Synthesis and Properties of New Derivatives of 4,5-Dicyanoimidazole and 4,4',5,5'-Tetracyano-2,2'-biimidazole

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Abstract: The synthesis and properties of new derivatives of 4,5-dicyanoimidazole (**1**, HDcim) and 4,4',5,5'-tetracyano-2,2'-biimidazole (**2**, H_2Tcbiim) are reported. Conditions for selective metalation at the 2-position of N-protected 4,5-dicyanoimidazoles are described. Various protecting groups were used. Oxidative coupling of N-protected 2-lithio-4,5-dicyanoimidazoles with cupric chloride gives new 1,1'-disubstituted derivatives of 4,4',5,5'-tetracyano-2,2'-biimidazole (**13–15**, R_2Tcbiim where R = CH_3, CH_2OCH_3, CH_2Ph). Ullmann coupling of 1-methyl-2-bromo-4,5-dicyanoimidazole (**6**) gives $(CH_3)_2$Tcbiim (**13**). Deprotection of R_2Tcbiim (when R = CH_3 or CH_2OCH_3) gives H_2Tcbiim (**2**). Several new routes to H_2Tcbiim are now available. Reaction of H_2Tcbiim with 1,*n*-dihaloalkanes (*n* = 2, 3, and 4) gives the corresponding 1,1'-alkyl-bridged derivatives **16–18** or $(CH_2)_n$Tcbiim (*n* = 2, 3, and 4). $(CH_2)_2$Tcbiim (**16**) has also been synthesized via an intramolecular Ullmann coupling reaction of **19**. The physical, structural, and electronic properties of these new cyanoimidazoles have been investigated by using UV–visible spectroscopy and cyclic voltammetry. Dicyanoimidazoles and tetracyanobiimidazoles are moderate to weak electron acceptors. $(CH_2)_2$Tcbiim (**16**) forms a 1:1 complex with tetrathiafulvalene (TTF). The donor (D)–acceptor (A) complex, [TTF][$(CH_2)_2$Tcbiim], forms as red needles from acetonitrile solution. X-ray crystallography of [TTF][$(CH_2)_2$Tcbiim] shows extended alternate or "mixed" stacking (...DADADA...). The photoluminescence spectrum of the complex shows an emission band centered at 660 nm with onset of emission at 530 nm.

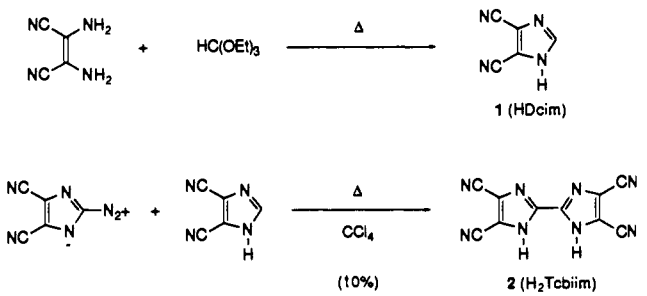
Cyanocarbons and cyanoazacarbons,[1] and compounds that contain the cyano group, have many interesting and useful properties. Cyanocarbons and cyanoazacarbons are interesting synthetic targets and undergo many unusual chemical reactions.[2,3] They behave as electron acceptors and may form charge-transfer complexes and synthetic organic "metals".[2-4] They have been incorporated into organic ferromagnets.[5] Cyano-containing molecules have been incorporated into commercial fibers, carbon fibers, and thermally stable ladder polymers.[6] Cyanocarbons and cyanoazacarbons are precursors to polymer cross-linking agents[7] or metal ion complexing agents.[7-9] Cyano-containing compounds may show nonlinear optical behavior.[10]

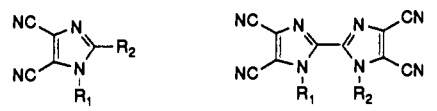
Our research group has been interested in the chemistry of nitrile-containing molecules for many years. In particular, we have been interested in how multiple nitrile substitution affects the chemical, electronic, and physical properties of imidazoles and biimidazoles. We have studied the properties of these compounds by themselves,[8a,11] as ligands in metal complexes,[8] and when incorporated into polymers.[12]

The two cyanoazacarbon backbones we have focused on are 4,5-dicyanoimidazole (**1**, HDcim) and 4,4',5,5'-tetracyano-2,2'-biimidazole (**2**, H_2Tcbiim). The synthesis of HDcim was first reported in 1950 by Woodward[2k] (Scheme I). The chemistry of HDcim and related heterocycles is quite extensive and has been reviewed.[13] Although a great deal of chemistry on 4,5-dicyanoimidazoles has been reported in the literature, there is little reference to tetracyanobiimidazoles. In fact, the chemistry of its derivatives and complexes has only been reported by this group.[8,11] The paucity of reports on H_2Tcbiim is due primarily to the difficulty in synthesizing this material. The original synthesis of H_2Tcbiim, reported in 1982,[8a] involves a coupling reaction between 2-diazo-4,5-dicyanoimidazole[2l,m] and 4,5-dicyanoimidazole (Scheme I). Unfortunately, the synthesis had several serious drawbacks. The yields of the desired product were very low and irreproducible, 2-diazo-4,5-dicyanoimidazole is a shock-sensitive explosive, and isolation of the product was a long and difficult process.

Since much of our previous work has been with metal complexes of dicyanoimidazoles and tetracyanobiimidazoles,[8] we sought new insights into the chemistry and properties of these compounds from an organic materials perspective. Accordingly, the objective of this work was to design, synthesize, and characterize new cyanoazacarbon derivatives based on 4,5-dicyanoimidazole and 4,4',5,5'-tetracyano-2,2'-biimidazole, generically shown below.

Scheme I





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(1) "Cyanocarbons" are defined as polycyano-substituted compounds with all carbon backbones and no hydrogen. This term was used by chemists at E. I. du Pont de Nemours over 30 years ago. "Cyanoazacarbons" or "azacyanocarbons" are similarly defined except the molecular backbone contains both carbon and nitrogen. This term has also been used in the pertinent literature (see ref 3). For some excellent reviews on cyanocarbons and cyanoazacarbons, see: (a) Fatiadi, A. J. *The Chemistry of Triple Bonded Groups*; Patai, S., Rappoport, Z., Eds.; J. Wiley & Sons: New York, 1983. (b) Freeman, F. *Synthesis* **1981**, 925. (c) *The Chemistry of the Cyano Group*; Rappoport, Z., Ed.; J. Wiley & Sons: New York, 1970. (d) Cairns, T. L.; McKusick, B. C. *Angew. Chem.* **1961**, *73*, 520.

(2) Chemists at E. I. du Pont de Nemours have made significant contributions to the synthesis and characterization of new cyanocarbons, cyanoazacarbons, and their derivatives. For some examples: (a) Acker, D. S.; Hertler, W. R. *J. Am. Chem. Soc.* **1962**, *84*, 3370. (b) Melby, L. R.; Harder, R. J.; Hertler, W. R.; Mahler, W.; Benson, R. E.; Mochel, W. E. *J. Am. Chem. Soc.* **1962**, *84*, 3374. (c) Cairns, T. L.; Carboni, R. A.; Coffmann, D. D.; Englehardt, V. A.; Heckert, R. E.; Little, E. L.; McGeer, E. G.; McKusick, B. C.; Middleton, W. J.; Scribner, R. M.; Theobald, C. W.; Winberg, H. E. *J. Am. Chem. Soc.* **1958**, *80*, 2775. (d) Merrifield, R. E.; Phillips, W. D. *J. Am. Chem. Soc.* **1958**, *80*, 2778. (e) Middleton, W. J.; Heckert, R. E.; Little, E. L.; Krespan, C. G. *J. Am. Chem. Soc.* **1958**, *80*, 2783. (f) Middleton, W. J.; Englehardt, V. A. *J. Am. Chem. Soc.* **1958**, *80*, 2788. (g) Fukanaga, T. *J. Am. Chem. Soc.* **1976**, *98*, 610. (h) Webster, O. W. *J. Am. Chem. Soc.* **1964**, *86*, 2898. (i) Webster, O. W. *J. Am. Chem. Soc.* **1966**, *88*, 4055. (j) Trofimenko, S.; Little, E. L.; Mower, H. F. *J. Org. Chem.* **1962**, *27*, 433. (k) Woodward, D. W. U.S. Patent 2534331, 1950. (l) Webster, O. W. U.S. Patent 3882140, 1975. (m) Sheppard, W. A.; Webster, O. W. *J. Am. Chem. Soc.* **1973**, *95*, 2695.

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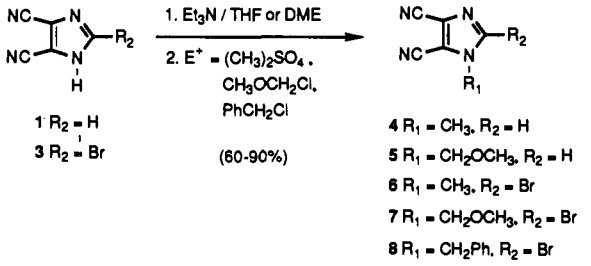
Scheme II



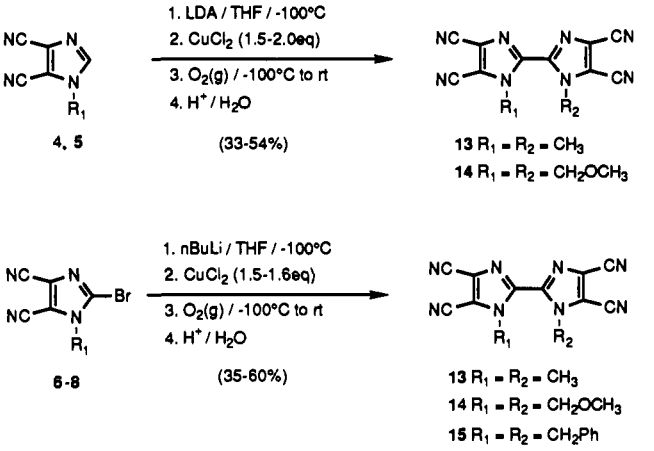
We undertook this investigation for several reasons: (1) The electron-withdrawing cyano groups were expected to lead to delocalized π-molecular orbitals, lower the energy of the HOMO and the LUMO, and increase electron-accepting behavior. (2) With appropriate substitution of R_1 and R_2, new derivatives of **1** and **2** could be planar, and their size and symmetry could match many organic donors (tetrathiafulvalene, for example). These factors were expected to assist charge-transfer complex formation. (3) An understanding of the structure–property relationships in these systems was desired as part of our program to develop new cyanoazacarbon materials. (4) Finally, derivatives of these compounds could be made into polymer cross-linking agents or metal ion complexing agents.

We attempted to tailor the properties of the cyanoazacarbons, **1** and **2**, by selectively changing R_1 and R_2. Versatile synthetic methodologies had to be developed to do this systematically and efficiently. Hence, our first objective was to cultivate new chemistry at the 1- and 2-positions of HDcim and find a new and improved synthesis of H_2Tcbiim.

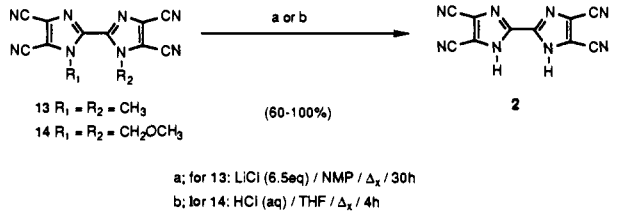
Results and Discussion

Synthesis of 4,5-Dicyanoimidazoles. Alkylation and protection of the pyrrolic nitrogen of 4,5-dicyanoimidazole (**1**) or 2-bromo-4,5-dicyanoimidazole (**3**) can easily be accomplished in THF or DME with triethylamine and 1 equiv of electrophile (Scheme II).[14,15]

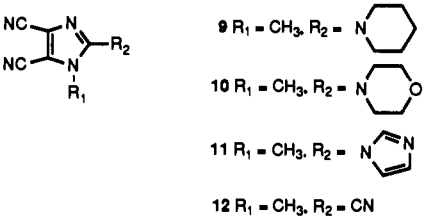
Scheme III



Scheme IV



We have developed several new methods for functionalizing 4,5-dicyanoimidazoles. Substitution using nucleophiles or electrophiles is now possible depending on the functionality desired at the 2-position. For example, nucleophilic aromatic substitution in 1-methyl-2-bromo-4,5-dicyanoimidazole (**6**) with nucleophiles such as piperidine, morpholine, imidazole, and cyanide gives the corresponding 2-substituted imidazoles **9–12** in good yields.[16]



Metalations of imidazoles have been reported in the literature.[17] There are no previous reports in the literature on the metalations of 4,5-dicyanoimidazoles. We have examined various conditions for lithiation and substitution at the 2-position (or C-2) of 4,5-dicyanoimidazoles.[18] Lithiation of C-2 of *N*-methyl-4,5-di-

(3) For other examples of cyanoazacarbons and their derivatives: (a) Hall, H. K.; Ramezanian, M.; Saeva, F. D. *Tetrahedron Lett.* **1988**, *29*, 1235. (b) Kim, J. B.; Padias, A. B.; Hall, H. K. *Macromolecules* **1990**, *23*, 21. (c) Ott, E. *Chem. Ber.* **1919**, *52*, 656.

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(6) (a) Peebles, L. H. *Encyclopedia of Polymer Science: Supplement*; Mark, H. F., Bikales, N. M., Eds.; J. Wiley & Sons: New York, 1976; Vol. 1. (b) Bloor, D. *Comprehensive Polymer Science*; Mann, G., Bevington, J. C., Eds.; Permagon Press: New York, 1989; Vol. 2. (c) Bansal, R. C.; Donnett, J. B. *Comprehensive Polymer Science*; Mann, G., Bevington, J. C., Eds.; Permagon Press: New York, 1989; Vol. 6.

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(8) (a) Rasmussen, P. G.; Hough, R. L.; Anderson, J. E.; Bailey, O. H.; Bayón, J. C. *J. Am. Chem. Soc.* **1982**, *104*, 6155. (b) Rasmussen, P. G.; Kolowich, J. B.; Bayón, J. C. *J. Am. Chem. Soc.* **1988**, *110*, 7042. (c) Rasmussen, P. G.; Anderson, J. E.; Bayón, J. C. *Inorg. Chim. Acta* **1984**, *87*, 159. (d) Rasmussen, P. G.; Bayón, J. C. *Inorg. Chim. Acta* **1984**, *81*, 115. (e) Rasmussen, P. G.; Bailey, O. H.; Bayón, J. C. *Inorg. Chem.* **1984**, *23*, 338. (f) Rasmussen, P. G.; Bailey, O. H.; Bayón, J. C. *Inorg. Chem.* **1984**, *23*, 343. (g) Rasmussen, P. G.; Bailey, O. H.; Bayón, J. C. *Inorg. Chim. Acta* **1984**, *86*, 107. (h) Rasmussen, P. G.; Bailey, O. H.; Kolowich, J. B.; Bayón, J. C. *Mol. Cryst. Liq. Cryst.* **1985**, *126*, 87.

(9) Enemark, J. H.; Holm, R. H. *Inorg. Chem.* **1964**, *3*, 1516.

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(11) (a) Allan, D. S.; Bergstrom, D. F.; Rasmussen, P. G. *Synth. Met.* **1988**, *25*, 139. (b) Rasmussen, P. G. *Tetracyanobiimidazole, a Polyploid of Distinction*; Hanson, A. E., Avery, J., Dahl, J. P., Eds.; E. Reidel: Holland, 1987.

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(14) The synthesis of **4** has been reported previously. (a) Yamada, Y.; Kumashiro, I.; Takenishi, T. *Bull. Chem. Soc. Jpn.* **1968**, *41*, 1237. (b) Reference 11a.

(15) The bromination of **1** to give **3** occurs in >80% yield. The syntheses of **3** and **6** have been reported previously. (a) Apen, P. G.; Rasmussen, P. G. *Heterocycles* **1989**, *29*, 1325. (b) Reference 11a.

(16) The synthesis of **9–12** via nucleophilic aromatic substitution has been described in detail and reported. (a) Apen, P. G.; Rasmussen, P. G. *Heterocycles* **1989**, *29*, 1325. (b) Apen, P. G. Ph.D. Thesis, The University of Michgian, Ann Arbor, MI, 1990.

(17) (a) Iddon, B. *Heterocycles* **1985**, *23*, 417 and references cited therein. See also: (b) Iddon, B.; Khan, N. *Tetrahedron Lett.* **1986**, *27*, 1635. (c) Iddon, B.; Khan, N. *J. Chem. Soc., Perkin Trans. 1* **1987**, 1445. (d) Iddon, B.; Khan, N. *J. Chem. Soc., Perkin Trans. 1* **1987**, 1453. (e) Brown, R. S.; Ulan, J. G. *J. Am. Chem. Soc.* **1983**, *105*, 2382. (f) van de Eijk, J. M.; Nolte, R. J. M.; Zwikker, J. W. *J. Org. Chem.* **1980**, *45*, 547.

cyanoimidazole followed by reaction with electrophiles (e.g., CO_2(s), $ClCO_2Et$, Me_2SO_4) gives the corresponding 1-methyl-2-substituted-4,5-dicyanoimidazoles in low yields.[19] Although these reactions give only low yields of the desired product, formation of the 2-anion had been clearly demonstrated. This methodology has lead to the development of new synthetic routes to H_2Tcbiim.

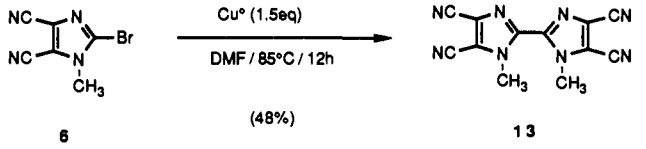
Synthesis of 4,4′,5,5′-Tetracyano-2,2′-biimidazole and Derivatives. The oxidative coupling of an aryllithium with copper(II) chloride has been documented for numerous systems.[20] This coupling reaction, which provides a direct route to symmetrical biaryls, has also been reported for aryllithiums containing a cyano group.[21] Once selective formation of the 2-anion of 1-protected 4,5-dicyanoimidazoles had been demonstrated,[18,19] coupling them was a straightforward task.

Various N-protecting and N-blocking groups have been used for imidazoles.[17,22] Alkylation of the 1-position was a simple task and is shown in Scheme II. Oxidative coupling of the 2-lithio derivatives (derived from **4–8**) with cupric chloride gives the corresponding tetracyanobiimidazoles **13–15** (Scheme III). Oxygen gas is bubbled through the reaction mixture during warming to assist oxidation and coupling of the arylcopper intermediate. Oxygenation of the reaction mixture gives 50–100% higher yields of coupled product. Several new tetracyanobiimidazole derivatives are now accessible.

When $R_1 = CH_3$ or CH_2OCH_3 (**4–7**), formation of the aryllithium by deprotonation or metal/halogen exchange prior to coupling gives good yields of the coupled product (Scheme III). When $R_1 = CH_2Ph$, formation of the aryllithium is only possible via metal/halogen exchange. If LDA is used with a benzyl protecting group, deprotonation of the benzylic protons interferes with lithiation at the 2-position of the imidazole ring.[23]

Attempts to prepare and couple the 1,2-dianion of 2-bromo-4,5-dicyanoimidazole (**3**) were unsuccessful. Treatment of **3** with 2.0 equiv of nBuLi in THF at −100 °C followed by addition of cupric chloride and aqueous acid workup gave only uncharacterizable products. The desired coupled product **2** was not recovered.

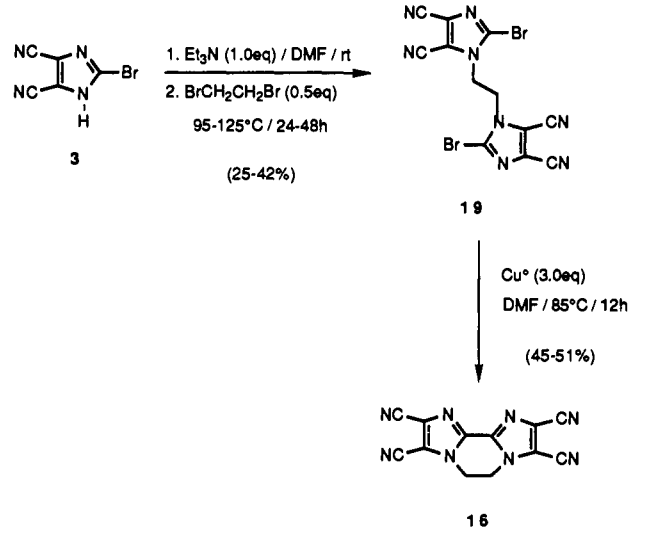
Ullmann coupling reactions of aryl halides have been reviewed.[24] It is known that electron-withdrawing groups on the aromatic ring increase the reactivity of aryl halides. 1-Methyl-2-bromo-4,5-dicyanoimidazole (**6**) undergoes copper-metal-promoted Ullmann coupling at 85 °C in DMF. These gentle conditions are exceptional since most Ullmann coupling reactions require temperatures in excess of 150 °C. The use of the methoxymethyl or benzyl protecting groups (**7**, **8**) did not allow coupling. Instead, protecting-group cleavage occurs and no coupled products were isolated.



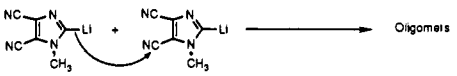
The methoxymethyl (MOM) group has been studied extensively as an imidazole protecting group.[17,22] Removal of the MOM groups from 1,1′-bis(methoxymethyl)-4,4′,5,5′-tetracyano-2,2′-biimidazole (**14**) was easily accomplished by heating **14** with dilute aqueous HCl in THF. H_2Tcbiim (**2**) was recovered in excellent yield (Scheme IV).[25]

Demethylation and methyl-group exchange in *N*-methyl-4,5-dicyanoimidazoles have been observed in several reaction systems.[16] The dealkylation of alkyl aryl ethers using LiCl in refluxing DMF has been reported.[26] *N*-Methyl-4,5-dicyanoimidazoles show

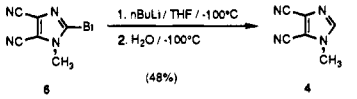
Scheme V



(18) Deprotonation at the 2-position of 1-methyl-4,5-dicyanoimidazole (**4**) using nonnucleophilic bases such as LDA at −80 °C gives the anion at C-2. Metal/halogen exchange with 1-methyl-2-bromo-4,5-dicyanoimidazole (**6**) using nBuLi at −80 °C also leads to metalation at C-2. However, in both cases, once the 2-anion is formed, it reacts with the cyano groups of other lithiated dicyanoimidazoles, producing unwanted side products. Metal/



halogen exchange reactions of bromobenzonitriles at −100 °C have been reported (see Parham, W. E.; Jones, L. D. *J. Org. Chem.* **1976**, *41*, 1187). These lower temperatures reduce the reactivity of alkyl- and aryllithium reagents toward cyano groups and prevent unwanted side reactions. In our case, metal/halogen exchange with **6** using nBuLi at −100 °C gives metalation cleanly at C-2. After quenching with H_2O, workup, and purification, **4** can be recovered. It should be noted that 2-bromo-4,5-dicyanoimidazole (**3**) has



been treated with 2.0 equiv of nBuLi in THF at −100 °C in an attempt to prepare the 1,2-dianion. After addition of an electrophile and workup, a complex mixture of products was recovered.

(19) The 2-lithio derivative is formed at −100 °C in THF by metal/halogen exchange with **6** using 1 equiv of nBuLi, or by deprotonation of **4** with 1 equiv of LDA. See Apen, P. G. Ph.D. Thesis, The University of Michigan, Ann Arbor, MI, 1990.

(20) (a) Rutsch, W.; Escher, A.; Neuenschwander, M. *Chimia* **1983**, *37*, 160. (b) *Comprehensive Organometallic Chemistry*; Wilkinson, G., Stone, F. G. A., Abel, E. W., Eds.; Permagon Press: New York, 1982; Vol. 2. (c) Negishi, E. I. *Organometallics in Organic Synthesis*; J. Wiley & Sons: New York, 1980; Vols. 1 and 2. (d) Posner, G. *An Introduction to Synthesis Using Organocopper Reagents*; J. Wiley & Sons: New York, 1980. (e) Muke, B.; Kauffmann, T. *Chem. Ber.* **1980**, *113*, 2739. (f) Kauffmann, T. *Angew. Chem., Int. Ed. Engl.* **1974**, *13*, 291. (g) Parks, J. E.; Wagner, B. E.; Holm, R. H. *J. Organomet. Chem.* **1973**, *56*, 53.

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(22) (a) Brown, R. S.; Manoharan, T. S. *J. Org. Chem.* **1989**, *54*, 1439. (b) Zimmerman, S. C.; Cramer, K. D.; Galan, A. A. *J. Org. Chem.* **1989**, *54*, 1256. (c) Brown, R. S.; Manoharan, T. S. *J. Org. Chem.* **1988**, *53*, 1107. (d) Whitten, J. P.; Matthews, D. P.; McCarthy, J. R. *J. Org. Chem.* **1986**, *51*, 1891. (e) Chadwick, D. J.; Ngochindo, R. I. *J. Chem. Soc., Perkins Trans. 1* **1984**, 481. (f) Curtis, N. J.; Brown, R. S. *J. Org. Chem.* **1980**, *45*, 4038. (g) Tang, C. C.; Davalian, D.; Huang, P.; Breslow, R. *J. Am. Chem. Soc.* **1978**, *100*, 3918. (h) Kirk, K. L. *J. Org. Chem.* **1978**, *43*, 4381.

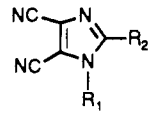
(23) This has been observed with other *N*-benzylimidazoles. See Sundberg, R. J.; Russell, A. F. *J. Org. Chem.* **1973**, *38*, 3324.

(24) (a) Sansbury, M. *Tetrahedron* **1980**, *36*, 3327. (b) Fanta, P. *Synthesis* **1974**, 9. (c) Fanta, P. *Chem. Rev.* **1964**, *64*, 613. (d) Reference 20b,d.

(25) A mixture of deprotected products (1-(methoxymethyl)-4,4′,5,5′-tetracyano-2,2′-biimidazole and H_2Tcbiim) was recovered from the synthesis of **14** (see Experimental Section). Apparently, aqueous acid workup, which is necessary to remove insoluble copper salts, leads to partial hydrolysis and removal of the MOM group. This may be why the *N*-(methoxymethyl)-4,5-dicyanoimidazoles (**5** and **7**) give the lowest yields of coupled product. When the mixture of deprotected products was heated in dilute aqueous HCl in THF, pure **2** was recovered.

(26) (a) Bhatt, M. V.; Kulkarni, S. U. *Synthesis* **1983**, 249. (b) Bernard, A. M.; Ghiani, M. R.; Piras, P. P.; Rivolini, A. *Synthesis* **1989**, 287. (c) Buchanan, D. H.; Takemura, N.; Sy, N. J. O. *J. Org. Chem.* **1986**, *51*, 4291.

Table I. UV-Visible Absorbance Maxima (λ_{max}) of 4,5-Dicyanoimidazoles



compd	R_1	R_2	λ_{max}[a]
4	CH_3	H	248
5	CH_3OCH_2	H	246
6	CH_3	Br	257
7	CH_3OCH_2	Br	257
8	CH_2Ph	Br	256
9	CH_3	1-piperidino	285, 223
10	CH_3	1-morpholino	292, 221
11	CH_3	1-imidazolyl	300 (sh), 251
12	CH_3	CN	249, 205

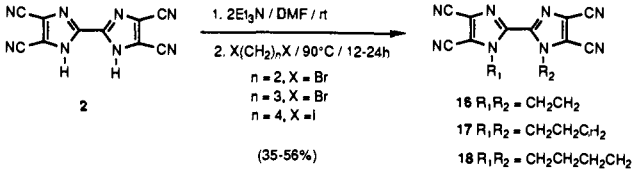
[a] [c] = 10^{-5}–10^{-4} M in acetonitrile; ϵ (molar absorptivity) = 10^3–10^4; sh = shoulder.

similar reactivity. Demethylation of 1,1′-dimethyl-4,4′,5,5′-tetracyano-2,2′-biimidazole (**13**) with LiCl in refluxing NMP gives good yields of **2** after aqueous acid workup and purification (Scheme IV). The methyl group, not normally considered a protecting group for imidazoles, is an excellent protecting group for 4,5-dicyanoimidazoles. In this case, LiCl-promoted demethylation of **13** takes advantage of the leaving group ability and stability of cyanoimidazole anions.

The overall yield of H_2Tcbiim (**2**) via these new routes starting from 4,5-dicyanoimidazole is 23–30% compared to ~10% in the original synthesis.[8a] The synthesis of **2** via these new routes can be done in three or four steps, and the hazards of the original synthesis are removed.

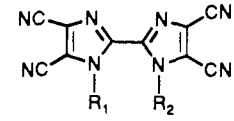
Synthesis of Bridged Derivatives of Tetracyanobiimidazole. The first 1,1′-bridged derivatives of 2,2′-biimidazole were prepared by Melloni and co-workers[27] in the early 1970s. More recently, Thummel and co-workers[28] have synthesized and studied the properties of a series of bridged 2,2′-biimidazoles. There are also several examples of nonbridged 2,2′-biimidazoles substituted with electron-withdrawing groups in the 4(4′)- and the 5(5′)-positions.[29]

It is possible to synthesize bridged derivatives of H_2Tcbiim (**2**) by the addition of 2 equiv of triethylamine and 1 equiv of a 1,*n*-dihaloalkane (*n* = 2, 3, and 4) to **2** in DMF. After heating at 95 °C for 12–24 h, the bridged derivatives **16–18** can be recovered in 35–56% yield.



There have been many reports of intermolecular Ullmann coupling reactions to form the corresponding biaryl.[24] There are, however, relatively few examples of intramolecular Ullmann-type coupling reactions.[30] An alternative synthesis of **16** is based on an intramolecular Ullmann coupling reaction (Scheme V). Alkylation of 2-bromo-4,5-dicyanoimidazole (**3**) with 0.5 equiv of dibromoethane gives moderate yields of the tethered bis(2-bromo-4,5-dicyanoimidazole) (**19**). Intramolecular Ullmann coupling of **19** under mild conditions gives good yields of **16**. This route to **16** avoids the protection and deprotection steps, and gram quantities can easily be prepared.

Table II. UV-Visible Absorbance Maxima (λ_{max}) of 4,4′,5,5′-Tetracyano-2,2′-biimidazoles



compd	R_1	R_2	λ_{max}[a]
2	H	H	300 (sh), 272, 210
13	CH_3	CH_3	305 (sh), 280, 213
14	CH_3OCH_2	CH_3OCH_2	305 (sh), 283, 207
15	$PhCH_2$	$PhCH_2$	305 (sh), 283, 207
16	$-CH_2CH_2-$		313, 299, 289, 265, 221
17	$-CH_2CH_2CH_2-$		310, 296, 285, 238, 215
18	$-CH_2CH_2CH_2CH_2-$		257, 238, 211

[a] [c] = 10^{-5}–10^{-4} M in acetonitrile; ϵ (molar absorptivity) = 10^3–10^4; sh = shoulder.

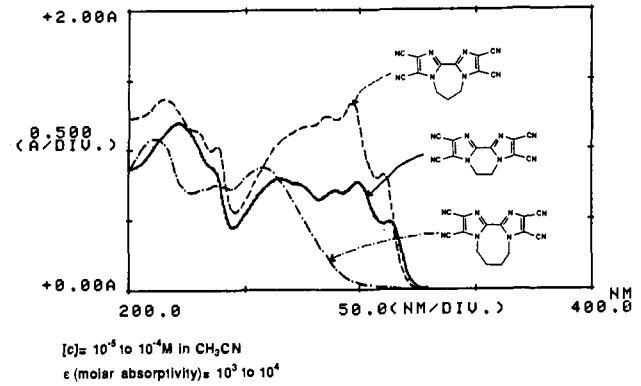


Figure 1. UV-visible absorbance spectra of 1,1′-alkyl-bridged tetracyanobiimidazoles (**16–18**).

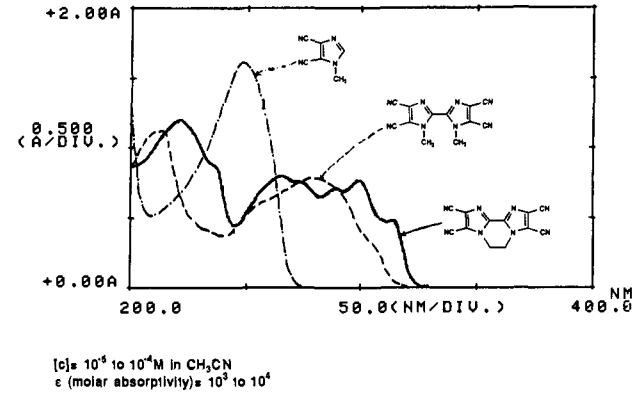


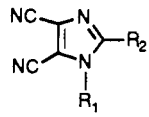
Figure 2. UV-visible absorbance spectra of selected cyanoimidazoles (**4**, **13**, and **16**).

UV-Visible Spectroscopy. UV-visible absorbance maxima for 1-alkyl-2-substituted-4,5-dicyanoimidazoles are listed in Table I. Substitution at the 2-position increases the wavelength of absorption of the aromatic chromophore, regardless of whether the substituent is electron-donating or electron-withdrawing. This observation is typical for aromatic systems.[31]

Electron-withdrawing groups at the 2-position increase λ_{max} of 1-alkylated 4,5-dicyanoimidazoles by about 8–10 nm. Electron-donating groups at the 2-position (**9**, **10**) lead to an increase in λ_{max} of 40–45 nm. This suggests that there is significant delocalization of the unpaired electrons of the 2-dialkylamine nitrogen into the cyanoimidazole ring.

(27) Melloni, P.; Fusar-Bassini, D.; Dradi, E.; Confalonieri, C. *J. Heterocycl. Chem.* **1974**, *11*, 731.
(28) Thummel, R. P.; Goulle, V.; Chen, B. *J. Org. Chem.* **1989**, *54*, 3057.
(29) (a) Matthews, D. P.; Whitten, J. P.; McCarthy, J. R. *J. Heterocycl. Chem.* **1987**, *24*, 689. (b) Matthews, D. P.; Whitten, J. P.; McCarthy, J. R. *J. Org. Chem.* **1986**, *51*, 3228. (c) Melloni, P.; Dradi, E.; Logemann, W.; de Carnieri, I.; Trane, F. *J. Med. Chem.* **1972**, *15*, 926. (d) Dedik, S. G.; Orlov, V. D.; Edzina, A.; Khodorkovskii, V. Yu.; Neiland, O. Ya. *Khim. Geterotsikl. Soedin.* **1989**, *25*, 1421.
(30) For examples: (a) Semmelhack, M. F.; Ryono, L. S. *J. Am. Chem. Soc.* **1975**, *97*, 3873. (b) Semmelhack, M. F.; Helquist, P.; Jones, L. D.; Keller, L.; Mendelson, L.; Ryono, L. S.; Smith, J. G.; Stauffer, R. D. *J. Am. Chem. Soc.* **1981**, *103*, 6460. (c) Reference 24a.
(31) Duben, A. J. *J. Chem. Ed.* **1985**, *62*, 373.

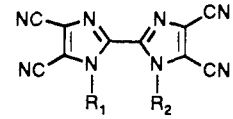
Table III. Cyclic Voltammetry Data for 1-Methyl-4,5-Dicyanoimidazoles



compd	R_1	R_2	E_{red} (V)[a]	reversibility
4[b]	CH_3	H	−2.23	quasi
6[b]	CH_3	Br	−2.18	irr
9	CH_3	1-piperidino	−2.35	quasi
10	CH_3	1-morpholino	−2.36	slight
11	CH_3	1-imidazolyl	−2.23	irr
12[b]	CH_3	CN	−1.73, −2.05	irr

[a] Measured in CH_3CN vs Ag/Ag^+ with 0.10 M Et_4NBF_4 as electrolyte. Ferrocene (Fc) was used as standard. The Fc/Fc^+ redox couple was +0.09 V vs Ag/Ag^+. Scan rate = 1 V s^{-1}. [b] The E_{red} (V) values of these compounds were taken from ref 11a. For consistency and accuracy, the values from ref 11a have been redetermined.

Table IV. Cyclic Voltammetry Data for 4,4′,5,5′-Tetracyano-2,2′-biimidazoles



compd	R_1	R_2	E_{red} (V)[a]	reversibility
13[b]	CH_3	CH_3	−1.82, −2.10	irr
14	CH_2OCH_3	CH_2OCH_3	−1.83, −2.20	irr
15	CH_2Ph	CH_2Ph	−1.91, −2.22	irr
16	$-CH_2CH_2-$		−1.84, −2.19	slight
17	$-CH_2CH_2CH_2-$		−1.91, −2.19	slight
18	$-CH_2CH_2CH_2CH_2-$		−2.04, −2.20	irr

[a] Measured in CH_3CN vs Ag/Ag^+ with 0.10 M Et_4NBF_4 as electrolyte. Ferrocene (Fc) was used as standard. The Fc/Fc^+ redox couple was +0.09 V vs Ag/Ag^+. Scan rate = 1 V s^{-1}. [b] The E_{red} (V) value of **13** was taken from ref 11a. For consistency and accuracy, the value from ref 11a has been redetermined.

The UV-visible absorbance maxima for tetracyanobiimidazoles are listed in Table II. The spectra of **2** and **13–15** show a characteristic shoulder at 300 nm and a broad maximum centered at approximately 280 nm. Generally, the absorbance maxima of tetracyanobiimidazoles are of longer wavelength than dicyanoimidazoles. This indicates that there must be some interaction between the two imidazole rings leading to a chromophore of increased length and a λ_{max} between 280 and 320 nm. UV-visible spectroscopy, an important tool in previous conformational studies on 2,2′-biimidazoles,[28,32] is useful for studying the conformational behavior of 4,4′,5,5′-tetracyano-2,2′-biimidazoles.

Representative UV-visible spectra are shown in Figures 1 and 2. The dimethylene and trimethylene-bridged species **16** and **17** show several absorbance maxima, all of longer wavelength than their nonbridged counterparts **2** and **13–15** and the tetramethylene derivative **18**. The two- and three-carbon bridges of **16** and **17** restrict rotation about the 2,2′ carbon–carbon single bond. As a result, the two imidazole rings of **16** and **17** are constrained and held in "planarity", and cooperative electronic interaction between the π-orbitals of the two aromatic rings is enhanced. In the tetramethylene derivative **18**, however, the four-carbon bridge forms an eight-membered ring and forces the imidazole rings to lie out of planarity. Cooperative effects are severely diminished and as can be seen in Figures 1 and 2, the absorbance spectrum of **18** more closely resembles the absorbance spectra of the 4,5-dicyanoimidazoles **4–12**. The nonbridged derivatives **2** and **13–15** have broad absorbance maxima ($\lambda_{max} \approx 280$ nm) intermediate to **16**, **17** ($\lambda_{max} \geq 310$ nm), and **18** ($\lambda_{max} = 257$ nm), suggesting that there is some interaction between the two imidazole rings even though rotation about the 2,2′-bond is not restricted due to 1,1′-alkyl bridges.

Cyclic Voltammetry. In the late 1950s and early 1960s, Du Pont chemists reported the synthesis and characterization of tetracyanoethylene[2c] (TCNE) and 7,7,8,8-tetracyanoquinodimethane[2a] (TCNQ), archetypal organic electron acceptors. Since then there has been much effort in the design, synthesis, and characterization of new polycyano-substituted electron acceptors based on TCNE or TCNQ.[33] Chemists have synthesized and studied few organic electron acceptors[4b] that do not possess the dicyanoethylene moiety of TCNE or the quinoid-like structure of TCNQ.

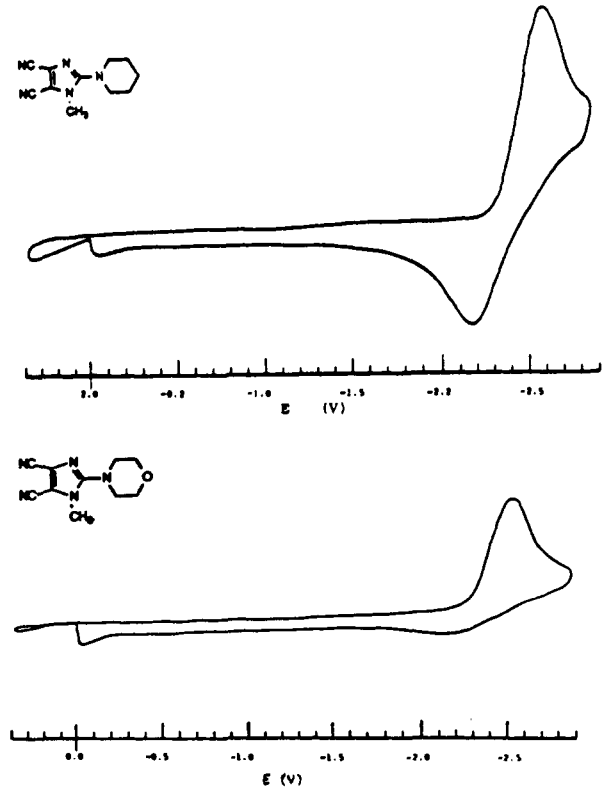


Figure 3. Cyclic voltammograms of 1-methyl-2-piperidino-4,5-dicyanoimidazole (**9**) and 1-methyl-2-morpholino-4,5-dicyanoimidazole (**10**).

Our group[11a] has investigated dicyanoimidazoles and tetracyanobiimidazoles as electron acceptors. These cyanoazacarbon derivatives have shown moderate to weak electron-accepting behavior.[34] The results of cyclic voltammetric measurements are summarized in Tables III and IV.[35]

(32) (a) Barone, V.; Lelj, F.; Minichino, C.; Russo, N.; Toscano, M. *J. Chem. Soc. Perkins Trans. 1* **1988**, 1975. (b) Deady, L. W. *Aust. J. Chem.* **1981**, *34*, 2569.

(33) For some examples: (a) Wudl, F.; Kaplan, M. L.; Teo, B. K.; Marshall, J. *J. Org. Chem.* **1977**, *42*, 1666. (b) Kaplan, M. L.; Haddon, R. C.; Bramwell, F. B.; Wudl, F.; Marshall, J. H.; Cowan, D. O.; Gronowitz, S. *J. Phys. Chem.* **1980**, *84*, 427. (c) Aumüller, A.; Hünig, S. *Angew. Chem., Int. Ed. Engl.* **1984**, *23*, 47. (d) Allemond, P. M.; Delhaes, P.; Soos, Z. G.; Nowak, M.; Hinkelman, K.; Wudl, F. *Synth. Met.* **1988**, *27*, B243. (e) Becker, J. Y.; Bernstein, J.; Bittner, S.; Levi, N.; Shaik, S. S.; Zer-Zion, N. *J. Org. Chem.* **1988**, *53*, 1689. (f) Martin, N.; Behnisch, R.; Hanack, M. *J. Org. Chem.* **1989**, *54*, 2563.

(34) With reduction potentials in the range of −1.7 to −2.4 V, cyanoimidazoles are much weaker electron acceptors than TCNE or TCNQ, but stronger electron acceptors than cyano-containing aromatics like phthalonitrile, isophthalonitrile, or benzonitrile. Our group has quantified the values for a series of cyano-containing electron acceptors and has found a correlation between the reduction potential of the acceptor and the LUMO energy of the acceptor. See ref 11a.

(35) The reduction potentials in Tables III and IV are reported as follows: Samples that show strong anodic currents are called quasi-reversible. Those that show very little reoxidation are termed slightly reversible. When absolutely no reoxidation occurs, those compounds are considered to have irreversible cyclic voltammograms. When there are two cathodic waves, two values for E_{red} (V) are reported. When the waves show reversible behavior (or quasi-reversibility), the value reported for E_{red} (V) is one-half the sum of the potentials at the peaks of the cathodic and anodic waves. If the waves show irreversible behavior (or only slight reversibility), the value reported is the potential of the cathodic peak at half height.

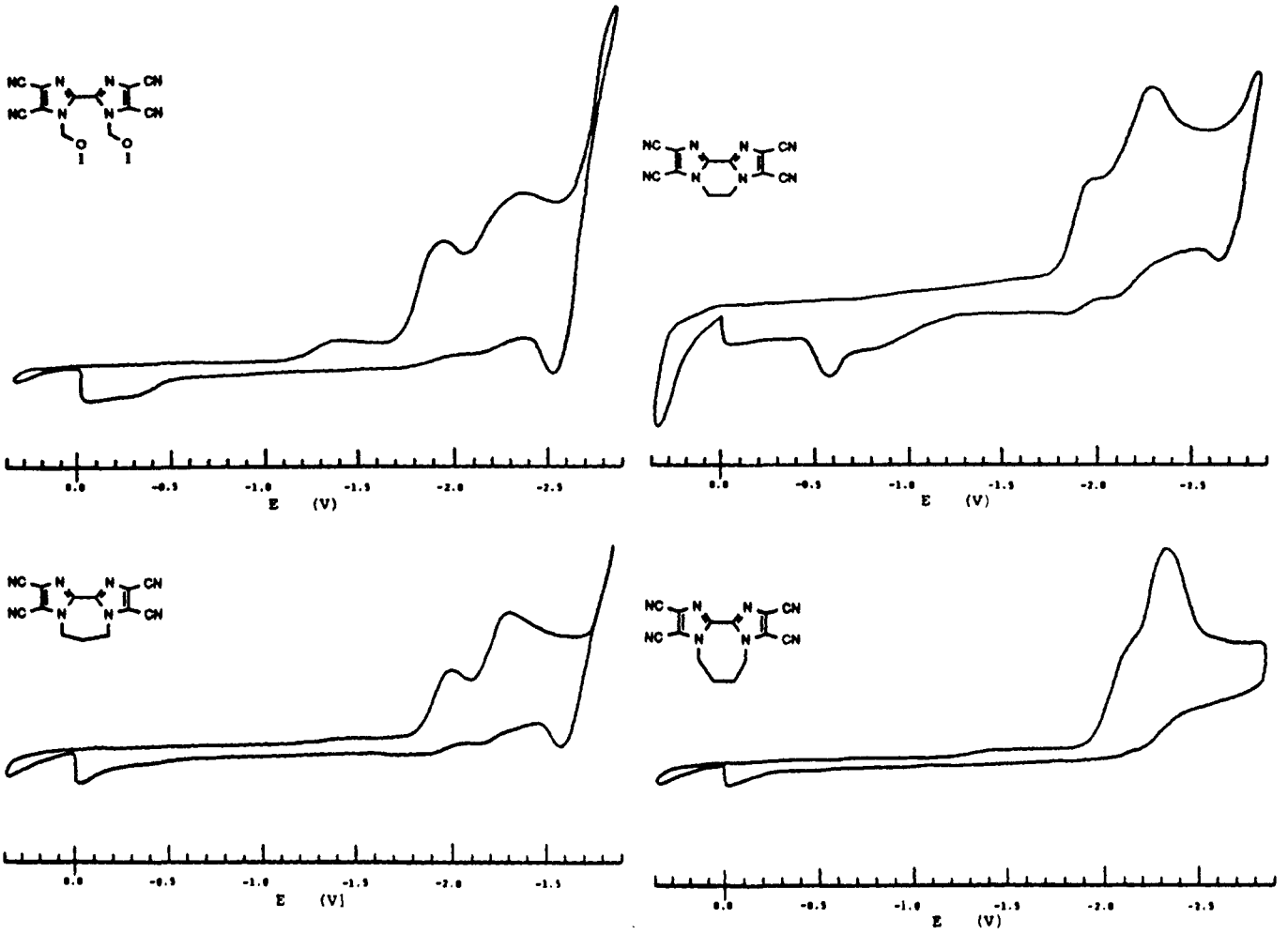


Figure 4. Cyclic voltammograms of selected tetracyanobiimidazoles (**14** and **16–18**).

The reduction potentials of 4,5-dicyanoimidazoles range from −1.7 to −2.4 V (Table III). The magnitude of the reduction potential depends on the nature of substitution at the 2-position of the 4,5-dicyanoimidazole. Not surprisingly, electron-donating groups increase the reduction potential while electron-withdrawing groups make reduction easier and lower the potential. In contrast to the 2-substituted 4,5-dicyanoimidazoles (Table III), the tetracyanobiimidazoles (Table IV) show little variation in the values of E_{red} (V).

Selected voltammograms are shown in Figures 3 and 4. Compounds **4** (not shown) and **9** (Figure 3) are the only compounds in this study that show clearly reversible waves. The 2-piperidino derivative **9** exhibits quasi-reversible behavior while an analogue of **9**, the 2-morpholino derivative **10**, shows little or no reversibility (Figure 3). There is no clear reason for this dissimilarity. All other compounds listed in Table III show irreversible electrochemical behavior. The radical anions of **6** and **10–12** react or decompose before reoxidation can occur. Increasing the scan rate does not change the waveform.

Tetracyanobiimidazole derivatives **13–18** show two reduction waves, which probably correspond to two one-electron reductions. This is consistent with what is seen for dicyanoimidazoles, which typically show only one reduction wave. The lone exception is 1-methyl-2,4,5-tricyanoimidazole (**12**), which shows two poorly resolved cathodic waves at −1.73 and −2.05 V.[11a]

None of the tetracyanobiimidazoles (Table IV, Figure 4) show quasi-reversible behavior although the dimethylene and trimethylene derivatives **16** and **17** show two extremely small anodic peaks. Increasing the scan rate does not alter the waveforms. Stopping the scan at −2.0 V to isolate the first reduction did not increase the magnitude of the subsequent reoxidation peak. The tetramethylene-bridged derivative **18** shows what appears to be two overlapping reduction waves. As the two aromatic rings are forced away from planarity (due to the four-carbon bridge), there is less π-orbital interaction between the rings, and electron deficiency and delocalization at the 2(2′)-positions are reduced. As a result, the first E_{red} (V) of **18** becomes slightly more negative, and the reduction waves of each ring begin to overlap one another.

The Donor–Acceptor Complex of TTF and $(CH_2)_2$Tcbiim. As determined by UV-visible spectroscopy, 4,5-dicyanoimidazoles do not form charge-transfer complexes in solution with TTF or *N*-vinylcarbazole.[36] Formation of donor–acceptor complexes in the solid state has shown promise. Evaporation of an equimolar solution of TTF and $(CH_3)_2$Tcbiim (**13**) leaves orange crystals of the 1:1 adduct [TTF][$(CH_3)_2$Tcbiim].[37] The X-ray crystal structure of [TTF][$(CH_3)_2$Tcbiim] could not be solved.[38]

It was hoped that ethane-bridged Tcbiim (**16**) would form charge-transfer complexes more easily than **13** or other cyanoimidazoles. UV-visible spectroscopy shows that **16** has the longest wavelength absorption of all the tetracyanobiimidazoles. In addition, compound **16**, like **13**, has symmetry that closely matches many organic donors.

However, solution spectra of TTF and **16** in CH_3CN showed no evidence for charge-transfer complex formation. Concentrations of the donor and acceptor were varied from 2×10^{-5} M to 0.10 M. Strong solvent–donor and solvent–acceptor interactions overwhelm donor–acceptor complex formation. It was not possible to use less polar solvents such as CH_2Cl_2 or THF due to the low solubilities of TTF and **16**.

(36) (a) Reference 12a. (b) Thurber, E. L. The University of Michigan, unpublished results.

(37) The stoichiometry of the complex was confirmed by elemental analysis. See Bergstrom, D. F. Ph.D. Thesis, The University of Michigan, Ann Arbor, MI, 1988.

(38) Rasmussen, P. G.; Bergstrom, D. F. The University of Michigan, unpublished results.

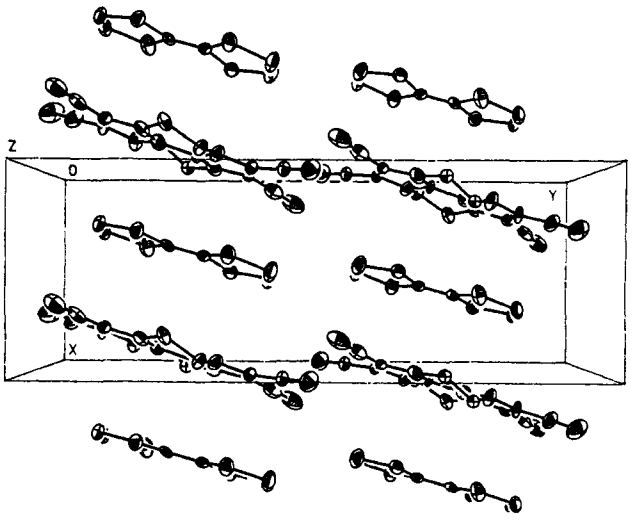
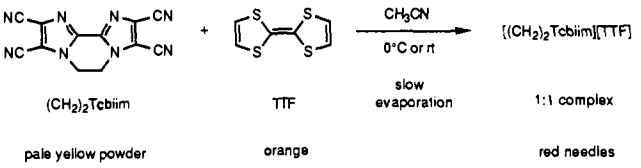


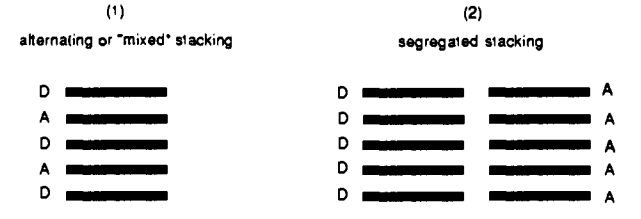
Figure 5. One-dimensional alternating or "mixed" stacking of the donor–acceptor complex of TTF and **16**.

A donor–acceptor complex of TTF and **16** could be formed in the solid state. Slow evaporation of an equimolar acetonitrile solution of TTF and **16** gave the 1:1 adduct, [TTF]-[$(CH_2)_2$Tcbiim], as red needles. The color of [TTF]-[$(CH_2)_2$Tcbiim] is notable. It is red, almost amber, while the color of TTF is orange and the color of ethane-bridged Tcbiim (**16**) is very pale yellow.



Crystals suitable for X-ray diffraction were obtained. The 1:1 complex crystallizes in a monoclinic crystal system in the $P2_1/c$ space group. The crystal packing diagram (Figure 5) shows the infinite one-dimensional alternate or "mixed" stacking of the donor (TTF) and the acceptor (**16**). The distance between planes of donor (TTF) and acceptor (**16**) within a stack is 3.5 Å, which is similar to the interplanar spacings in other "mixed" stack donor–acceptor complexes. The stacking tilt angle is 18.8°. The ethane bridge of **16** is disordered between two sites at refined occupancies of 73% and 27%, respectively.[39]

The solid-state structure of donor–acceptor complexes or organic charge-transfer salts usually fall into one of two broad categories:[40] (1) those with alternating sequences of donors (D) and acceptors (A) in the same stack, and (2) those with segregated stacks of donors (D) and acceptors (A). [TTF][$(CH_2)_2$Tcbiim] falls into the first category.



There are numerous examples in the literature of each stacking mode. In general, complexes of weak donors and strong acceptors

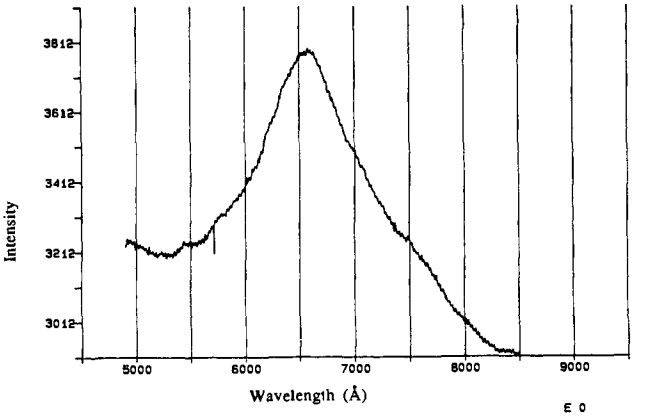


Figure 6. Luminescence spectrum of the donor–acceptor complex of TTF and **16**.

or strong donors and weak acceptors form "mixed" stacks.[41] Examples include hexamethylbenzene–chloranil,[41a] naphthalene–tetracyanobenzene,[41e] and pyrene–tetracyanoethylene.[41h] Complexes of strong donors with strong acceptors show either type of stacking.[42] There are also instances where strong donors and strong acceptors show polymorphism.[43] That is, some donor–acceptor pairs crystallize in both structure types depending on the stoichiometry of the complex salt and the conditions of crystallization. Tetramethyltetraselenafulvalene (TMTSF)-TCNQ[43a] and hexamethylenetetraselenafulvalene (HMTSF)-TCNQ[43b] exhibit polymorphic behavior.

The "mixed" stacking motif of [TTF][$(CH_2)_2$Tcbiim] is consistent with complexes composed of strong electron donors, such as TTF, and weak electron acceptors, such as **16**. The new structure reported here, [TTF][$(CH_2)_2$Tcbiim], complements the few examples where TTF forms a "mixed" stack charge-transfer complex with an organic electron acceptor. These examples, reported by Torrance and co-workers,[42d] were of the donor–acceptor complexes of TTF with chloranil and fluoranil.

Luminescence Spectroscopy. A change in the color of the donor (D)–acceptor (A) complex compared to the individual donor and acceptor is often evidence for charge transfer. Strong charge transfer along with high polarizability leads to segregated stacking in a D–A complex. Segregated stacks are usually black solids and are often electrically conducting. The colors of "mixed" stack D–A complexes range from red to deep purple.

UV–visible spectroscopy on a solution of the donor (TTF) and acceptor (**16**) did not reveal a charge-transfer band although evaporation of the solution gives a D–A complex, [TTF]-[$(CH_2)_2$Tcbiim], as red needles. Information about this charge-transfer phenomenon was obtained from the solid-state photoluminescence spectrum of [TTF][$(CH_2)_2$Tcbiim] (Figure 6). In the luminescence experiment, the D–A complex was irradiated at 450 nm with laser light at a temperature below 10 K. The resulting electronic-emission spectrum was monitored.

(39) The structure-determination summary and tables of bond lengths and angles, atomic positions, and thermal parameters are included in the supplementary material. An ORTEP plot of TTF and **16** and additional views of the crystal packing of the D–A complex are also included in the supplementary material.

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The onset of emission (λ = 530 nm) is consistent with charge-transfer absorption in the blue-green region of the visible spectrum and the red color of the complex.

The emission spectrum is characterized by a broad band from 530 to 850 nm. This broadness is caused by changes in bond length and donor–acceptor separation (the vibrational energy states of the D–A complex) and is associated with the excited state of the D–A complex. Relaxation from the charge-transfer excited state to the ground state shows up as a distribution of energies (from 530 to 850 nm) due to superimposed vibrational energy states. The maximum emission intensity at 660 nm corresponds to the greatest transition probability.

Conclusions

This paper has described the design, synthesis, and characterization of new cyanoazacarbon derivatives based on HDcim and H_2Tcbiim. Protecting and blocking groups for 4,5-dicyanoimidazoles have been developed. The methoxymethyl and methyl groups have been found to be particularly effective protecting groups for 4,5-dicyanoimidazoles. Lithiation of N-blocked 4,5-dicyanoimidazoles followed by oxidative coupling of the 2-anion gives several new 1,1′-dialkyl-4,4′,5,5′-tetracyano-2,2′-biimidazoles **13–15**. An Ullmann coupling reaction of **6** to give **13** has been developed and this reaction is easily scaled up. Removal of the N-protecting groups of **13** and **14** gives good to excellent yields of H_2Tcbiim (**2**). These new routes to **2** circumvent the problems associated with the original synthesis. As a result, the study and the synthesis of new organic structures based on H_2Tcbiim was significantly easier.

Several new 1,1′-bridged derivatives of Tcbiim (**16–18**) have been synthesized by the alkylation of H_2Tcbiim with 1,*n*-dihaloalkanes (*n* = 2, 3, and 4) or via an intramolecular Ullmann coupling reaction of **19**. UV-visible spectroscopy and cyclic voltammetry have been used to gain insight into the conformational and electron-accepting properties of these new materials. All cyanoimidazoles were found to be weak to moderate electron acceptors. Changing the substitution at R_1 and R_2 does influence the electronic behavior of the cyanoazacarbon skeleton. Ethane-bridged Tcbiim (**16**) forms a charge-transfer complex with tetrathiafulvalene (TTF). The donor (D)–acceptor (A) complex of TTF and **16** crystallizes from acetonitrile solution in alternate or "mixed" stacks of donor and acceptor (...DADADA...). This is the first reported example of a cyanoimidazole forming a charge-transfer complex with an organic donor. Photoluminescence spectroscopy of [TTF][$(CH_2)_2$Tcbiim] shows a broad emission band centered at 660 nm with onset of the band at 530 nm. This is consistent with a charge-transfer absorption in the blue-green region of the visible spectrum.

Experimental Section

General Procedures. Melting points were recorded on a Mel-Temp apparatus and are uncorrected. Thin-layer chromatography was done on Eastman Kodak silica gel sheets containing fluorescent indicator. Column chromatography was done using 70–230- or 230–400-mesh silica gel (Aldrich). Infrared spectra were recorded on a Nicolet 5-DX FTIR spectrophotometer. ^{1}H NMR (300 MHz) and ^{13}C NMR (75 MHz) were recorded on a Bruker AM-300 spectrometer. Chemical shift values are reported relative to tetramethylsilane in the appropriate solvent. All ^{13}C NMR were done under broad-band proton decoupling. Mass spectra were recorded on a Finnigan Model 4021 mass spectrometer. Elemental analyses were done at The University of Michigan on a Perkin-Elmer 2400 CHN analyzer or done by Oneida Research Services, Inc., Whitesboro, NY.

Solvents were purified and distilled under nitrogen prior to use. THF and DME were distilled from sodium benzophenone ketyl. Acetonitrile (HPLC grade) was distilled from CaH_2. DMF was distilled from BaO and stored over 3A or 4A sieves. Triethylamine was purified by drying over KOH and distilling from BaO or P_2O_5. 4,5-Dicyanoimidazole was obtained from Nippon Soda Co. Ltd., recrystallized from H_2O, and dried prior to use. Cupric chloride was dried prior to use. Other reagents were used as purchased from Aldrich Chemical Co.

UV-visible spectroscopy was done on a Shimadzu UV-160 UV-visible spectrophotometer. Cyclic voltammetry was done with a Princeton Applied Research (PAR) Model 173 potentiostat/galvanostat, a PAR Model 175 universal programmer, and a PAR Model 179 digital coulometer. Voltammograms were plotted on a Hewlett-Packard 7005B x-y recorder. For cyclic voltammetry, acetonitrile (HPLC grade) was distilled immediately prior to use. Et_4NBF_4 (99%, Aldrich) was recrystallized from freshly distilled acetonitrile and dried in vacuo prior to use. The supporting electrolyte was 0.1 M Et_4NBF_4 in acetonitrile. Samples were 0.003–0.005 M in the supporting electrolyte solution. All solvents and solutions were degassed prior to use. The working electrode was a platinum wire and the counter electrode a platinum foil. The reference electrode was Ag/$AgNO_3$ (0.1 M). Luminescence spectroscopy was done by Prof. A. H. Francis and S. Sibley at The University of Michigan.

Alkylation of 4,5-Dicyanoimidazoles (General Procedures). Method A. A flask was charged with the appropriate 4,5-dicyanoimidazole (**1** or **3**) in THF. Triethylamine (1.0 equiv) was added at room temperature and the solution stirred for 15–30 min. The desired electrophile (1.0 equiv) was added dropwise at 0 °C or room temperature and the solution stirred overnight (16–24 h) at room temperature. If a precipitate formed, it was filtered and rinsed with solvent. The organic layer was then concentrated, and the residue was taken up in CH_2Cl_2 or EtOAc, washed with dilute NH_4OH (aq) and/or H_2O, and dried. Solvent was removed to give the crude product. **Method B.** A solution of the appropriate 4,5-dicyanoimidazole (**1** or **3**) (3 mmol) in 15 mL of $CH_3OCH_2OCH_3$ was stirred over excess P_2O_5 (s) at room temperature for 3–5 h. At this time, the reactions appeared to be complete by TLC. The mixture was poured into 50 mL of dilute NaOH (aq) and extracted with CH_2Cl_2 (50, 2 × 10 mL). The organics were combined, washed with H_2O, dried ($MgSO_4$), and concentrated to give the crude product.

1-(Methoxymethyl)-4,5-dicyanoimidazole (5). Method A. The crude residue was crystallized from hexanes, giving **5** as an off-white solid. Repeated crystallization from Et_2O gave an analytically pure sample (63–78%). **Method B.** Crystallization of the crude product with Et_2O/hexanes at 0 °C gave **5** as an off-white solid (42%): TLC 2/1 EtOAc/hexanes R_f 0.55; mp 42–43 °C; UV-vis (CH_3CN) λ_{max} (ϵ) 246 (8600); IR (KBr) 3123, 2967, 2941, 2241, 1492, 1347, 1195, 1171, 1108, 921, 780 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 7.88 (s, 1 H), 5.46 (s, 2 H), 3.45 (s, 3 H); ^{13}C NMR ($CDCl_3$) δ 141.6, 123.6, 112.0, 111.5, 107.5, 78.3, 57.6. Anal. Calcd for $C_7H_6N_4O$: C, 51.85; H, 3.73; N, 34.55. Found: C, 51.73; H, 3.50; N, 34.24.

1-(Methoxymethyl)-2-bromo-4,5-dicyanoimidazole (7). Method A. The crude solid can be recrystallized from MeOH/H_2O (4/1), giving **7** as white crystals (89%). **Method B.** The crude product was recrystallized from a MeOH/H_2O mixture, giving **7** as white crystals (59%): TLC 1/1 EtOAc/hexanes R_f 0.58; mp 79–80 °C; UV-vis (CH_3CN) λ_{max} (ϵ) 256 (9600); IR (KBr) 3018, 3013, 2963, 2944, 2245, 2240, 1477, 1432, 1405, 1340 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 5.46 (s, 2 H), 3.47 (s, 3 H); ^{13}C NMR ($CDCl_3$) δ 126.7, 123.9, 114.7, 110.6, 107.1, 78.8, 57.9. Anal. Calcd for $C_7H_5N_4OBr$: C, 34.88; H, 2.09; N, 23.24. Found: C, 35.18; H, 2.15; N, 23.24.

1-Benzyl-2-bromo-4,5-dicyanoimidazole (8). A flask equipped with a condenser was charged with 3.479 g of 2-bromo-4,5-dicyanoimidazole (17.7 mmol) in 20 mL of DME. Triethylamine (2.5 mL, 17.7 mmol) was added. The solution was stirred for 30 min at room temperature and 2.0 mL of $PhCH_2Cl$ (1.0 equiv) was added. The solution was heated to reflux. After 16 h, a precipitate was filtered and rinsed with CH_2Cl_2. Workup as usual gave an off-white solid that was recrystallized from EtOH. After drying, 2.967 g of **8** (58%) were recovered: TLC 1/1 EtOAc/hexanes R_f 0.73; mp 97–98 °C; UV-vis (CH_3CN) λ_{max} (ϵ) 257 (7000); IR (KBr) 3056, 3033, 2954, 2240, 2221, 1455, 1425, 1302, 753, 706, 699 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 7.45–7.41 (m, 3 H), 7.31–7.27 (m, 2 H), 5.32 (s, 2 H); ^{13}C NMR ($CDCl_3$) δ 132.3, 129.8, 129.6, 127.9, 126.6, 123.7, 114.7, 110.8, 107.6, 52.4. Anal. Calcd for $C_{12}H_7N_4Br$: C, 50.20; H, 2.46; N, 19.51. Found: C, 50.08; H, 2.41; N, 19.39.

Copper(II) Chloride Promoted Coupling Reactions (General Procedures). Via Deprotonation with LDA. A flask was charged with 1–5 mmol of LDA (1.0 equiv) [1–5 mmol of iPr_2NH (1.0 equiv) and 1–2 mL of 2.5 M nBuLi (1.0 equiv) in hexanes] in 10 mL of THF. The solution was cooled to −100 °C and 1-protected 4,5-dicyanoimidazole **4** or **5** (1.0 equiv) in 15 mL of THF was added dropwise over 20 min. The clear orange-red solution was stirred for 10 min at −100 °C. Dry $CuCl_2$ (1.5–2.0 equiv) was added in one portion at −100 °C. The dark brown-black suspension was stirred for 10 min and allowed to warm to room temperature. During warming, O_2 (g) was bubbled through the reaction mixture. At room temperature, the reaction mixture was poured into 1 M HCl (aq) and extracted with EtOAc or $CHCl_3$ (3 × 50 mL). The organics were combined, washed with dilute HCl (aq) and H_2O, dried ($MgSO_4$ or K_2CO_3), and concentrated to give the crude product. **Via Metal/Halogen Exchange.** A flask was charged with 1-protected 2-bromo-4,5-dicyanoimidazole **6**, **7**, or **8** (1–20 mmol) in 10–50 mL of THF. This was cooled to −100 °C and 1.0 equiv of nBuLi (2.5 M in hexanes) was added dropwise slowly. The clear orange-red solution was

stirred at low temperature for 15 min. Dry $CuCl_2$ (1.5–1.6 equiv) was added in one portion. The dark brown-black suspension was stirred at low temperature for 10 min and O_2 (g) was bubbled through the reaction mixture during warming. The dark solution was poured into 1 M HCl (aq) and extracted with EtOAc or CH_2Cl_2 (3 × 50 mL). The organics were combined, washed with dilute HCl (aq) and H_2O, dried ($MgSO_4$ or K_2CO_3), and concentrated to give the crude product.

1,1′-Dimethyl-4,4′,5,5′-tetracyano-2,2′-biimidazole (13). Via Deprotonation with LDA or Metal/Halogen Exchange. Recrystallization from MeOH/H_2O or DMF/H_2O gave **13** as a pale yellow powder (54–58%). **Ullmann Coupling of 6.** A mixture of 11.2896 g of 1-methyl-2-bromo-4,5-dicyanoimidazole (**6**) (53.3 mmol) and 5.113 g of Cu (80.5 mmol, 1.5 equiv) in 100 mL of DMF was heated to 85 °C for 12 h. The dark reaction mixture was filtered to remove the undissolved solids and washed with DMF (300 mL). The dark brown DMF solution was cooled to 0 °C and 500 mL of 0.5 M HCl (aq) was added. A yellow solid fell from solution and was collected and rinsed with H_2O and a small amount of MeOH. The product was dried, giving 3.1509 g of a yellow powder. A second crop (0.0831 g) was recovered. The solids were recrystallized from DMF/H_2O. The total yield of **13** via Ullmann coupling was 3.2340 g (48%): TLC 1/1 EtOAc/hexanes R_f 0.75; mp 266–268 °C; UV-vis (CH_3CN) λ_{max} (ϵ) 300 (sh), 280 (7200), 213 (9000); IR (KBr) 2926, 2250, 2241, 1457, 1402, 1359, 1051, 745 cm^{-1}; ^1H NMR (acetone-d_6) δ 4.27 (s); ^{13}C NMR (DMSO-d_6) δ 139.2, 119.9, 116.4, 111.8, 108.2, 36.1; MS (EI) m/z 262 (M^+, 82), 261 (100), 247, 236, 158, 132, 131, 77, 67. Anal. Calcd for $C_{12}H_6N_8 \cdot {}^1/_4H_2O$: C, 54.01; H, 2.43; N, 42.02. Found: C, 54.44; H, 2.28; N, 41.77.

1,1′-Bis(methoxymethyl)-4,4′,5,5′-tetracyano-2,2′-biimidazole (14). Via Deprotonation with LDA or Metal/Halogen Exchange. Recrystallization of the crude solid from aqueous MeOH gave **14** as a pale yellow powder (27%): TLC 1/1 EtOAc/hexanes R_f 0.76; mp 146–148 °C; UV-vis (CH_3CN) λ_{max} (ϵ) 305 (sh), 283 (7700), 209 (10,000); IR (KBr) 2947, 2240, 1367, 1350, 1275, 1183, 1106, 919, 760 cm^{-1}; ^1H NMR ($CDCl_3$) δ 6.06 (s, 4 H), 3.47 (s, 6 H); ^{13}C NMR (acetone-d_6) δ 140.0, 123.3, 116.4, 112.1, 108.5, 80.4, 57.0; MS (EI) m/z 322 (M^+), 72, 45 (100), 43. Anal. Calcd for $C_{14}H_{10}N_8O_2 \cdot {}^1/_4H_2O$: C, 51.44; H, 3.21; N, 34.30. Found: C, 51.47; H, 3.18; N, 34.07. A mixture of 1-(methoxymethyl)-4,4′,5,5′-tetracyano-2,2′-biimidazole and H_2Tcbiim (5–10% yield of coupled product) can be recovered from the above reaction: TLC 5/1 EtOAc/MeOH R_f 0.86, 0.67, 3/1 EtOAc/hex R_f 0.33, 0.14; IR (KBr) 3533, 3457, 3200–2400 (v br), 2257, 2240, 1355, 1020, 929, 514 cm^{-1}; ^1H NMR (acetone-d_6) δ 6.29 (s, 2 H), 3.50 (s, 3 H).

1,1′-Dibenzyl-4,4′,5,5′-tetracyano-2,2′-bimidazole (15). Via Metal/Halogen Exchange Only. The crude solid can be purified by column chromatography (1/2 EtOAc/hexanes) or by trituration under iPrOH to give **15** as an off-white powder (60%): TLC 1/2 EtOAc/hexanes R_f 0.63; mp 238–240 °C; UV-vis (CH_3CN) λ_{max} (ϵ) 304 (sh), 283 (4200), 207 (9100); IR (KBr) 3071, 3040, 3007, 2956, 2242, 2231, 1453, 1429, 1362, 1354, 728, 695 cm^{-1}; ^1H NMR (acetone-d_6) δ 7.37–7.34 (m, 6 H), 7.27–7.25 (m, 4 H), 6.05 (s, 4 H); ^{13}C NMR (DMSO-d_6) δ 138.5, 134.0, 128.9, 128.5, 127.5, 121.6, 115.7, 111.6, 107.9, 51.6; MS (EI) m/z 414 (M^+), 323, 180, 153, 128, 91 (100), 65. Anal. Calcd for $C_{24}H_{14}N_8 \cdot {}^1/_4H_2O$: C, 68.83; H, 3.46; N, 26.77. Found: C, 69.00; H, 3.25; N, 26.44.

4,4′,5,5′-Tetracyano-2,2′-biimidazole (2). Method A. A solution of 2.7757 g of **13** (10.59 mmol) and 2.8535 g of LiCl (6.4 equiv) in 50 mL of NMP was heated to reflux for 36 h. The solution turned dark brown. The reaction mixture was poured into 100 mL of 1 M NaOH (aq) and washed with Et_2O (3 × 25 mL). The aqueous layer was acidified to pH 1 with concentrated HCl. A brown solid precipitated from solution, was collected, rinsed with dilute HCl (aq), and then taken up in acetone. Activated charcoal was added and the insoluble matter filtered. Dilute HCl (aq) was added to the filtrate and this solution extracted with Et_2O (3 × 50 mL). The organics were combined, dried ($MgSO_4$), and concentrated to give a pale yellow solid. Upon drying, 1.4685 g of **2** was recovered (59%). **Method B.** A solution of 0.463 g of **14** (1.43 mmol) in 20 mL of THF and 10 mL of 1.2 M HCl (aq) was heated to 60 °C for 3 h. The solution was poured into 50 mL of dilute HCl (aq) and extracted with EtOAc (2 × 50 mL). The organics were combined and dried (Na_2SO_4), and the solvent was removed to give a pale yellow powder. Drying gave 0.332 g of **2** (97%): TLC 5/1 EtOAc/MeOH R_f 0.60; mp >300 °C dec; UV-vis (CH_3CN) λ_{max} (ϵ) 300 (sh), 272 (8400), 210 (8100); IR (KBr) 3533, 3468, 3189, 3154, 3065, 3000–2400 (br), 2248, 1393, 1355, 1171, 944, 512 cm^{-1}; ^{13}C NMR (acetone-d_6) δ 141.4, 118.4, 110.8; MS (EI) m/z 234 (M^+, 100). (TLC, melting point, and spectral data are identical with those of an authentic sample.[8a])

Synthesis of 1,*n*-Alkyl-Bridged Derivatives of 2 (General Procedure). To a solution of **2** (1.0–2.0 mmol) in 10–15 mL of DMF was added 2.0 equiv of Et_3N. The solution was stirred for 30 min and 1.0 equiv of 1,*n*-dihaloalkane was added. The solution was heated at 95 °C for 12–24 h and then poured into H_2O. A tan precipitate was collected and rinsed with H_2O, giving the crude product after drying.

1,1′-Dimethylene-4,4′,5,5′-tetracyano-2,2′-biimidazole (16). The crude solid was recrystallized from AcOH/H_2O or DMF/H_2O to give **16** as pale yellow plates (56%): TLC 3/1 EtOAc/hexanes R_f 0.73; mp 292–293 °C; UV-vis (CH_3CN) λ_{max} (ϵ) 313 (3700), 299 (5900), 289 (5400), 265 (6100), 221 (9200); IR (KBr) 3006, 2242, 1455, 1446, 1427, 1341, 1227, 1095, 1068 cm^{-1}; ^1H NMR (DMSO-d_6) δ 4.72 (s); ^{13}C NMR (DMSO-d_6) δ 138.2, 121.2, 113.7, 111.7, 107.8, 43.4; MS (EI) m/z 260 (M^+, 100), 259, 234, 207, 155, 130, 118, 116, 102, 90, 77, 76. Anal. Calcd for $C_{12}H_4N_8 \cdot {}^1/_2H_2O$: C, 53.54; H, 1.87; N, 41.63. Found: C, 53.91; H, 1.34; N, 41.84.

1,1′-Trimethylene-4,4′,5,5′-tetracyano-2,2′-biimidazole (17). Recovered **17** as a light tan powder (48%). An analytical sample was obtained by recrystallization from DMF/H_2O: TLC 3/1 EtOAc/hexanes R_f 0.60; mp ≥340 °C dec; UV-vis (CH_3CN) λ_{max} (ϵ) 310 (3600), 296 (5800), 285 (5400), 238 (4400), 215 (5900); IR (KBr) 2951, 2930, 2241, 1464, 1448, 1419, 1323 cm^{-1}; ^1H NMR (DMSO-d_6) δ 4.53 (t, 4 H, J = 5.3 Hz), 2.56 (m, 2 H); ^{13}C NMR (DMSO-d_6) δ 140.3, 121.2, 115.3, 111.8, 108.2, 49.0, 24.0; MS (EI) m/z 274 (M^+, 100), 259, 246, 234, 143, 102, 91, 77, 41. Anal. Calcd for $C_{13}H_6N_8 \cdot {}^1/_4H_2O$: C, 56.01; H, 2.33; N, 40.25. Found: C, 56.30; H, 2.19; N, 40.00.

1,1′-Tetramethylene-4,4′,5,5′-tetracyano-2,2′-biimidazole (18). The crude product was recrystallized from AcOH/H_2O to give **18** as an off-white powder (35%): TLC 3/1 EtOAc/hexanes R_f 0.74; mp >310 °C dec; UV-vis (CH_3CN) λ_{max} (ϵ) 257 (6600), 238 (5600), 211 (7400); IR (KBr) 2965, 2932, 2240, 1478, 1448, 1436, 1424, 1396, 1389, 1362, 1349, 1314, 871, 510 cm^{-1}; ^1H NMR (acetone-d_6) δ 4.6–4.4 (br s, 4 H), 2.4–2.2 (br s, 4 H); ^{13}C NMR (DMSO-d_6) δ 139.0, 121.2, 115.6, 111.9, 108.1, 47.5, 25.5; MS (EI) m/z 288 (M^+, 72), 259, 234, 143, 77, 55 (100). Anal. Calcd for $C_{14}H_8N_8 \cdot {}^1/_4H_2O$: C, 57.44; H, 2.92; N, 38.29. Found: C, 57.77; H, 3.02; N, 38.26.

1,1′-Dimethylenebis(2-bromo-4,5-dicyanoimidazole) (19). Triethylamine (1.2 mL, 1.0 equiv) was added to a solution of 1.6858 g of 2-bromo-4,5-dicyanoimidazole (8.56 mmol) in 8 mL of DMF. The solution was stirred for 20 min and 1,2-dibromoethane (0.37 mL, 0.5 equiv) was added. The solution was heated to 125 °C for 20 h and poured into H_2O (75 mL). A tan solid was collected and rinsed with H_2O and then triturated in boiling acetone. Recovered 0.7593 g of **19** as an off-white powder (42%). Yields for scaled-up reactions (0.100–0.200 mol) vary (25–42%): TLC 2/1 EtOAc/hexanes R_f 0.57; mp 282–283 °C; IR (KBr) 2993, 2242, 1455, 1430, 1394, 1377, 1370, 1362, 1357, 1352, 1306, 674 cm^{-1}; ^1H NMR (DMSO-d_6) δ 4.63 (s); ^{13}C NMR (DMSO-d_6) δ 128.2, 122.0, 114.9, 111.1, 107.1, 47.3; MS (EI) m/z 422, 420, 418 (M^+), 341, 339 (100), 260, 211, 209, 184, 182, 129, 91, 77. Anal. Calcd for $C_{12}H_4N_8Br_2$: C, 34.31; H, 0.96; N, 26.68. Found: C, 34.36; H, 1.06; N, 26.58.

Intramolecular Ullmann Coupling of 19 To Give 16. A mixture of 7.2332 g of **19** (17.22 mmol) and 3.093 g of Cu (48.71 mmol, 2.83 equiv) in 200 mL of DMF was heated to 85 °C for 12 h. The reaction mixture was filtered warm to remove insoluble solids and those solids were washed with DMF (100 mL). The filtrate was cooled to 0 °C and 600 mL of 1 M HCl (aq) was added. A yellow solid fell from solution and was collected and rinsed with H_2O. The last traces of copper salt impurities were removed by dissolution of the crude product in CH_3CN, filtration of the insoluble matter, and concentration of the organics. The remaining solid was then recrystallized from DMF/H_2O and dried to give 2.2912 g of **16** (51%): TLC 3/1 EtOAc/hexanes R_f 0.73; mp 289–291 °C (authentic sample, mp 292–293 °C); ^1H NMR (DMSO-d_6) δ 4.72 (s).

[TTF][(CH$_2$)$_2$Tcbiim]. An equimolar mixture of tetrathiafulfavlene (0.05–0.10 mmol) and **16** (0.05–0.10 mmol) was dissolved in CH_3CN (1–5 mL). Slow evaporation of the yellow-orange solution at 0 °C or room temperature gives the 1:1 complex, [TTF][$(CH_2)_2$Tcbiim], as red needles: mp ≥180 °C (turns brown), ≥200 °C (brown-black), ≥210 °C (black/chars); IR (KBr) 3107, 3076, 3064, 2991, 2240, 1458, 1448, 1416, 1342, 1226, 790, 690, 679, 663, 648, 505 cm^{-1}. Anal. Calcd for $(C_6H_4S_4)(C_{12}H_4N_8)$: C, 46.54; H, 1.74; N, 24.12. Found: C, 46.50; H, 1.74; N, 23.94.

Acknowledgment. This work was supported by the National Science Foundation and by the donors of the Petroleum Research Fund, administered by the American Chemical Society. P.G.A. acknowledges support from a Sokol Fellowship while at The University of Michigan. We are grateful to Professor R. Lawton and Professor P. Knochel at The University of Michigan for their

helpful discussions and suggestions. We especially thank Professor A. H. Francis and S. Sibley for luminescence spectroscopy measurements. We also thank Dr. J. Kampf for the X-ray crystallography.

Supplementary Material Available: A listing of the structure-determination summary of [TTF][$(CH_2)_2$Tcbiim] including tables of bond lengths and bond angles, tables of atomic positions and thermal parameters, and additional crystal-packing diagrams and an ORTEP plot of [TTF][$(CH_2)_2$Tcbiim] (14 pages); tables of structure factors for $C_{18}H_8N_8S_4$ (10 pages). Ordering information is given on any current masthead page.

Enzyme-Catalyzed Aldol Condensation for Asymmetric Synthesis of Azasugars: Synthesis, Evaluation, and Modeling of Glycosidase Inhibitors[1]

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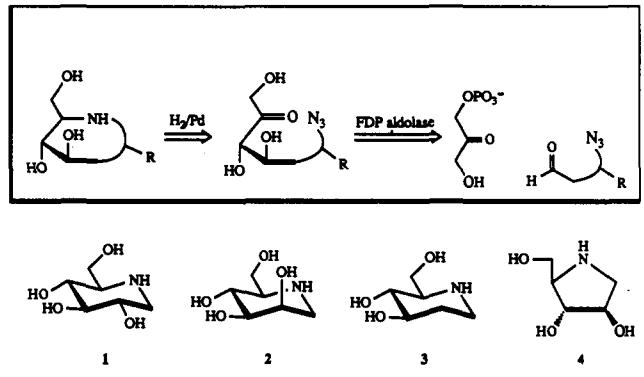
Abstract: A combined fructose 1,6-diphosphate aldolase reaction and catalytic reductive amination has been used in the asymmetric synthesis of azasugars structurally corresponding to *N*-acetylglucosamine, *N*-acetylmannosamine, and deoxyhexoses. The 6-deoxyazasugars were prepared by direct hydrogenolysis of the aldolase product without removal of the 6-phosphate group. Both (*R*)- and (*S*)-3-azido-2-acetamidopropanal used as substrates in the aldolase reactions were prepared from the corresponding lipase-resolved 2-hydroxy species followed by formation of an aziridine intermediate and opening of the aziridine with azide. Evaluation of these azasugars and their diastereomerically pure tertiary amine oxides as well as 5-thioglucose and its sulfoxide derivatives as glycosidase inhibitors was carried out. It was found that all synthetic azasugars and 5-thioglucose were strong inhibitors, but oxidation of the ring heteroatom weakened the inhibition. With the aid of molecular modeling and inhibition analysis, a structure-K_i relation of inhibitors was established which provides useful information for the design of new glycosidase inhibitors.

Many pyranoses and furanoses with the ring oxygen replaced by an imino group are natural products and useful as potent glycosidase inhibitors.[2] This discovery has stimulated interests in the development of effective procedures for the synthesis of various azasugars[3] and analogues[4] for the investigation of glycosidase reactions[5] and the development of specific glycosidase inhibitors for treating metabolic disorders such as diabetes[2,4b,6] or as antiviral,[2,7] antibacterial,[2,8] and anticancer[2,9] agents.

Scheme I



We have recently reported[10] asymmetric syntheses of azasugars **1**–**4** based on aldolase-catalyzed reaction and Pd-catalyzed re-

(1) Supported by the NIH (GM44154).

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0002-7863/91/1513-6187$02.50/0