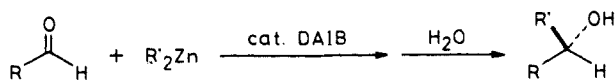


Table I. Enantioselective Addition of Dialkylzincs to Aldehydes^a

aldehyde	alkylating agent	conditions		alkylated product		
		solvent	time, h	% yield ^b	$[\alpha]^{22}_D$, deg (c, solvent)	% ee ^c (confign)
C ₆ H ₅ CHO	(C ₂ H ₅) ₂ Zn	toluene	6	97	-47.6 (6.11, CHCl ₃) ^d	98 (S) ^e
C ₆ H ₅ CHO	(C ₂ H ₅) ₂ Zn	hexane-toluene	6	94 ^f		98 (S)
C ₆ H ₅ CHO	(C ₂ H ₅) ₂ Zn	ether-toluene	6	98 ^f		99 (S)
C ₆ H ₅ CHO	(C ₂ H ₅) ₂ Zn	THF-toluene	64	44 ^f		91 (S)
C ₆ H ₅ CHO	(CH ₃) ₂ Zn	toluene	70	59 ^f	-49.7 (2.01, <i>c</i> -C ₅ H ₁₀) ^g	91 ^h (S)
<i>p</i> -ClC ₆ H ₄ CHO	(C ₂ H ₅) ₂ Zn	toluene	12	86	-23.5 (0.82, C ₆ H ₆) ⁱ	93 (S)
<i>p</i> -CH ₃ OC ₆ H ₄ CHO	(C ₂ H ₅) ₂ Zn	toluene	12	96	-32.1 (1.25, C ₆ H ₆) ⁱ	93 (S)
(<i>E</i>)-C ₆ H ₅ CH=CHCHO	(C ₂ H ₅) ₂ Zn	toluene	6	81	-5.7 (100, CHCl ₃) ^j	96 (S)
C ₆ H ₅ CH ₂ CH ₂ CHO	(C ₂ H ₅) ₂ Zn	toluene	12	80	+23.9 (1.44, C ₂ H ₅ OH) ^k	90 ^l (S)
<i>n</i> -C ₆ H ₁₃ CHO	(C ₂ H ₅) ₂ Zn	toluene	24	81	+5.1 (1.31, CHCl ₃) ^m	61 ^l (S)

^a Reaction was carried out in degassed solvent at 0 °C by using 2 mol % (-)-DAIB and 1.2 equiv of the alkylating agent per aldehyde. ^b Isolated yield. ^c Determined by HPLC using a Bakerbond DNBPG chiral column unless otherwise specified. ^d See ref 8. ^e Absolute configuration: MacLeod, R.; Welch, F. J.; Mosher, H. S. *J. Am. Chem. Soc.* **1960**, *82*, 876. ^f HPLC analysis. ^g $[\alpha]^{20}_D +43.1^\circ$ (*c* 7.19, *c*-C₅H₁₀) for (*R*)-1-phenylethanol: Yamaguchi, S.; Mosher, H. S. *J. Org. Chem.* **1973**, *38*, 1870. ^h Determined by HPLC analysis of the (*R*)- α -methoxy- α -(trifluoromethyl)phenylacetate (Develosil 100-5 column, 1:100 ethyl acetate-hexane eluent). ⁱ Reported values for (*S*)-1-(*p*-chlorophenyl)propanol in 43% ee and (*S*)-1-(*p*-methoxyphenyl)propanol in 51% ee are $[\alpha]^{22}_D -10.4^\circ$ (*c* 5, C₆H₆) and $[\alpha]^{22}_D -17.2^\circ$ (*c* 5, C₆H₆), respectively [Capillon, J.; Guette, J. *Tetrahedron* **1979**, *35*, 1817]. ^j $[\alpha]^{23}_D -6.6^\circ$ (*c* 3.18, CHCl₃) for (*S*)-1-phenylpent-1-en-3-ol in 75% ee: Sato, T.; Gotoh, Y.; Wakabayashi, Y.; Fujisawa, T. *Tetrahedron Lett.* **1983**, *24*, 4123. ^k $[\alpha]_D +26.8^\circ$ (*c* 5.0, C₂H₅OH) for (*S*)-1-phenyl-3-pentanol: see ref in footnote j. ^l Determined by HPLC analysis of the (*R*)-1-(1-naphthyl)ethyl carbamate (Develosil 100-3, 1:2 ether-hexane). ^m $[\alpha]^{24}_D +9.6^\circ$ (*c* 8.3, CHCl₃) for (*S*)-3-nonanol: Mukaiyama, T.; Hojo, K. *Chem. Lett.* **1976**, 893.

context. Under the influence of 2 mol % of (-)-DAIB, diethylzinc reacted with benzaldehyde (1.2:1 molar ratio) in toluene smoothly at 0 °C, and (*S*)-1-phenylpropanol was obtained in 98–99% ee and in 98% chemical yield. Table I exemplifies the efficient



asymmetric alkylation. The enantiomeric excess was determined carefully by HPLC analysis using a chiral stationary phase. Enantioselectivity of the reaction of *p*-substituted benzaldehydes is generally high. Certain α,β -unsaturated or aliphatic aldehydes can be also alkylated with a high degree of enantioselectivity. Use of nonpolar solvents such as hexane, toluene, ether, or their mixtures gave consistently satisfactory results. THF as solvent retarded the reaction and lowered the enantioselectivity to some extent. Attempted alkylation of acetophenone failed.

Notably, stoichiometry of the substrate, alkylating agent, and auxiliary has marked effects on the reaction rate and course. Benzaldehyde does not react with diethylzinc at 0 °C in toluene. When a 1:1:1 or 1:2:2 mixture of benzaldehyde, diethylzinc, and (-)-DAIB in toluene was allowed to stand at 0 °C, the aldehyde was consumed slowly but only benzyl alcohol was obtained. No ethylation product could be detected. If, however, the amount of diethylzinc to (-)-DAIB was doubled, the ethylation reaction took place smoothly, as under the above described catalytic conditions, leading to the desired alcohol in 98% ee and in 88% (benzaldehyde:diethylzinc:DAIB = 1:2:1, 12 h) or 49% (1:1:0.5 ratio, 12 h) yield. These results indicate that two zinc species per aldehyde are responsible for the alkylation reaction.

This method is practical and operationally very simple. A typical procedure is illustrated as follows: In a flame-dried Schlenk tube was placed (-)-DAIB (371 mg, 1.88 mmol) and dry toluene (200 mL), and the whole mixture was degassed and covered with argon. To this was added a 4.19 M toluene solution of diethylzinc (27.0 mL, 113 mmol) and the resulting solution was stirred at 15 °C for 15 min (ethane evolution was confirmed by ¹H NMR). After cooling to -78 °C, benzaldehyde (10.0 g, 94.2 mmol) was then added and the mixture was warmed up to 0 °C, stirred for 6 h, and quenched by adding a saturated ammonium chloride solution. Usual extractive workup and distillation gave (*S*)-1-phenylpropanol in 98% ee (12.4 g, 97% yield) as an oil, $[\alpha]^{22}_D -47.6^\circ$ (*c* 6.11, CHCl₃) [lit.⁸ $[\alpha]_D -45.45^\circ$ (*c* 5.15, CHCl₃)]. The ee was determined by HPLC analysis (column, Bakerbond DNBPG; eluent, 0.25% 2-propanol in hexane; flow rate, 1.0 mL/min; detection, 254-nm light). Racemic 1-phenylpropanol

exhibited two base-line-separated peak arising from the *S* isomer (*t*_R 47.8 min) and *R* isomer (*t*_R 50.0 min) with equal intensities, whereas the synthetic alcohol showed these peaks in ratio of 99.2:0.8.

Two-Dimensional Chemical Exchange NMR in the Solid: Proton Dynamics in Phthalocyanine

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Carbon-13 solid-state cross-polarization magic angle spinning (CP-MAS) has proved to be a powerful method for investigating dynamical processes in solids.¹ In investigations of molecules with several resonances, the intrinsically lower resolution of CP-MAS NMR spectra compared to liquid-state spectra makes the interpretation of the spectra cumbersome due to peak overlap. In some cases, such as porphyrins or phthalocyanines, these problems arising in the ¹³C spectra have been overcome by observing ¹⁵N instead of ¹³C.²⁻⁴ This requires considerable synthetic effort because the NMR measurements must be performed on an enriched sample to overcome the low sensitivity. We present here results which show that ¹³C 2-D exchange spectroscopy^{5,6} can extend the resolution, allowing the spectroscopist to extract the details of the exchange process from a natural abundance sample even when the ¹³C resonances strongly overlap in the one-dimensional spectrum. There is another example in which 2-D exchange spectroscopy has been exploited in a solid to determine a proton exchange rate but it was in a system where

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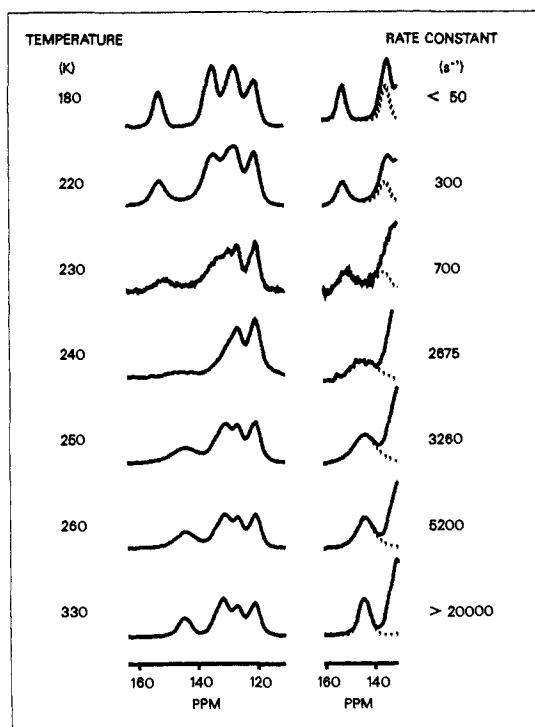
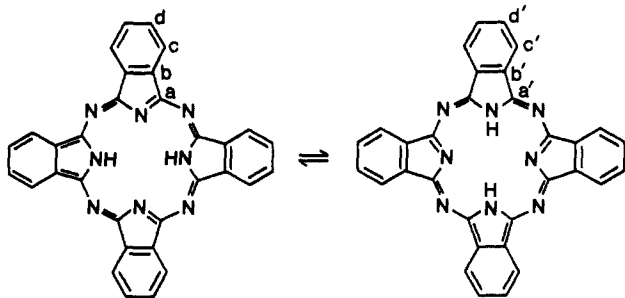


Figure 1. ^{13}C cross-polarization magic angle spinning spectra of phthalocyanine taken as a function of temperature from 180 to 330 K. Spectra were obtained on a Bruker CXP 200 spectrometer at a nominal resonance frequency of 50 MHz using a probe manufactured by Doty Scientific. Temperature was regulated by using a home-built temperature controller. The spinning rate varied between 2000 and 3000 Hz, depending upon temperature. Approximately 100 scans were taken per spectrum, using spin-locked cross polarization with a cross-polarization contact time of 0.8 ms and ^1H and ^{13}C rf fields matched at approximately 60 kHz. The repetition time was 30 s. The right-hand column is a comparison of the observed (solid line) and computed data (dashed line) for the downfield portion of the corresponding spectrum. Exchange spectra were computed by assuming a two-site exchange. The computed spectra include only the contributions from resonances a and a' (see Figure 2). In the fast-exchange limit (330 K) as well as the slow-exchange limit (180 K), the lines are accurately fit with a Gaussian line shape whereas the line shape of the exchange-broadened spectra is Lorentzian. No correction was made for possible spectral distortions due to the fact that the spinning rate and the exchange rate are similar in many of the spectra.

Scheme I



resolution was not a problem.⁷ The use of 2-D spectroscopy to extend resolution should be applicable to a large class of solid compounds.

The N-H tautomerism in porphyrins has been studied in the solid state by ^{15}N NMR for tetraolyl- and tetraphenylporphyrin.^{2,3} In both cases the protons are found to undergo an exchange reaction between the two tautomeric positions. In a very recent ^{15}N CP-MAS study, a similar behavior has been described for phthalocyanine (PC) (Scheme I).^{3,4}

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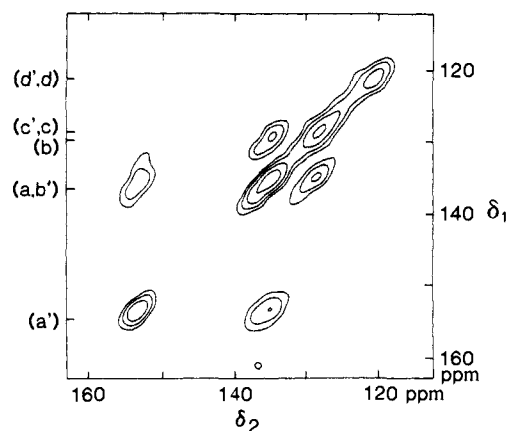


Figure 2. Contour plot of the two-dimensional chemical exchange spectrum of phthalocyanine obtained at 205 K with a mixing time of 250 ms. There were 256 by 256 points in the original data, 16 scans per spectrum. The cross-polarization parameters were the same as those in Figure 1. The data in the δ_2 dimension were taken in quadrature with the imaginary portion of the spectra zeroed after the first Fourier transformation to obtain pure absorption line shapes.

Figure 1 shows the one-dimensional CP-MAS spectra of PC (α -crystal form) over the temperature range from 180 to 330 K along with computer-simulated spectra which will be described below. It is clear from the line shapes that some dynamical process is taking place. Between 220 and 260 K, exchange broadening is observed, whereas below 200 K the slow exchange limit and above 300 K the fast exchange limit are reached. Due to spectral overlap, the eight resonances expected in the low-temperature spectra cannot be assigned and the nature of the process causing the broadening cannot be unequivocally identified.

A two-dimensional CP-MAS exchange spectrum at 205 K is shown in Figure 2. The spectrum was obtained by a CP version⁸ of the 2-D exchange experiment.^{5,6} In this experiment, off-diagonal peaks (cross-peaks) appear between those diagonal peaks that undergo chemical exchange (or spin diffusion, which can be neglected in this case). Cross-peaks can be clearly identified between two pairs of peaks. These signals can be assigned to the carbons a, a' and b, b', respectively. Their chemical shifts are very near to the ones found in the liquid-state spectrum of the related molecule tetraphenylporphyrin.^{9,10} The differences in resonance frequency between c and c' and between d and d' are too small to be resolved. The increase in resolution by having cross-peaks in two frequency dimensions allows definition of the peak positions of the two exchanging peaks.

Having confirmed the two-site exchange pattern and knowing the peak positions in the absence of chemical exchange, the one-dimensional spectra can be profitably reexamined. First, we note that the resonances a and a' in the low-temperature spectrum are averaged at high temperature into a single peak at a resonance position equal to the arithmetic mean of the two low-temperature frequencies. This indicates that the potential for the tautomerization is nearly symmetrical. The increased line width of the averaged peak could be caused by a slight asymmetry of this potential, leading to two strongly overlapping signals. From the line width, the populations of the two sites can be estimated to be between 60:40 and 50:50.¹¹⁻¹³ Limbach et al. obtained a value of 60:40³ whereas neutron diffraction yields 50:50.¹⁴ The right-hand column in Figure 1 is a comparison of calculated

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spectra and experimental data (dashed lines). Because of the complexity of the overlap, it is only possible to calculate the spectra for the relatively resolved resonance which moves from about 150 to 140 ppm as a function of exchange. The exchange spectra were computed assuming a two-site exchange (see caption to Figure 1), and no correction was made for possible spectral distortions due to the fact that the exchange rate and magic angle sample spinning rate are similar.¹⁵ Spectra were calculated as a function of exchange rate using 55:45 as the population ratio of the two sites at room temperature and visually compared to the experimental data until a reasonably good fit was obtained. Errors in estimated exchange due to magic angle sample spinning interferences are probably less than 10% and those due to overlap and broad lines are about the same magnitude. It is probable that the errors in this work are greater than those obtained from ¹⁵N studies of this and similar compounds because of the simplicity of the ¹⁵N spectra. The results are indicated in Figure 1. Because of the extremely poor solubility of phthalocyanine, to our knowledge no liquid-state studies have been performed. However, our results can be compared to the ones obtained for dissolved tetra-*tert*-butyltetraazaporphyrin, where a very similar exchange rate was found.¹⁷

In conclusion, we have demonstrated the utility of 2-D exchange spectroscopy in a case where the 1-D spectra are impossible to interpret. It has generally been believed that the only way to get kinetic information on these systems is through difficult isotopic labeling.

Acknowledgment. This work was performed under the auspices of the U.S. Department of Energy.

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Convenient Synthesis and Structural Aspects of 1,3,5-Tri[2,6]pyridacyclohexaphane-2,4,6-trione and Precursors¹

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Analogues of porphyrins, in which one or more of the pyrrole subunits have been substituted by an electron-rich heterocycle (such as furan² and/or thiophene³), have been prepared⁴ by the acid cyclocondensation of an appropriately substituted heterocycle with either aldehydes or ketones. However, the incorporation of an electron-poor heterocycle, e.g., pyridine, has not been accomplished since traditional electrophilic procedures are not applicable.

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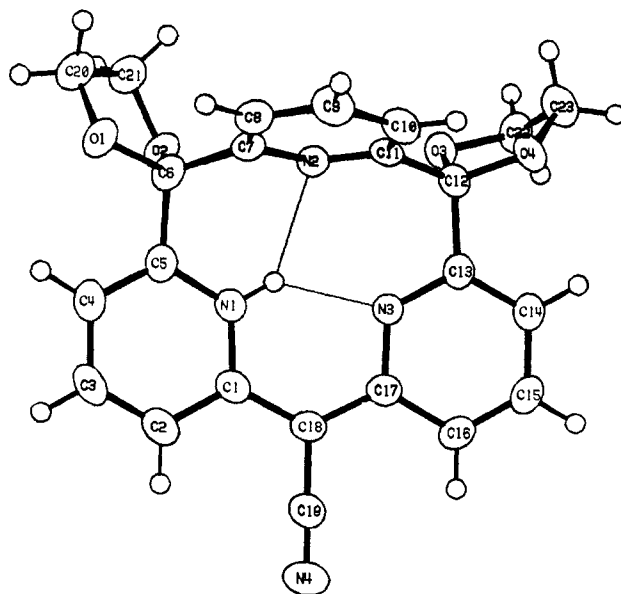


Figure 1. Macrocycle 4 illustrating one of the two disordered, bifurcated, intramolecular hydrogen bonds. Bond lengths averaged over chemically equivalent bonds: N1-C1 1.358, N1-C5 1.353, N2-C7 1.338, O1-C6 1.416, O1-C20 1.425, C1-C2 1.415, C2-C3 1.355, C3-C4 1.395, C4-C5 1.361, C5-C6 1.530, C6-C7 1.523, C7-C8 1.380, C8-C9 1.379, C20-C21 1.494, C1-C18 1.431, C18-C19 1.421, C19-N4 1.15 Å; esd's are 0.002-0.003 Å.

The simplest member of this C-bridged, electron-deficient series is 1,3,5-tri[2,6]pyridacyclohexaphane-2,4,6-trione (**1**),⁵ which should be an ideal structure to probe the electronic and/or steric effects of N electrons within a highly rigid cavity, as well as being ideally suited to be the perfect proton sponge. Our original low-yield route into this structural family was via a low-temperature (-100 °C), nucleophilic substitution;⁶ however, unfavorable conformational problems impeded cyclization. We herein report a procedure that circumvents this problem and affords facile entry into the construction of a convenient precursor to trione **1**.

Diketone **2**⁷ was synthesized by treatment of 2-lithio-6-bromopyridine⁸ with either 2,6-dicarbalkoxy- or 2,6-dicyanopyridine at <-50 °C in Et₂O. Ketalization of **2** conducted under either standard acidic⁹ or basic¹⁰ conditions gave (90%) **3**. Cyclization was accomplished (50%) by treatment of bis-ketal **3** with LiCH₂CN, generated from anhydrous CH₃CN in 5% TMEDA-toluene with LiH. The mixture was refluxed for 2 days; then, after cooling, water was added. After standard workup, the resultant dark yellow oil was chromatographed (Al₂O₃; CH₂Cl₂) to afford the yellow crystalline macrocycle **4** (Scheme I).^{11,12}

The ¹H NMR spectrum of **4** showed a broad singlet at δ 16.5 indicative of a strong N-H...N interaction;¹³ this proton was not

(5) IUPAC nomenclature: 19,20,21-Triazatetracyclo[13.3.1.1^{3,7}.1^{9,3}]he-neicosane-1(19),3,5,7(21),9,11,13(20),15,17-nonaene-2,8,14-trione.

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(11) **4**: mp 268-269 °C; ¹H NMR (CDCl₃) δ 4.15-4.36 (m, 8 H, OCH₂), 6.95-7.06 (m, 2 H), 7.24-7.80 (m, 7 H), 16.5 (br s, NH); ¹³C NMR (CDCl₃) δ 65.9 (OCH₂), 69.0 (CCN), 104.9 (OCO), 109.7 (C3'), 119.4, 119.6 (C3 and C5'), 122.6 (C≡N), 136.6 (C4'), 138.9 (C4), 150.7 (C2'), 154.4 (C6'), 157.4 (C2); MS, *m/e* 415 (M⁺ + 1, 31), 414 (M⁺, 100), 370 (10), 326 (28); IR (KBr) 2162 cm⁻¹ (C≡N). Anal. Calcd for C₂₃H₁₈N₄O₄: C, 66.66; H, 4.38; N, 13.52. Found: C, 66.36; H, 4.09; N, 13.25.

(12) Crystal data for **4**: C₂₃H₁₈N₄O₄, MW = 414.4, monoclinic P2₁/n, *a* = 11.104 (4) Å, *b* = 7.544 (2) Å, *c* = 22.375 (4) Å, β = 91.66 (2)°, *Z* = 4, *D*_c = 1.469 g cm⁻³, *R* = 0.035 for 2103 observed reflections (1° < θ < 25°, Mo Kα).