg, Manitoba, Canada where he attended Collège Jeanne Sauvé, a French immersion high school. After grade 11 he had the opportunity to study for two years at the Lester B. Pearson College of the Pacific, a United World College outside of Victoria, British Columbia. From there he continued onto Colby College with the generous support of the Davis Scholars program.

At Colby, Kevin began his first year unsure of what he wanted to major in. After toying with the idea of Biology, he was inspired by an organic chemistry class in the spring of his first year and decided to major in Biochemistry. He also found time to minor in music and travel to Chile for the spring of his junior year. After Colby he plans on studying medicine at Harvard Medical School.
Acknowledgements

I would first like to thank Jeff Katz, my mentor for this project and a major influence over my academic life at Colby. His immense patience allowed me to have a (relatively) smooth transition into lab, and permitted me, even with little previous experience, to do exciting research. He also provided support and encouragement through my application process for medical school, giving me not only the confidence to apply to schools that I didn’t think I could get into, but also the perspective to realize that things would turn out well.

I would also like to thank Mike Feldman, my lab partner, classmate through every semester, and teammate. It’s been nice to know that someone else also took the tough route through college and could commiserate during the difficult times. I would also like to thank Cary Fridrich for his music and good nature, as well as Katie Sigalow and Amy Campfield for being great labmates.

I would also like to thank the other faculty in the Chemistry Department. Specifically, Brad Mundy for fostering my initial interest in organic chemistry and for serving as reader for my thesis. Also, Steve Dunham for being a great advisor and guiding me wisely on my academic path through Colby.

Finally, I would like to thank all of the people who have made my senior year at Colby truly memorable. My roommates, teammates, classmates, and other friends have supported and nurtured me, and I have been truly fortunate to know such people.
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Abstract

Bicyclooxacalixarenes were synthesized in high yield via a selective, room temperature $S_{N}Ar$ reaction of phluoroglucinol with 2,6-dichloropyridines. Functionality on the 2,6-dichloropyridine was varied by changing the electron-withdrawing groups in the 3 and 5 positions (using chlorine, nitro groups, and cyano groups) and the side-chains in the 4-position (using ethyl, butyl, phenyl and $p$-tolyl groups). The resulting cage-like molecules were studied by X-ray crystallography and tested for metal complexation.
Introduction

Calixarenes are [1n]metacyclophanes that were originally named because the first calixarenes, which were tetramers (Figure 1), had conformations similar to a type of Greek vase known as a calyx crater. These cyclic oligomers were formed by the condensation of formaldehyde with p-alkylphenols under alkaline conditions, with research during the 1970s showing that 4, 6 and 8-membered cyclophanes could be made predictably (Figure 1).

![Figure 1: Formation of tetra-butylicalix[4]arene under alkaline conditions](image)

These compounds were easy to make and used inexpensive starting materials to form remarkable conformations and ideal scaffolds for further derivatization. This ease of synthesis has made them popular subjects for further research, as seen by the number of recent, related publications.

Concurrently, oxygen-linked calixarenes (oxacalixarenes) were synthesized with modest yields in 1966. Nucleophilic aromatic substitution ($S_{N\text{Ar}}$) was used.

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reacting resorcinol with dinitro-difluorobenzene (Figure 2).

![Chemical reaction diagram]

**Figure 2**: Oxacalixarene formation using difluorobenzenes as electrophiles and dihydroxybenzenes as nucleophiles\(^3\).

SNAr syntheses such as this one depend on electron-withdrawing groups increasing the reactivity of the halogenated benzene rings to provide effective electrophiles. Work published in 1974 introduced new oxacalixarenes but solubility limitations hampered purification and characterization\(^4\). Another report from 1976 again showed the synthesis of oxygen and sulfur-linked calixarenes, but again due to solubility problems characterization was limited to mass spectrometry\(^5\). This dramatically reduced solubility compared to the original calixarenes demonstrates just one way that calixarenes can change chemically with the addition of heteroatoms.

Work on oxacalixarenes, after a nearly 30 year absence from the chemical literature,\(^6,7\) was taken up by the Katz research group during 2003\(^8\). It was found that tetranitrooxacalix[4]arenes could be generated in high yields (upwards to 92\%) at room temperature in very short periods of time. A large range of functional components could be added without compromising the success of the reaction, allowing in some

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cases to improve the solubility of the new molecules. X-Ray crystallography was the definitive tool for determining their structure (Figure 3).

![Reaction scheme for the synthesis of calix[4]arenes](image1)

**Figure 3:** Reaction scheme for the synthesis of calix[4]arenes.

One of the synthesized molecules, seen in Figure 4, opened up a new possibility: the two accessible phenolic groups in the para-positions of the nucleophilic benzene rings could be linked with another benzene ring, creating a second macrocyclic system that would also be an oxacalixarene. Also, if the oxacalixarene forms first, formation of the second macrocyclic system could be as simple as adding another equivalent of the electrophile to create a bicyclooxacalixarene. These new compounds would then potentially form a cage with a cavity, and yield a unique three-dimensional structure.

![Tetranitrooxacalix[4]arene with two accessible hydroxyl groups](image2)

**Figure 4:** (A) Tetranitrooxacalix[4]arene with two accessible hydroxyl groups. (B) Oxacalixarene turned on its side to show the potential of adding another equivalent of the electrophile.

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Bicyclocalixarenes were first synthesized and named by Volker Bohmer in 1992. He described them as calixarenes “in which two opposite para positions are linked” such that “the additional macrocyclic system formed by the bridge is also a calix[4]arene. Bohmer’s bicyclocalixarenes were synthesized via a long, somewhat impractical route, and the resulting molecules were not symmetric. Other examples of cage-like structures, with and without oxygen-linked rings, have either required multiple-step syntheses or given macrocyclic systems that were not calixarenes.

By adding another equivalent of electrophile to the reaction that formed the molecule seen in Figure 4, the Katz group synthesized a bicyclooxacalixarene (Figure 5).

![Figure 5: X-ray structure of the bicyclooxacalixarene synthesized by the Katz group.](image)

Research on this type of molecule was quickly followed by a new idea that has become the focus of this project. As can be seen in Figure 5, the bicyclooxacalixarenes form a cage with a central cavity. In the case of the cage made only with benzene shown in Figure 5, the hydrogen atoms of the inward-pointing benzene rings fill this inner cavity; the possible uses for this cage could be greatly expanded if more room could be opened up inside the cage. Using pyridine instead of benzene removes the inner hydrogens while adding the possibility of using the lone-pairs of the pyridine rings as lewis-basic sites for metal.

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complexation. The space-filling models shown in Figure 6 demonstrate how much more room would be created by using pyridine instead of benzene as an electrophile to make bicyclocalixarenes.

![Space-filling models](image)

**Figure 6:** A comparison of *Spartan*-minimized, space-filling models of a bicyclocalixarene (left) with a bicyclocalixarene containing pyridine (right).

The goal of this project is therefore the synthesis and characterization of bicyclooxacalixarenes incorporating pyridine. As with past oxacalixarene formation reactions\(^3\,^4\), a nucleophilic aromatic substitution (S\(_{\text{NAr}}\)) mechanism will be used. A 2:3 stoichiometry will be used to favor the formation of bicyclooxacalixarenes with an electrophile (pyridine) and nucleophile (phloroglucinol). Hopefully, the incorporation of pyridine will create bicyclooxacalixarenes with more space in their inner cavity, as predicted by *Spartan* minimizations (Figure 6).

![Scheme](image)

**Scheme 1:** One example of the bicyclooxacalixarenes that will be synthesized.

A variety of bicyclooxacalixarenes will be made by varying electron-withdrawing groups.
and side-chains attached to the electrophilic pyridine ring (Figure 7). Hopefully these modifications will allow us to better understand how electron-deficient the electrophile has to be for reaction to occur, and to find a bicyclooxacalixarene that is soluble and easy to work with for further study.

Figure 7: Bicyclooxacalixarenes to be synthesized.
Discussion

The first bicyclooxacalixarene to be synthesized was hexacyanobicyclooxacalixarene 3 with an ethyl side chain, made from its precursors dichloropyridine 1 and phloroglucinol 2 (Scheme 2). This synthesis was notable because of its high selectivity (yields of 65-80% with no other major products) and the relative ease with which it could be done (room temperature, short reaction time). This procedure had already been used by the Katz research group to synthesize oxacalixarenes, but in this case the bicyclooxacalixarene product that it yielded presented some problems, mostly because its poor solubility made it difficult to work with.

Scheme 2: Synthesis of bicyclooxacalixarene 3.

The poor solubility of compound 3 is at least in part due to the acid/base characteristics of the ethyl group in the 4-position of the electrophile, dichloropyridine 1. This ethyl group can form an extended enolate that is resonance stabilized, as seen in Figure 8, most likely lowering the pKa of the hydrogens of the α-carbons to about 10-14. The addition of Cs$_2$CO$_3$ to the reaction seen in Figure 8 gives an immediate color change to a deep purple color that only disappears when the reaction is acidified during the workup. This color change suggests that the enolate forms immediately, and may form in the bicyclooxacalixarene when it is in solution. Also, product 3 moved poorly through silica
with organic solvents, streaking heavily unless dilute acetic acid was added. Presumably the acid re-protonates the product to make it neutral, allowing it to move more quickly and consistently. We hoped to synthesize an electrophile without an acidic α-hydrogen to avoid these acid/base characteristics.

![Figure 8: Resonance stabilization of extended enolate formed by bicyclooxacalixarene 3 causing low pKa of hydrogens marked by arrows on far left.](image)

We also believed that solubility could be improved in organic solvents by using more hydrophobic groups on the electrophile. A wide variety of dichloropyridine electrophiles were therefore synthesized, via the two-step process seen in Scheme 3, and outlined in Table 1. The electrophiles were synthesized with the goal of either avoiding the acidic α-hydrogens or extending the alkyl chain in the 4-position to increase solubility.
Scheme 3: General synthesis of dichloropyridine electrophiles.\textsuperscript{13,14}

**Table 1: Synthesis of electrophiles with various R groups in the 4-position.**

<table>
<thead>
<tr>
<th>R group</th>
<th>Yield of Dichloropyridine (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ethyl (1)</td>
<td>36</td>
</tr>
<tr>
<td>Methyl (4)</td>
<td>40</td>
</tr>
<tr>
<td>para-Tolyl (6)</td>
<td>18</td>
</tr>
<tr>
<td>Phenyl (8)</td>
<td>15</td>
</tr>
<tr>
<td>Heptyl (9)</td>
<td>40</td>
</tr>
<tr>
<td>n-Butyl (11)</td>
<td>52</td>
</tr>
<tr>
<td>tert-Butyl (12)</td>
<td>0**</td>
</tr>
</tbody>
</table>

**Synthesis of t-butyl dihydroxypyridine was unsuccessful, so the dichloropyridine was never attempted.**

The yields shown were not optimized and therefore cannot be used with any degree of precision to identify trends in the efficiency of dichloropyridine synthesis, especially because difficulties recrystallizing the p-tolyl and phenyl products (6 and 8) lowered their yields significantly. However, the fact that the first step of the synthesis shown in Scheme 3 failed with the t-butyl group suggests that the cyclization reaction cannot take place with too much steric hindrance. The chlorination reaction worked with all of the di-hydroxypyridines that we were able to synthesize.

The p-tolyl and phenyl dichloropyridines (6 and 8 respectively) were the first to be tested for bicyclooxacalixarene formation with the same 3:2 ratio of electrophile to nucleophile seen in Scheme 2. NMR spectra of the p-tolyl products showed dimer formation, but no evidence of bicyclooxacalixarene products, while the NMR spectrum of


the phenyl reaction was inconclusive. The decision was therefore made to first attempt the formation of a diphenyloxacalixarene by changing the ratio of the reactants, as shown in Scheme 4, because the oxacalixarene formation is thought to be more favorable and to occur before the formation of the second ring, which gives the bicyclooxacalixarene.

![Scheme 4: Formation of tetracyanooxacalixarene 13 with phenyl side chain.](image)

Oxacalixarene 13, as well as another one with an n-butyl side chain (14), were made. Despite the successful formation of these oxacalixarenes, none of the electrophiles listed in Table 1, besides the original ethyl electrophile, were successfully made into bicyclooxacalixarenes (attempted in reactions 15-17). It seems that larger side-groups on the electrophile slow the formation of the more complex cage structure. We were also not as confident of the purity of the other dichloropyridines in Table 1 as we were of the dichloropyridine with the ethyl side chain, which may explain the failed synthesis with the methyl group in the 4-position (reaction 15). The original dichloropyridine synthesis was designed to have the ethyl side chain and may not have worked as well with the other side chains. As a result, the products were most likely not as pure, though the impurities were often difficult to detect by NMR because of either very few hydrogens (as with the methyl side chain) or many hydrogen peaks clumped together (as was the case with the phenyl side chain). Further attempts at purifying the other electrophiles in Table 1 may
provide better results than those reported at this time. Limitations of time, as well as the desire to pursue other products that were more soluble, caused us to move on with the remainder of the project without synthesizing bicyclooxacalixarenes with the other electrophiles listed in Table 1.

The bicycloocalixarene that solved many of the solubility problems was the next to be synthesized: hexacyanobicyclooxacalixarene 20, without any side chain in the 4-position. Its precursor, dichlorodicyanopyridine 19 (with hydrogen in the 4 position) could not be synthesized via the reaction shown in Scheme 3. It was therefore synthesized via the two-step reaction shown in Scheme 5.

**Scheme 5: Synthesis of dichloro-dicyanopyridine**

Dichloropyridine 19 was then used to form the corresponding hexacyanobicyclooxacalixarene 20. This reaction worked extremely well, and after just over an hour, isolation with ethyl acetate and water gave a reasonably clean product, as ascertained by its $^1$H NMR spectrum. More importantly, the product was readily soluble in ethyl acetate, acetone and acetonitrile, and could easily be purified by running it through a silica plug with 100% ethyl acetate as an eluent to give a 63% yield with no other major products. Professor Katz was able to obtain yields of upwards to 95%, demonstrating the extraordinary efficiency of this reaction. Without the acyclic $\alpha$-hydrogen shown in Figure 8,
the bicyclooxacalixarene is much easier to handle, even without the presence of a side chain at the 4-position of the electrophile. This result suggests that the relative insolubility of bicyclooxacalixarene 3 with the ethyl side chain results largely from its acid/base properties.

We still wanted to attempt synthesis of a cage using a dichloropyridine with weaker electron-withdrawing groups than the cyano-groups used up to this point. Our goal was to determine just how electron-deficient the electrophilic pyridine ring had to be. We decided to use commercially available 2,3,5,6-tetrachloropyridine, to determine whether this electrophile was still reactive enough to allow displacement of chlorine in both the 2 and 6 positions. This reaction proceeded, but required heating and longer reaction times, as expected with a less reactive electrophile. The reaction was still surprisingly selective however, and bicyclooxacalixarene 21 was the only major product. A cage using a nitro group in the 3-position of the electrophile was also attempted (reaction 22); I was not successful, but Professor Katz synthesized and selectively purified both the syn and anti products of trinitrobicyclooxacalixarene 22.

As mentioned in the introduction, relatively similar compounds to our bicyclooxalixarenes had been synthesized in the past. Two examples exist in the literature of bicyclic metacyclophanes, one with and one without nitrogen-containing aromatic rings. They show the effect of having carbon-linkages and not oxygen-linkages and how hydrogen-bonding hydroxy groups can drastically affect structure. Böhmer's original bicyclocalixarene (Figure 9) maintains a cone-like structure with its upper four benzene rings due to the hydrogen-bonding array between the methoxy and hydroxy groups at the top of the benzene rings.

Figure 9: 2-D structure and X-ray structure of the original Bicyclooxacalixarene.9

Also, it is interesting to note that the benzene rings coming off the sides (with cyclobexane in the 4-position) are not perpendicular with the central benzene rings. Instead, the carbon bridging is bent for two reasons: to maintain the approximately 109° angle characteristic of sp³ hybridized carbon, and to preserve the hydrogen-bonding network visible at the top of the x-ray structure (Figure 10). This hydrogen-bonding network maintains the cone-like structure characteristic of calixarenes in this bicyclocalixarene.

The second bicyclophane example is from 1999 and contains imidazolium rings (Figure 10) that are carbon-linked to two central benzene rings¹².
Figure 10: 2-D structure (above) and X-ray structures, from two angles, of an imidazolium-linked cyclophane. 

Here one notes that the carbon links bend the angle of the imidazolium rings away from perpendicular to the central benzene rings. This angle doesn’t appear to be from the hydrogen atoms pointing into the central cavity, as they are relatively far apart. Rather, it is caused by the sp$^3$ hybridization of the carbon atoms linking the rings together.

In bicyclooxacalixarenes 3, 20 and 21 the oxygen-linkages remain perpendicular to the central benzene because the oxygen atom is sp$^2$ hybridized to allow donation of the oxygen lone pairs into the electron-poor rings containing the cyano groups (Figure 11). This donation is reflected in the shorter bond lengths between the oxygens and the electron-deficient pyridine rings, which are 1.35 Å in the crystal structure. The bonds to the relatively electron-rich benzene rings measure 1.40 Å on average, 0.05 Å longer. The added double-bond character caused by resonance shortens the bonds (Figure 11).
Figure 11: Resonance stabilization from the donation of oxygen lone-pair electrons into electron-poor benzene ring in bicyclooxacalixarene 21.

The sp$^2$ geometry of the oxygen atoms also determines the angle $\varphi$ of Figure 12: it is 117°, slightly distorted from the expected 120°, but far from the 104-107° seen in sp$^3$ hybridized oxygens containing one or two lone pairs. Please refer to the appendix for more information about the X-ray structures (page 31).

Figure 12: X-ray structure of hexacyanobicyclooxacalixarene 21.

In the introduction I explained that the move to using pyridine in the construction of these bicyclooxacalixarenes was made to open up a cavity in the middle of these cages to allow for metal complexation (see Figure 6 of the introduction). However, attempts at
metal complexation with the cages were unsuccessful. No observable changes were seen (as evidenced by thin-layer chromatography and NMR) when a variety of salts were added, leading me to believe that complexation did not occur. This result isn't entirely surprising, because X-ray structures of our compounds show a distance of 2.760 Å between the nitrogen atoms of the pyridine rings and the center of the cavity, whereas metal-nitrogen bond lengths tend to be between 1.9 and 2.1 Å for 1st row transition metals (Table 2) and only slightly longer for other metals. A past attempt at nitrogen-metal complexation attempts with cyclophanes\(^\text{17}\) also showed significantly lower bond lengths than the 2.760 Å required by our cages. This difference, along with the rigid nature of the cage conformations, probably makes bonding between a metal and the pyridine nitrogens difficult, if not impossible.

<table>
<thead>
<tr>
<th>Metal</th>
<th>M-NH(_3) Bond Length (Å)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cr</td>
<td>2.069</td>
</tr>
<tr>
<td>Co</td>
<td>1.965</td>
</tr>
<tr>
<td>Ni</td>
<td>2.074</td>
</tr>
<tr>
<td>Cu</td>
<td>1.987</td>
</tr>
<tr>
<td>Zn</td>
<td>2.044</td>
</tr>
</tbody>
</table>

**Table 2:** M-NH\(_3\) bond lengths with a selection of metals\(^\text{18}\).

Despite the fact that metal complexation has not yet proven to be successful, work continues, and other attempts at nitrogen-containing calixarenes may allow for shorter nitrogen-metal bond lengths. Other interesting aspects of these new molecules also remain to be researched. For instance, one of the salient qualities of the SNAr reaction used in these syntheses is its amazing selectivity for the bicyclooxamacixarene based solely on the ratio of the reactants provided. Future research should definitely include testing the basis for this selectivity, perhaps by altering reaction conditions to offer better detection of


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alternate products or testing whether the conversion of oxacalixarenes to bicyclooxacalixarenes is favorable.

Another possibility for future research is the replacement of phloroglucinol with other nucleophiles. A reliable synthesis for triphenyl-benzene-triamine (Figure 13) was found\textsuperscript{19}, which may create the possibility of more soluble cages because of side chains coming off of the linking heteroatoms. However, it remains to be seen if the triamine will be reactive enough. Having a benzene ring on both sides of the nitrogen may remove too much of its reactivity by occupying its lone pairs in resonance, reducing their nucleophilicity. The bulky phenyl groups may also hinder the reaction sterically. If a similar triamine can be synthesized with methyl groups in place of the phenyl groups it may be more reactive.

![Figure 13: Triphenyl-benzene-triamine](image)

In summary, bicyclooxacalixarenes containing pyridine were synthesized via a simple, high-yielding procedure with short reaction times at room temperature. Initially, I synthesized cage 3 with ethyl side chains, but was hampered by its acidity. It was then thought that solubility could be improved by adding side chains to the 4-position of the dichloropyridine electrophile, but I was unsuccessful using side chains other than the original ethyl group. Finally, a more soluble, higher yielding product was found in

hexacyanobicyclooxacalixarene 21, which has a hydrogen at the 4-position. A less reactive electrophile was also used to synthesize hexachloro cage 22. Compounds 3, 21 and 22 have structures with sp²-hybridized oxygen linking the rings. Metal complexation studies have not been successful to date, most likely due to unfavorable nitrogen-metal bond lengths, but studies in that area are ongoing.

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Experimental

2,6-Dichloro-3,5-dicyano-4-ethylpyridine (1). Dihydroxyopyridine 22 (2.0 g, 10 mmol), phosphorus oxychloride (2.82 mL, 30.2 mmol) and tetramethylaminochloride (1.14 g, 10.4 mmol) were heated and stirred vigorously in a sealed flask at 130°C for 2 hours. The solution was poured over ice to give a precipitate. The product was filtered and washed with cold water, and then recrystallized in ethanol, giving brown crystals 1 (0.42 g, 36%). δ_H (400 MHz, DMSO-d_6) 3.12 (2H, q, -CH_2), 1.39 (3H, t, -CH_3). This reaction, and other chlorinations using oxychloride, used the procedure taken from: Henegar, K.; Ashford, S.; Baughman, T.; Sih, J.; Gu, R. J. Org. Chem. 1997, 62, 6588-6597.

**Hexacyano-bicyclooxacalixarene with R=ethyl (3).** Dichloropyridine 1 (110 mg, 0.480 mmol) and phloroglucinol 2 (40 mg, 0.32 mmol) were suspended in DMSO (3 mL) under ambient atmosphere. Cesium carbonate was added (400 mg, 1.20 mmol), with the mixture immediately turning a deep purple color. The mixture was allowed to stir at room temperature for an hour. The product was extracted with ethyl acetate (2x10 mL) and water (10mL), while adding hydrochloric acid solution (1 M) up to pH 5. The organic layer was washed with brine to give 100 mg of a mixture thought to contain the desired compound. The product was purified by flash chromatography after dry loading in acetone with 10% ethyl acetate in hexanes with 0.5% acetic acid, moving up to 30% ethyl acetate in hexanes with 1% acetic acid as eluent. (73 mg, 65%). λ_max (solid phase)/cm⁻¹ 3091, 2981, 2232, 1587, 1423, 1383, 1360, 1289, 1129, 1035, 977, 920, 672 cm⁻¹; δ_H (400 MHz, acetone-d_6) 7.04 (6H, s, Ar), 3.08 (6H, q), 1.38 (9H, t); δ_C (100 MHz, acetone-d_6) 168.8, 166.4, 154.4, 116.9, 113.0, 92.0, 28.0, 14.1. Rf (40% EA/Hex) 0.450.

2,6-Dichloro-3,5-dicyano-4-methylpyridine (4). 2,6-Dichloro-3,5-dicyano-4-methylpyridine prepared by Prof. Katz (1.0 g, 5.6 mmol), phosphorus oxychloride (1.54 mL, 16.5 mmol) and tetramethylaminochloride (0.62 g, 5.6 mmol) were heated and stirred vigorously in a sealed flask at 130°C for 14 hours. The solution was poured over ice to give a precipitate. The product was filtered and washed with cold water, and then recrystallized in ethanol, giving brown crystals 4 (0.43 g, 40%). δ_H (400 MHz, DMSO-d_6) 3.02 (3H, s, -CH_3).

3,5-Dicyano-4-para-tolyl-2,6-dihydroxypyridine (5). Cyanoacetamide (14.56 g, 174.2 mmol) and ammonium hydroxide (2.5 mL) were suspended in 100 mL of water under ambient atmosphere. Para-tolualdehyde (10.6 mL, 90.1 mmol) was added and the mixture was allowed to stir at room temperature for 24 hours. When the mixture became very thick, an additional 50 mL of water was added after 4 hours and again after 5 hours to allow the mixture to continue stirring. A white powder was vacuum filtered out of the mixture and recrystallized in ethanol. The reaction gave the white powder 5. δ_H (400 MHz, DMSO-d_6) 8.13 (1H, s, OH), 7.85 (2H, d, Ar), 7.40 (2H, d, Ar), 2.32 (3H, s, CH3). This reaction, and other reactions to form dihydroxy precursors, used the procedure taken from: Gunther, L.; Dehnert, J. Ger. Offen. 1973.

2,6-Dichloro-3,5-dicyano-4-para-tolylpyridine (6). Dihydroxypyridine 5 (1.0 g, 3.7
mmol), phosphorus oxychloride (1.12 mL, 12.0 mmol) and tetramethylaminochloride (0.43 g, 3.7 mmol) were heated and stirred vigorously in a sealed flask at 135°C for 17 hours. The product was poured over ice, giving a precipitate. The precipitate was filtered and washed with cold water. It was then recrystallized in ethanol after a fine white powder was filtered out, giving 630 mg of white crystals 6 (18%). m.p. 135°C. 8H (400 Mhz, DMSO-d6) 7.88 (2H, d, Ar), 7.46 (2H, d, Ar), 2.41 (3H, s, CH3).

3,5-Dicyano-4-phenyl-2,6-dihydroxypyridine (7). Cyanoacetamide (14.56 g, 174.2 mmol) and ammonium hydroxide (2.5 mL) were suspended in 100 mL of water under ambient atmosphere. Phenylaldehyde (10.6 mL, 90.1 mmol) was added and the mixture was allowed to stir at room temperature for 24 hours. A white powder was vacuum filtered off and recrystallized in ethanol to give white powder 7. δH (400 Mhz, Acetone-d6) 7.68 (5H, m, Ar).

2,6-Dichloro-3,5-dicyano-4-phenylpyridine (8). Dihydroxypyridine 7 (1.0 g, 3.9 mmol), phosphorus oxychloride (1.1 mL, 12 mmol) and tetramethylaminochloride (0.43 g, 3.9 mmol) were heated and stirred vigorously in a sealed flask at 135°C for 17 hours. The products were poured over ice giving a precipitate, which was filtered and washed with cold water. The product was recrystallized in ethanol, giving 510 mg of white crystals 8 (15%). m.p. 207-209°C. δH (400 Mhz, Acetone-d6) 7.4 (5H, m, Ar).

4-n-heptyl-2,6-dichloro-3,5-dicyanopyridine (9). 3,5-Dicyano-4-n-heptyl-2,6-dihydroxypyridine prepared by Professor Katz (1.0 g, 3.9 mmol), phosphorus oxychloride (1.05 mL, 11.3 mmol) and tetramethylaminochloride (0.43 g, 3.9 mmol) were heated and stirred vigorously in a sealed flask at 135°C for 23 hours. The products were poured over ice giving a precipitate, which was filtered and washed with cold water. The product was recrystallized in ethanol, giving powder 9 (450 mg, 40%). δH (400 Mhz, DMSO-d6) 2.95 (2H, t, CH2), 1.64 (2H, m, CH2), 1.34 (2H, m, CH2), 0.90 (3H, t, CH3).

4-n-butyl-3,5-dicyano-2,6-dihydroxypyridine (10). Cyanoacetamide (14.56 g, 174.2 mmol) and ammonium hydroxide (2.5 mL) were suspended in 100 mL of water under ambient atmosphere. Valeraldehyde (9.6 mL, 90.1 mmol) was added and the mixture was allowed to stir at room temperature for 24 hours. A white powder 10 was vacuum filtered off and recrystallized in ethanol. δH(400 Mhz, DMSO-d6) 2.45 (2H, t, CH2), 1.55 (2H, m, CH2), 1.41 (2H, m, CH2), 0.91 (3H, t, CH3).

4-n-butyl-2,6-dichloro-3,5-dicyanopyridine (11). Dihydroxypyridine 10 (1.0 g, 4.3 mmol), phosphorus oxychloride (1.17 mL, 12.5 mmol) and tetramethylaminochloride (0.47 g, 4.3 mmol) were heated and stirred vigorously in a sealed flask at 135°C for 23 hours. The product was poured over ice giving a precipitate, which was filtered and washed with cold water. The product was recrystallized in ethanol, giving powder 11 (0.580g, 52%). δH (400 Mhz, DMSO-d6) 2.95 (2H, t, CH2), 1.64 (2H, m, CH2), 1.34 (2H, m, CH2), 0.90 (3H, t, CH3).

4-tetra-butyl-3,5-dicyano-2,6-dihydroxypyridine (12). Cyanoacetamide (14.56 g, 174.2 mmol) and ammonium hydroxide (2.5 mL) were suspended in 100 mL of water
under ambient atmosphere. Pivaldehyde (9.80 mL, 90.1 mmol) was added and the mixture
was allowed to stir at room temperature for 24 hours. A white powder was vacuum filtered
off and was only partially recrystallized. NMR showed little possibility of product
formation.

**Tetra-cyanooxacalixarene with R=phenyl (13).** Dichloropyridine 8 (68 mg, 0.24 mmol)
and methyl-3,5-dihydroxybenzoate (40 mg, 0.24 mmol) were suspended in DMSO (3.0
mL) under ambient atmosphere. Cesium carbonate (196 mg, 0.600 mmol) was added and
the reaction was stirred vigorously for an hour. The product was extracted with ethyl
acetate (2x 10 mL) and water (10 mL). The organic layer was washed with brine and dried
over Na₂SO₄. The resulting product was purified by flash chromatography after dry
loading in acetone with 30% ethyl acetate in hexanes, moving up to 50% ethyl acetate in
hexanes as eluent. The purification gave small amounts of white powder 13. δH (400 Mhz,
Aceton-d₆) 7.71 (10H, m, Ar), 7.62 (4H, d, Ar), 7.38 (2H, t, Ar), 3.90 (6H, s, CH₃).

**Tetra-cyanooxacalixarene with R=n-butyl (14).** Dichloropyridine 11 (60 mg, 0.24
mmol) and methyl-3,5-dihydroxybenzoate (40 mg, 0.24 mmol) were suspended in DMSO
(3 mL) under ambient atmosphere. Cesium carbonate (196 mg, 0.600 mmol) was added,
immediately giving the reaction a purple color. The reaction was stirred vigorously for an
hour. The product was extracted with ethyl acetate (2x10 mL) and water (10mL). The
organic layer was washed with brine and dried over Na₂SO₄. The product was purified by
flash chromatography after dry loading in acetone with 30% ethyl acetate in hexanes,
moving up to 50% ethyl acetate in hexanes as eluent. The reaction gave small amounts of
white powder 14. δH (400 Mhz, DMSO-d₆) 7.56 (4H, d, Ar), 7.27 (1H, t, Ar), 3.10 (2H,
t, CH₂), 1.78 (2H, m, CH₂), 1.52 (2H, m, CH₂), 1.01 (3H, t, CH₃).

**Hexacyano-bicyclooxacalixarene with R=methyl (15).** 2,6-Dichloro-3,5-dicyano-4-methylpyridine prepared by Prof. Katz (36 mg, 0.17 mmol)
and phloroglucinol 2 (14 mg, 0.11 mmol) were suspended in DMSO-d₆ (1 mL) under
ambient atmosphere. Cesium carbonate was added (134 mg, 0.410 mmol), and the
mixture immediately turning a reddish color. The mixture was allowed to stir at room
temperature for an hour while monitoring with NMR. The product was extracted with
ethyl acetate (2x 10 mL) and water (10 mL), and hydrochloric acid was added to the
solution (1 M) up to pH 5. The organic layer was washed with brine, and then evaporated
down under reduced pressure to give a red oil. The product gave a messy NMR spectrum
with none of the desired peaks in the aromatic region.

**Hexa-cyano-bicyclooxacalixarene with R=para-tolyl (16).** Dichloropyridine 6 (69 mg,
0.24 mmol) and methyl-3,5-dihydroxybenzoate (40 mg, 0.24 mmol) were suspended in
DMSO (3 mL) under ambient atmosphere. Cesium carbonate (196 mg, 0.600 mmol) was
added and the reaction was stirred vigorously for three hours. The product was extracted
with ethyl acetate (2x 10 mL) and water (1 OmL). The organic layer was washed with
brine and dried over Na₂SO₄. An initial TLC showed three spots. The mixture was then
purified by flash chromatography after loading in 50% ethyl acetate in hexanes, then run
with 30% ethyl acetate in hexanes as eluent. The column gave three separate compounds,
two of which appeared to be dimers instead of the desired calixarene, and one that gave an
inconclusive NMR.

**Hexacyano-bicyclooxacalixarene with R=phenyl (17).** Dichloropyridine 8 (33 mg, 0.12 mmol) and phloroglucinol 2 (10 mg, 0.08 mmol) were suspended in DMSO-δ6 (1 mL). Tri-ethylamine (0.033 mL, 0.24 mmol) was added and the reaction was monitored by NMR over 24 hours. The product's NMR spectra were questionable and poor solubility prevented further purification of the reaction.

2-Chloro-3,5-dicyano-6-aminopyridine (18). Malononitrile (6.87 mg, 104 mmol) and triethylformamate (8.65 mL, 52.0 mmol) were suspended in pyridine (4.2 mL, 52 mmol) under ambient atmosphere. This reaction was heated and stirred at 80°C for 20 min. and then allowed to cool to room temperature. Concentrated hydrochloric acid (80 mL) was carefully added, and then the reaction was heated at 80ºC for 1 hr. Then water (100 mL) was added and the precipitate was filtered off. The product was ashed with water, ethanol and diethyl ether. δH (400 Mhz, DMSO-δ6) 8.57 (1H, s, Ar), 8.42 (3H, s, NH3). The Procedure was based on: Graffner-Nordberg M.;Kolmodin K.; Aqvist J.; Queener S.; Hallberg A. J. Med. Chem. 2001. 44, 2397.

2,6-Dichloro-3,5-dicyanopyridine (19). Aminopyridine 18 (2.0 g, 11 mmol) and copper II chloride (2.25 g, 16.8 mmol) were suspended in acetonitrile (100 mL) under argon. Isoamyl nitrite (2.26 mL, 16.8 mmol) was added and the reaction was heated at 65°C for 5 hours. The reaction was acidified (1 M HCl) and extracted with dichlormethane (2x50 mL) and water (50 mL). The organic layer was washed with brine and dried over Na2SO4. The product was purified by flash chromatography using dichloromethane as eluent, giving 0.98g of solid 18 (45%). δH (400 Mhz, DMSO-δ6) 9.05 (1H, s, Ar). Procedure based on: Vazquez D.; Peinador.; Quintela J. Tetrahedron. 2004. 60, 275-283.

**Hexacyanobicyclooxacalixarene (20).** Dichloropyridine 19 (48 mg, 0.24 mmol) and phloroglucinol 2 (20 mg, 0.16 mmol) were suspended in DMSO (3 mL) under ambient atmosphere. Cesium carbonate was added (400 mg, 1.20 mmol), and the reaction was allowed to stir at room temperature for two hours. The product was extracted with ethyl acetate (2x 10 mL) and water (10mL). The organic layer was washed with brine and dried over Na2SO4. The product was purified with a silica plug with ethyl acetate as eluent to give a yellowish powder (189 mg, 63.0%); δmax (solid phase)/cm⁻¹ 3090, 2940, 2980, 2881, 2231, 1733, 1576, 1457, 1420, 1383, 1370, 1246, 1128, 1034, 1006, and 986; δH (400 Mhz, acetone-δ6) 7.11 (3H, s, Ar), 8.86 (6H, s, Ar); 8c (100 MHz, acetone-δ6) 154.7, 152.3, 117.3, 114.0, 110.9 and 92.3. Rf (40% EA/Hex) 0.361.

**Hexachlorobicyclooxacalixarene (21).** 2,3,5,6-tetrachloropyridine (1.0 g, 4.6 mmol) and phloroglucinol 2 (38 mg, 3.1 mmol) were suspended in DMSO (40 mL) under ambient atmosphere. Cesium carbonate was added (3.0 g, 9.2 mmol), and the reaction was allowed to stir at room temperature for 24 hours. The product was extracted with methylene chloride (2x 10 mL) and water (10 mL). The organic layer was washed with brine and dried over Na2SO4. The product was purified with a silica plug with methylene chloride as eluent to give yellowish powder 22 (445 mg, 45%). δmax (solid phase)/cm⁻¹ 3087, 2924, 2853, 1736, 1612, 1573, 1388, 1308, 1258, 1125, 1095, and 995; δH (400 Mhz,
acetone-d$_6$) 7.79 (3H, s, Ar), 6.57 (6H, s, Ar); $\delta$C (100 MHz, benzene-d$_6$) 156.6, 154.8, 141.8, 116.0, 110.4. R$_f$ (20% EA/Hex) 0.730.

**Tri-nitrobicyclooxacalixarene (22).** 2,4-dichloro-3-nitropyridine (250 mg, 1.3 mmol) and phloroglucinol 2 (109 mg, 0.86 mmol) were suspended in DMSO (10 mL). Cesium carbonate was added (1.1 g, 3.5 mmol) and the reaction was run for 18 hours at room temperature. The product was extracted with ethyl acetate (2x25 mL) and water (25mL). The organic layer was washed with brine and dried over Na$_2$SO$_4$. The product was purified by flash chromatography with 20% ethyl acetate in hexanes, moving up to 40% ethyl acetate in hexanes as eluent. NMR was inconclusive, though Prof. Katz was able to successfully run this same reaction and characterize the desired compound, separating out both syn and anti products.

**3,5-Dicyano-4-ethyl-2,6-dihydroxypyridine (23).** Cyanoacetamide (14.56 g, 174.2 mmol) and ammonium hydroxide (2.5 mL) were suspended in 100 mL of water under ambient atmosphere. Proprionaldehyde (6.50 mL, 90.1 mmol) was added and the mixture was allowed to stir at room temperature for 24 hours. A white powder was vacuum filtered out of the mixture and recrystallized in ethanol. The reaction gave the white powder 23. $\delta$H (400 MHz, DMSO-d$_6$) 3.03 (2H, q, -CH$_2$), 1.24 (3H, t, -CH$_3$).
References


### X-ray Crystallographic Data for 4-acetone

**Identification code**: katz38gm; compound 4-acetone

**Empirical formula**: C\textsubscript{36}H\textsubscript{24}N\textsubscript{6}O\textsubscript{20}

**Formula weight**: 860.61

**Temperature**: 167(2) K

**Wavelength**: 0.71073 Å

**Crystal system**: Monoclinic

**Space group**: C\textsubscript{2}/c

**Unit cell dimensions**:
- \(a = 9.3865(8)\) Å, \(\alpha = 90^\circ\)
- \(b = 21.2279(17)\) Å, \(\beta = 91.3940(10)^\circ\)
- \(c = 18.8177(15)\) Å, \(\gamma = 90^\circ\)

**Volume, \(Z\)**: 91.3940(10) Å\(^3\), 4

**Density (calculated)**: 1.525 Mg/m\(^3\)

**Absorption coefficient**: 0.128 mm\(^{-1}\)

**\(F(000)\)**: 1768

**Crystal size**: 0.65 x 0.35 x 0.14 mm

**\(\theta\) range for data collection**: 1.92 to 28.31°

**Limiting indices**: \(-12 < h < 12, -27 < k < 28, -24 < l < 24\)

**Reflections collected**: 16695

**Independent reflections**: 4489 (\(R_{int} = 0.1268\))

**Completeness to \(\theta = 28.31^\circ\)**: 95.9 %

**Absorption correction**: None

**Refinement method**: Full-matrix least-squares on \(F^2\)

**Data / restraints / parameters**: 4489 / 0 / 283

**Goodness-of-fit on \(F^2\)**: 1.071

**Final R indices \([I>2\sigma(I)]\)**: \(R1 = 0.0559, wR2 = 0.1647\)
R indices (all data)  
\[ R_1 = 0.0627, \quad wR_2 = 0.1712 \]

Largest diff. peak and hole  
0.435 and -0.296 e-/Å

Selected Distances and Angles for 4-acetone

Angles between phenyl planes

\begin{align*}
\text{C5+C6+C7+C8+C9+C10} & \quad \text{and} \quad \text{C5A+C6A+C7A+C8A+C9A+C10A} & 0^\circ \\
\text{C16A+C15A+C1+C2+C3+C4} & \quad \text{and} \quad \text{C5+C6+C7+C8+C9+C10} & 91.5^\circ \\
\text{C16A+C15A+C1+C2+C3+C4} & \quad \text{and} \quad \text{C5A+C6A+C7A+C8A+C9A+C10A} & 91.4^\circ \\
\text{C16+C4A+C3A+C2A+C1A+C15} & \quad \text{and} \quad \text{C5+C6+C7+C8+C9+C10} & 88.6^\circ \\
\text{C16+C4A+C3A+C2A+C1A+C15} & \quad \text{and} \quad \text{C5A+C6A+C7A+C8A+C9A+C10A} & 88.5^\circ \\
\text{C16+C4A+C3A+C2A+C1A+C15} & \quad \text{and} \quad \text{C16A+C15A+C1+C2+C3+C4} & 132.3^\circ \\
\text{C14+C11+C12+C13+C12A+C11A} & \quad \text{and} \quad \text{C5+C6+C7+C8+C9+C10} & 92.9^\circ \\
\text{C14+C11+C12+C13+C12A+C11A} & \quad \text{and} \quad \text{C5A+C6A+C7A+C8A+C9A+C10A} & 92.9^\circ \\
\text{C14+C11+C12+C13+C12A+C11A} & \quad \text{and} \quad \text{C16A+C15A+C1+C2+C3+C4} & 113.7^\circ \\
\text{C14+C11+C12+C13+C12A+C11A} & \quad \text{and} \quad \text{C16+C4A+C3A+C2A+C1A+C15} & 113.7^\circ \\
\end{align*}

Distances between the centers of phenyl planes

\[ \text{C5+C6+C7+C8+C9+C10} \quad \text{and} \quad \text{C5A+C6A+C7A+C8A+C9A+C10A} \quad 4.827 \text{ Å} \]

Distances between the central carbon atoms and the center of the plane of those carbon atoms

\begin{align*}
\text{C14} & \quad \text{to the center of the plane} & 2.667 \text{ Å} \\
\text{C16} & \quad \text{to the center of the plane} & 2.700 \text{ Å} \\
\text{C16A} & \quad \text{to the center of the plane} & 2.700 \text{ Å} \\
\end{align*}

Angles between the central carbon atoms and a dummy atom at the center of the plane of those carbon atoms

\begin{align*}
\text{C14-dummy atom-C16} & 119.6^\circ \\
\text{C16-dummy atom-C16A} & 120.8^\circ \\
\text{C16A-dummy atom-C14} & 119.6^\circ \\
\end{align*}
Bond lengths [Å] and angles [°] for 4-acetone

\begin{align*}
\text{C(1)-C(2)} & = 1.381(2) \\
\text{C(1)-C(15)#1} & = 1.394(2) \\
\text{C(1)-N(1)} & = 1.4546(19) \\
\text{C(2)-C(3)} & = 1.373(2) \\
\text{C(3)-C(4)} & = 1.392(2) \\
\text{C(3)-N(2)} & = 1.4675(18) \\
\text{C(4)-O(1)} & = 1.3562(17) \\
\text{C(4)-C(16)#1} & = 1.3885(19) \\
\text{C(5)-C(10)} & = 1.379(2) \\
\text{C(5)-C(6)} & = 1.387(2) \\
\text{C(5)-O(1)} & = 1.3993(17) \\
\text{C(6)-C(7)} & = 1.377(2) \\
\text{C(7)-C(8)} & = 1.382(2) \\
\text{C(7)-O(2)} & = 1.3998(18) \\
\text{C(8)-C(9)} & = 1.389(2) \\
\text{C(9)-C(10)} & = 1.380(2) \\
\text{C(9)-O(3)} & = 1.3999(16) \\
\text{C(11)-O(2)} & = 1.3605(19) \\
\text{C(11)-C(14)} & = 1.3820(18) \\
\text{C(11)-C(12)} & = 1.394(2) \\
\text{C(12)-C(13)} & = 1.373(2) \\
\text{C(12)-N(3)} & = 1.460(2) \\
\text{C(13)-C(12)#1} & = 1.373(2) \\
\text{C(14)-C(11)#1} & = 1.3820(18) \\
\text{C(15)-O(3)} & = 1.3585(17) \\
\text{C(15)-C(16)} & = 1.389(2) \\
\text{C(15)-C(1)#1} & = 1.394(2) \\
\text{C(16)-C(4)#1} & = 1.3885(19) \\
\text{O(4)-N(1)} & = 1.2194(17) \\
\text{O(5)-N(1)} & = 1.2188(18) \\
\text{O(6)-N(2)} & = 1.2133(18) \\
\text{O(7)-N(2)} & = 1.2133(18) \\
\text{O(8)-N(3)} & = 1.207(2) \\
\text{O(9)-N(3)} & = 1.219(2) \\
\text{C(17)-C(18)} & = 1.450(7) \\
\text{C(18)-O(10)} & = 1.192(3) \\
\text{C(18)-C(19)} & = 1.430(7) \\
\text{C(2)-C(1)-C(15)#1} & = 121.38(13) \\
\text{C(2)-C(1)-N(1)} & = 117.32(13) \\
\text{C(15)#1-C(1)-N(1)} & = 121.28(13) \\
\text{C(3)-C(2)-C(1)} & = 118.72(14) \\
\text{C(2)-C(3)-C(4)} & = 121.64(13) \\
\text{C(2)-C(3)-N(2)} & = 118.03(13) \\
\text{C(4)-C(3)-N(2)} & = 120.33(13) \\
\text{O(1)-C(4)-C(16)#1} & = 123.47(13) \\
\text{O(1)-C(4)-C(3)} & = 117.81(12) \\
\text{C(16)#1-C(4)-C(3)} & = 118.71(13) \\
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\text{C(10)-C(5)-O(1)} & = 118.58(13)
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**Experimental details for 4-acetone**

The selected crystal was covered with Paratone-N oil, placed onto the tip of a glass rod drawn out to a fiber, and frozen in the cold stream (−106 °C) provided by a Rigaku/MSC X-stream 2000 low-temperature system. The X-ray intensity data for this colorless block of C36H24N6Ow with approximate dimensions 0.65 x 0.35 x 0.14 mm were measured with phi and omega scans at 167 K on a Bruker SMART APEX CCD-based X-ray diffractometer system equipped with a Mo-target X-ray tube (λ = 0.71073 Å). The detector was placed at a distance of 5.00 cm from the crystal. A total of 1850 frames were collected (a hemisphere of data) with an exposure time of 30 sec/frame. The frames were integrated with the Bruker SAINT software package using a narrow-frame integration algorithm giving a total of 16,695 reflections to a maximum 2θ angle of 57° of which 4489 reflections were independent. The structure was solved (direct methods) and refined using the Bruker SHELXTL version 6.1 Software Package using literature scattering factors (Wilson, A. J. C., Ed. *International Tables for Crystallography*; Kluwer Academic Publishers: Dordrecht, The Netherlands, 1992; Vol. C.), and the monoclinic space group C2/c, with Z = 4. No absorption correction was applied. The final anisotropic full-matrix least-squares refinement of F² converged at R1 = 6.27%, wR2 = 17.12% and a goodness-of-fit of 1.071 for all data. All non-hydrogen atoms were modeled.
anisotropically. Hydrogen atoms were placed at calculated distances and use a riding model, which means that the positional and thermal parameters are derived from the atom each hydrogen atom is bound to, while maintaining the calculated distance and optimal angles. The largest peak and hole in the final difference map were 0.435 and $-0.296 \text{ e}^-/\text{Å}^3$, respectively. The calculated density is $1.525 \text{ g/cm}^3$ and $F(000)$ is $1768 \text{ e}^-$. 
**X-ray Crystallographic Data for 10-2EtOAc**

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<td>(b = 11.8209(8) \text{ Å} ) (\beta = 105.6600(10)^\circ)</td>
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<td>(c = 21.1429(15) \text{ Å} ) (\gamma = 90^\circ)</td>
</tr>
<tr>
<td>Volume, (Z)</td>
<td>3814.8(5) \text{ Å}^3, 4</td>
</tr>
<tr>
<td>Density (calculated)</td>
<td>1.399 Mg/m³</td>
</tr>
<tr>
<td>Absorption coefficient</td>
<td>0.104 mm⁻¹</td>
</tr>
<tr>
<td>F(000)</td>
<td>1656</td>
</tr>
<tr>
<td>Crystal size</td>
<td>0.52 x 0.39 x 0.34 mm</td>
</tr>
<tr>
<td>(\theta) range for data collection</td>
<td>1.99 to 28.31°</td>
</tr>
<tr>
<td>Limiting indices</td>
<td>-20 &lt; (h) &lt; 20, -15 &lt; (k) &lt; 15, -27 &lt; (l) &lt; 27</td>
</tr>
<tr>
<td>Reflections collected</td>
<td>33503</td>
</tr>
<tr>
<td>Independent reflections</td>
<td>9113 (R_int = 0.0652)</td>
</tr>
<tr>
<td>Completeness to (\theta = 28.31^\circ)</td>
<td>96.0 %</td>
</tr>
<tr>
<td>Absorption correction</td>
<td>None</td>
</tr>
<tr>
<td>Refinement method</td>
<td>Full-matrix least-squares on (F^2)</td>
</tr>
<tr>
<td>Data / restraints / parameters</td>
<td>9001 / 0 / 545</td>
</tr>
<tr>
<td>Goodness-of-fit on (F^2)</td>
<td>1.074</td>
</tr>
<tr>
<td>Final R indices [(I &gt; 2\sigma(I))]</td>
<td>R1 = 0.0519, wR2 = 0.1476</td>
</tr>
<tr>
<td>R indices (all data)</td>
<td>R1 = 0.0594, wR2 = 0.1536</td>
</tr>
<tr>
<td>Largest diff. peak and hole</td>
<td>1.013 and -0.435 e./Å</td>
</tr>
</tbody>
</table>
Selected Distances and Angles for 10-2EtOAc

Angles between aromatic planes

<table>
<thead>
<tr>
<th>Bond Sequence</th>
<th>Angle (°)</th>
</tr>
</thead>
<tbody>
<tr>
<td>C6+C7+C8+C9+C10+C11 and C17+C18+C19+C20+C21+C22</td>
<td>1.0*</td>
</tr>
<tr>
<td>N3+C23+C24+C25+C26+C27 and C6+C7+C8+C9+C10+C11</td>
<td>85.3*</td>
</tr>
<tr>
<td>N3+C23+C24+C25+C26+C27 and C17+C18+C19+C20+C21+C22</td>
<td>84.4*</td>
</tr>
<tr>
<td>N1+C1+C2+C3+C4+C5 and C6+C7+C8+C9+C10+C11</td>
<td>88.6*</td>
</tr>
<tr>
<td>N1+C1+C2+C3+C4+C5 and C17+C18+C19+C20+C21+C22</td>
<td>88.7*</td>
</tr>
<tr>
<td>N1+C1+C2+C3+C4+C5 and N3+C23+C24+C25+C26+C27</td>
<td>119.0*</td>
</tr>
<tr>
<td>N2+C12+C13+C14+C15+C16 and C6+C7+C8+C9+C10+C11</td>
<td>90.5*</td>
</tr>
<tr>
<td>N2+C12+C13+C14+C15+C16 and C17+C18+C19+C20+C21+C22</td>
<td>89.8*</td>
</tr>
<tr>
<td>N2+C12+C13+C14+C15+C16 and N3+C23+C24+C25+C26+C27</td>
<td>114.6*</td>
</tr>
<tr>
<td>N2+C12+C13+C14+C15+C16 and N1+C1+C2+C3+C4+C5</td>
<td>126.0*</td>
</tr>
</tbody>
</table>

Distances between the centers of phenyl planes

<table>
<thead>
<tr>
<th>Bond Sequence</th>
<th>Distance (Å)</th>
</tr>
</thead>
<tbody>
<tr>
<td>C6+C7+C8+C9+C10+C11 and C17+C18+C19+C20+C21+C22</td>
<td>4.487</td>
</tr>
</tbody>
</table>

Distances between the pyridine nitrogen atoms and the center of the plane of those nitrogen atoms

<table>
<thead>
<tr>
<th>Bond Sequence</th>
<th>Distance (Å)</th>
</tr>
</thead>
<tbody>
<tr>
<td>N1 to the center of the plane</td>
<td>2.761</td>
</tr>
<tr>
<td>N2 to the center of the plane</td>
<td>2.741</td>
</tr>
<tr>
<td>N3 to the center of the plane</td>
<td>2.734</td>
</tr>
</tbody>
</table>

Angles between the pyridine nitrogen atoms and a dummy atom at the center of the plane of those nitrogen atoms

<table>
<thead>
<tr>
<th>Bond Sequence</th>
<th>Angle (°)</th>
</tr>
</thead>
<tbody>
<tr>
<td>N1-dummy atom-N2</td>
<td>120.4*</td>
</tr>
<tr>
<td>N2-dummy atom-N3</td>
<td>119.4*</td>
</tr>
<tr>
<td>N1-dummy atom-N3</td>
<td>120.2*</td>
</tr>
<tr>
<td>Bond</td>
<td>Length  [Å]</td>
</tr>
<tr>
<td>-----------------------</td>
<td>------------</td>
</tr>
<tr>
<td>C(1)-N(1)</td>
<td>1.322(18)</td>
</tr>
<tr>
<td>C(1)-O(1)</td>
<td>1.3526(17)</td>
</tr>
<tr>
<td>C(1)-C(2)</td>
<td>1.3991(19)</td>
</tr>
<tr>
<td>C(2)-C(3)</td>
<td>1.387(2)</td>
</tr>
<tr>
<td>C(2)-C(28)</td>
<td>1.439(2)</td>
</tr>
<tr>
<td>C(3)-C(4)</td>
<td>1.389(2)</td>
</tr>
<tr>
<td>C(4)-C(5)</td>
<td>1.4035(18)</td>
</tr>
<tr>
<td>C(4)-C(29)</td>
<td>1.430(2)</td>
</tr>
<tr>
<td>C(5)-N(1)</td>
<td>1.3236(18)</td>
</tr>
<tr>
<td>C(5)-O(2)</td>
<td>1.3484(17)</td>
</tr>
<tr>
<td>C(6)-C(11)</td>
<td>1.382(2)</td>
</tr>
<tr>
<td>C(6)-C(7)</td>
<td>1.3831(19)</td>
</tr>
<tr>
<td>C(6)-O(2)</td>
<td>1.4044(16)</td>
</tr>
<tr>
<td>C(7)-C(8)</td>
<td>1.3793(19)</td>
</tr>
<tr>
<td>C(8)-C(9)</td>
<td>1.3817(19)</td>
</tr>
<tr>
<td>C(8)-O(3)</td>
<td>1.4072(16)</td>
</tr>
<tr>
<td>C(9)-C(10)</td>
<td>1.373(2)</td>
</tr>
<tr>
<td>C(10)-C(11)</td>
<td>1.3827(19)</td>
</tr>
<tr>
<td>C(10)-O(6)</td>
<td>1.4104(16)</td>
</tr>
<tr>
<td>C(12)-N(2)</td>
<td>1.3210(18)</td>
</tr>
</tbody>
</table>
C(27)-N(3)-C(23)  117.90(12)
O(7)-C(35)-O(8)  120.5(3)
O(7)-C(35)-C(34)  124.5(2)
O(8)-C(35)-C(34)  115.0(2)
C(37)-C(36)-O(8)  109.3(2)
O(9)-C(39)-O(10)  122.1(2)
O(9)-C(39)-C(38)  125.7(2)
O(10)-C(39)-C(38) 112.08(17)
O(10)-C(40)-C(41) 107.43(16)
C(35)-O(8)-C(36)  116.5(2)
C(39)-O(10)-C(40)  117.04(16)
Experimental details for 10•2EtOAc

The selected crystal was covered with Paratone-N oil, placed onto the tip of a glass rod drawn out to a fiber, and frozen in the cold stream (−106 °C) provided by a Rigaku/MSC X-stream 2000 low-temperature system. The X-ray intensity data for this colorless block of C₆H₄N₆O₂0 with approximate dimensions 0.52 x 0.39 x 0.34 mm were measured with phi and omega scans at 167 K on a Bruker SMART APEX CCD-based X-ray diffractometer system equipped with a Mo-target X-ray tube (λ = 0.71073 Å). The detector was placed at a distance of 5.00 cm from the crystal. A total of 1850 frames were collected (a hemisphere of data) with an exposure time of 30 sec/frame. The frames were integrated with the Bruker SAINT software package using a narrow-frame integration algorithm giving a total of 33,503 reflections to a maximum 2θ angle of 57° for which 9113 reflections were independent. The structure was solved (direct methods) and refined using the Bruker SHELXTL version 6.1 Software Package using literature scattering factors (Wilson, A. J. C., Ed. International Tables for Crystallography; Kluwer Academic Publishers: Dordrecht, The Netherlands, 1992; Vol. C.), and the monoclinic space group P2(1)/c, with Z = 4. No absorption correction was applied. The final anisotropic full-matrix least-squares refinement of F² converged at R1 = 5.94%, wR2 = 15.36% and a goodness-of-fit of 1.074 for all data. All non-hydrogen atoms were modeled anisotropically. Hydrogen atoms were placed at calculated distances and use a riding model, which means that the positional and thermal parameters are derived from the atom each hydrogen atom is bound to, while maintaining the calculated distance and optimal angles. The largest peak and hole in the final difference map were 1.013 (near one disordered ethyl acetate solvent in the lattice for which the disorder was not modeled) and −0.435 e-/Å³, respectively. The calculated density is 1.399 g/cm³ and F(000) is 1656 e-.