in both TLC behavior and spectroscopic properties.[18,19]

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Supplementary Material Available: Experimental details and copies of NMR spectra of key intermediates and synthetic quinocarcin (24 pages). Ordering information is given on any current masthead page.

(18) We were aware of the possibility of dramatic changes in the NMR of the final compound depending on the pH of the solution. In fact we found it necessary to separate a sample of authentic quinocarcin utilizing the exact procedure used in separation of the synthetic sample in order to obtain identical NMR spectra.

(19) We are indebted to Dr. T. Hirata of Kyowa Hakko Kogyo Co., Ltd., Tokyo, for samples of authentic quinocarcin and DX-52-1.

Synthetic Studies in the Brefeldin Series: Asymmetric Enamine–Enal Cycloaddition and Intramolecular Nozaki Reactions

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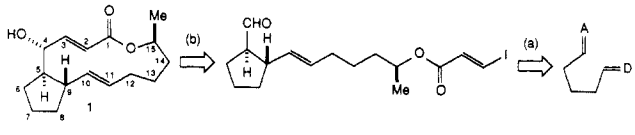
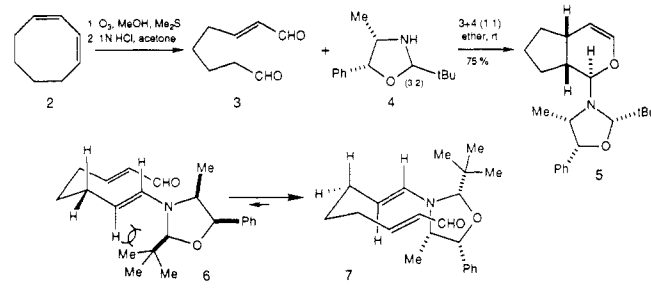
We recently reported on our stereochemical studies of the intramolecular enamine–enal cycloaddition reaction.[1] In continuation of these efforts, we have been engaged in studies directed toward the asymmetric synthesis of brefeldin C[2] and stereoisomers. We now describe (a) the utilization of a chiral amine in the cycloaddition reaction as a means to acquire carbocyclic ring systems in nonracemic form and (b) the diastereoselective *macroannelation* of enantiomeric five-membered carbocycles via a chromium-mediated coupling reaction.[3] The combination of these reaction processes has resulted in the first enantioselective synthesis of the macrolide antibiotic (+)-brefeldin C.

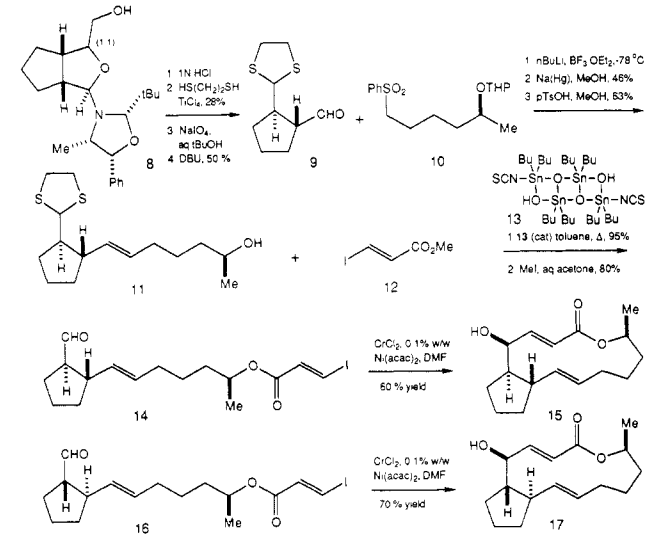


The cyclization substrate **3** was readily prepared from 1,3-cyclooctadiene by controlled ozonolysis. Earlier, we had shown that **3** undergoes a [4 + 2] cycloaddition of an in situ generated enamine with the enal function when treated with an achiral secondary amine (e.g., *N*-methylaniline).[1] We have now screened chiral secondary amines for their ability to promote cycloaddition with high levels of stereoinduction. Optimal results were obtained with oxazolidines derived from the condensation of pivalaldehyde with (+)- or (−)-norephedrin.[4] The reaction of a 1:1 mixture

Scheme I



Scheme II



of **3** and **4** (as a 3:2 ratio of isomers) proceeded to completion over a 12-h period at room temperature to provide a 17:1 ratio of two cycloadducts **5** (Scheme I). The cis stereochemistry of the oxazolidine ring substituents of the major isomer ($[\alpha]^{27}_D = -120.2$, ether) was determined by NOEDS experiments and is consistent with the stereochemistry of oxazolidines derived from the condensation of ephedrine and aldehydes.[5] The relative stereochemistry of the bicyclic dihydropyran is in accord with our earlier studies; the absolute stereochemistry was tentatively assigned as depicted based on an evaluation of the enamine intermediate (Si face selectivity at β-carbon of enamine **7** leads to product; rotamer **6** suffers steric interference with the *tert*-butyl substituent)[6] and later confirmed by the conversion of **5** into (+)-brefeldin C. The stage at which enrichment of cis stereochemistry (about the oxazolidine ring) occurs is not known.

The cycloaddition reaction is well suited for the asymmetric synthesis of vicinally substituted cyclopentyl ring systems. The synthesis of trans disubstituted precursors to brefeldin C isomers is shown in Scheme II. The oxidation of **5** with mCPBA in methanol buffered with pyridine was followed by an in situ reduction with $NaBH_4$ to afford **8** in 31% overall yield. Hydrolysis, thioacetalization, and diol cleavage provided a monothioacetal of *cis*-(meso)-dialdehyde in >90% ee. For the present application the trans isomer was required; accordingly, the cis isomer was epimerized with DBU to afford **9** ($[\alpha]^{27}_D = -40.7$, ether; trans/cis > 25:1). A Julia olefination[7] was achieved by the action of

(1) Schreiber, S. L.; Meyers, H. V.; Wiberg, K. B. *J. Am. Chem. Soc.* **1986**, *108*, 8274.

(2) Isolation and structure elucidation: (a) Sunagawa, M.; Ohta, T.; Nozoe, S. *Heterocycles* **1979**, *13*, 267. Biosynthetic studies: (b) Sunagawa, M.; Ohta, T.; Nozoe, S. *J. Antibiot.* **1983**, *36*, 25. (c) Yamamoto, Y.; Hori, A.; Hutchinson, C. R. *J. Am. Chem. Soc.* **1985**, *107*, 2471. (d) De La Parra, M. G.; Hutchinson, C. R. *J. Antibiot.* **1987**, *40*, 1170.

(3) (a) Takai, K.; Kimura, K.; Kuroda, T.; Hiyama, T.; Nozaki, H. *Tetrahedron Lett.* **1983**, *24*, 5281. Recently, the importance of catalytic quantities of late transition metals has been discovered, see: (b) Jin, H.; Uenishi, J.; Christ, W. J.; Kishi, Y. *J. Am. Chem. Soc.* **1986**, *108*, 5644. (c) Takai, K.; Tagashira, M.; Kuroda, T.; Oshima, K.; Utimoto, K.; Nozaki, H. *J. Am. Chem. Soc.* **1986**, *108*, 6048. For intramolecular ring closures of allyl halides and aldehydes with $CrCl_2$, see: (d) Still, W. C.; Mobilio, D. *J. Org. Chem.* **1983**, *48*, 4785. (e) Shibuya, H.; Kawashima, K.; Hori, K.; Murakami, N.; Kitagawa, I. *Chem. Lett.* **1986**, 85.

(4) Preparation of oxazolidines: (a) Senkus, M. *J. Am. Chem. Soc.* **1945**, *67*, 1515. (b) Bergmann, E. D.; Gil-Av, E.; Pichas, S. *J. Am. Chem. Soc.* **1953**, *75*, 358. For related use of chiral organotin enamines derived from amino alcohols in addition reactions to unsaturated alkenes, see: (c) deJeso, B.; Pommier, J.-C. *Tetrahedron Lett.* **1980**, 4511. (d) Stetin, C.; deJeso, B.; Pommier, J.-C. *J. Org. Chem.* **1985**, *50*, 3863.

(5) Agami, C.; Rizk, T. *Tetrahedron Lett.* **1985**, *41*, 537.

(6) Similar analysis of the trans (about the oxazolidine ring) isomer leads to the same expectation; note the "pseudo" C_2 symmetry in this case. For the use of chiral enamines derived from C_2 symmetric amines in enantioselective alkylation reactions, see: Whitesell, J. K.; Felman, S. W. *J. Org. Chem.* **1977**, *42*, 1663.

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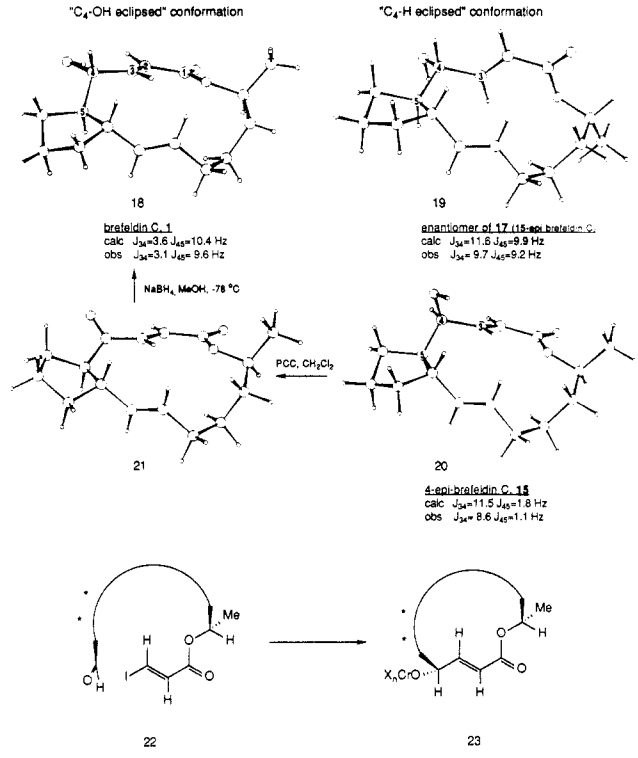
Scheme III



BF_3·Et_2O and the lithium anion of **10**[8] on aldehyde **9** with subsequent reduction. The expected *trans*-olefin product was obtained along with varying quantities of recovered aldehyde **9** (ca. 20%). After deprotection, the alcohol **11** ($[\alpha]^{27}_D$ = −50.6, ether) was transesterified with the β-iodo acrylate **12** with use of Otera's distannoxane catalyst **13**.[9] The latter transformation is notable as many attempts to couple the alcohol to the (sensitive) carboxylic acid derivative of **12** with conventional coupling reagents failed. Hydrolysis of the thioacetal ($[\alpha]^{27}_D$ = −12.4, ether) provided the cyclization substrate **14** ($[\alpha]^{27}_D$ = −6.6, ether). In a similar fashion, the diastereomeric substrate **16** was produced from **3** with use of (+)-norephedrin and pivalaldehyde in the cycloaddition reaction.

Macrocyclization of **14** and **16** by application of Kishi's modification[3b] of the Nozaki reaction proved to be both diastereoselective and as efficient as the more conventional ring closure methods previously examined in the brefeldin A series.[10b] Although the activation of the $CrCl_2$ reagent with catalytic amounts of $Pd(OAc)_2$ led to substantial quantities of diene products, the use of $Ni(acac)_2$ produced gratifying results. Subjection of **14** to these conditions provided a 4:1 mixture of 4-*epi*-brefeldin C (**15**) (mp = 119.5–120.5 °C) and (+)-brefeldin C (**1**).[11] Similar treatment of **16** resulted in intramolecular coupling and formation of the macrolide **17** with >10:1 facial selectivity.[12] The same sense of asymmetric induction, *relative to the preexisting* C_{15} *stereocenter*, is observed in the two addition reactions, although to varying extents (4:1, >10:1). We attempted to acquire some insight into the origins of the diastereoselection through computational modeling of the cyclization products (Scheme III), although we note that the small energy difference between diastereomeric transition-state structures in at least the first example complicates any such analysis.

The NMR spectra of brefeldin C and A show a striking similarity and are fully consistent with a solution conformation **18** that is identical with that found in the solid state of the latter macrolide.[10a] The low-energy conformation of 15-*epi*-brefeldin C (the enantiomer of **17**[13]) was calculated to be **19** by a multiconformer search with use of dihedral drivers of rotatable macrolide ring bonds (conformer **18** served as the input structure; the stereochemistry at C_{15} was inverted).[14] The low-energy conformer of **15** was found to be as shown in Scheme III (labeled as **20**). The observed spin–spin coupling constants of **1**, **15**, and **17** as well as brefeldin A analogues[15] are fully consistent with solution conformations of these compounds corresponding to **18**–**20**. Note that these conformations differ primarily by rotations about the C_3–C_4 bond. In the two intramolecular Nozaki reactions examined in this study, selectivity is observed for products that contain their allylic C_4–H bond eclipsed to the $\Delta^{2,3}$-olefin. This form of local conformational control[16,17] is illustrated by the generic structures **22** → **23** and may result from a minimization of steric ($A^{1,3}$) interactions with the chromium alkoxide salt in the transition state leading to cyclization product. The asymmetric induction follows from the conformational preferences of esters of secondary alcohols (depicted)[18] and the ring constraint of the cyclization reaction. The dominant effect of the C_{15} stereocenter (relative to the C_5 and C_9 stereocenters of the cyclopentyl ring) is consistent with the finding that the intermolecular Nozaki addition of **12** to the aldehyde derived from **11** (aqueous acetone, MeI) resulted in a 1:1 mixture of diastereomeric products.

The oxidation of **15** (=**20**) provided the corresponding ketone which is expected to exist in conformation **21**. The subsequent reduction proceeded, in analogy to the brefeldin A series,[19] in a stereospecific manner to give rise to synthetic (+)-brefeldin C (**1**) which exhibited TLC properties and 490 MHz ^{1}H NMR spectra that were identical with a sample of the natural product kindly supplied by Professor S. Nozoe (Tohoku University). The stereochemical outcome of this reaction can be understood in terms of a least hindered approach of the hydridic reagent to the ketone in conformer **21** (peripheral addition).[20]

In order for the reaction sequence described above to be translated into a practical total synthesis of brefeldin C, yield improvements for several transformations will be necessary. Despite this shortcoming, two new transformations of potential value in organic synthesis have been illustrated. The intramolecular enamine–enal cycloaddition has been shown to proceed with substantial asymmetric induction from certain chiral secondary amines. The intramolecular Nozaki coupling reaction has been utilized to form macrocyclic rings with useful levels of diastereoselection.

(7) (a) Julia, M.; Paris, J.-M. *Tetrahedron Lett.* **1973**, *49*, 4833. (b) Kocienski, P. J.; Lythgoe, B.; Ruston, J. *J. Chem. Soc., Perkin Trans. 1* **1978**, 829. For the use of BF_3·OEt_2 in sulfone anion additions, see: Achmatowicz, B.; Baranowska, E.; Daniewski, A. R.; Pankowski, J.; Wicha, J. *Tetrahedron Lett.* **1985**, *26*, 5597.

(8) Prepared in eight steps from methyl acetoacetate: (a) $RuCl_2$ [(*S*)-Binap], H_2. (b) DHP, PPTS, CH_2Cl_2. (c) DIBAL, CH_2Cl_2, −78 °C. (d) $(EtO)_2POCH_2CO_2Et$, NaH, THF. (e) H_2, Pd/C, EtOAc. (f) LAH, THF. (g) PPh_3, I_2, benzene, Δ. (h) $NaSO_2Ph$, DMF, 55 °C. The β-hydroxy ester [from (a)] was shown to have ca. 99% ee (optical rotation).

(9) Otera, J.; Yano, T.; Kawabata, A.; Nozaki, H. *Tetrahedron Lett.* **1986**, *27*, 2383.

(10) Structure determination of brefeldin A: (a) Weber, H. P.; Hauser, D.; Sigg, H. P. *Helv. Chim. Acta* **1971**, *54*, 2763. Syntheses: (b) Gais, H.-J.; Lied, T. *Angew Chem., Int. Ed. Engl.* **1984**, *23*, 145, and references therein.

(11) An acrylate byproduct resulting from the reductive deiodination of **14** was also isolated in 10% yield.

(12) An isomeric macrolide (not C_4 epimer), presumed to be a C_5 epimer from epimerization, results in 15% yield along with the acrylate byproduct.

(13) The enantiomer of **17** is rendered in order to facilitate a comparison of ring conformations.

(14) Conformational analysis was performed in the multiconformer mode of MacroModel at 60° resolution with rotations driven about the C_3–C_4, C_4–C_5, C_{14}–C_{15}, and C_{15}–O_{16} bonds. The C_{12}–C_{13} bond served as the ring closure bond (cf.: Still, W. C.; Romero, A. *J. Am. Chem. Soc.* **1986**, *108*, 2105). We thank Professor Still for a copy of his modeling program.

(15) The stereochemical assignments of **15** and **17** are in accord with the similar ^{1}H NMR data of brefeldin A analogues: Honda, M.; Hirata, K.; Sueoka, H.; Katsuki, T.; Yamaguchi, M. *Tetrahedron Lett.* **1981**, *22*, 2679.

(16) For related examples, see: Schreiber, S. L.; Sammakia, T.; Hulin, B.; Schulte, G. *J. Am. Chem. Soc.* **1986**, *108*, 2106 and references cited therein.

(17) For examples of similar local ester conformations in rings, see: Vedejs, E.; Dent, W. H.; Gapinski, D. M.; McClure, C. K. *J. Am. Chem. Soc.* **1987**, *109*, 5437 and references cited therein.

(18) Schweizer, W. B.; Dunitz, J. D. *Helv. Chim. Acta* **1982**, *65*, 1547.

(19) Corey, E. J.; Wollenberg, R. H. *Tetrahedron Lett.* **1976**, 4705. (b) Corey, E. J.; Wollenberg, R. H.; Williams, D. R. *Ibid.* **1977**, 2243. (c) Bartlett, P. A.; Green, F. R. *J. Am. Chem. Soc.* **1978**, *100*, 4858.

(20) Still, W. C.; Galynker, I. *Tetrahedron* **1981**, *37*, 3981.

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Supplementary Material Available: Experimental data for compounds **3–5**, **8–12**, and **14–17** (25 pages). Ordering information is given on any current masthead page.

Determination of the Structural and the Electronic Properties of Surfaces Using Scanning Tunneling Microscopy Coupled with Chemical Modifications

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Scanning tunneling microscopy[1] (STM) is a new technique that can provide real-space atomic-resolution images of surfaces in vacuum,[2] air,[3] and liquids.[4] The ability to image surfaces in air and in liquids with high resolution suggests that it may be possible to probe the molecular details of interfacial reactions in situ by using STM.[5] This technique should be particularly effective for probing surface reactivity because tunneling images contain both structural and electronic information (i.e., the two key factors that determine reactivity). However, few STM studies in air or in liquids have attempted to probe the contributions of these two important properties to observed images.[6,7] In this communication we report a new approach to this problem that involves the use of well-defined charge-transfer intercalation reactions to perturb the electronic properties at the surface of the layered transition-metal material TaS_2.

TaS_2 consists of covalently bound S–Ta–S layers that are held together by weak Van der Waals (VdW) interactions between the sulfur planes of adjacent layers. The sulfur atoms are in a hexagonal close-packed (hcp) arrangement with the tantalum metal centers coordinated in either octahedral or trigonal prismatic holes, depending on the crystal polytype.[8] Our studies focus on the octahedral form of this compound, 1T-TaS_2. Of particular importance to these structural-electronic investigations is the charge density wave (CDW) state in 1T-TaS_2.[8,9] The CDW state is a temperature dependent periodic distortion of the lattice and the electron density within the S–Ta–S layers. The lattice distortions (ca. 0.1 Å) are smaller than the lateral resolution of the STM[1] (1–2 Å), but the periodic variation of the electron density (wavelength ~12 Å) is sufficiently large to be resolved. Hence a key question to address is how does the CDW affect observed tunneling images? At temperatures ≤77 K the CDW state dominates the tunneling images of 1T-TaS_2 because the majority of the conduction electrons have condensed into this state.[10] Our studies have been carried out at room temperature where there are significantly more free carriers[9] and hence as with normal

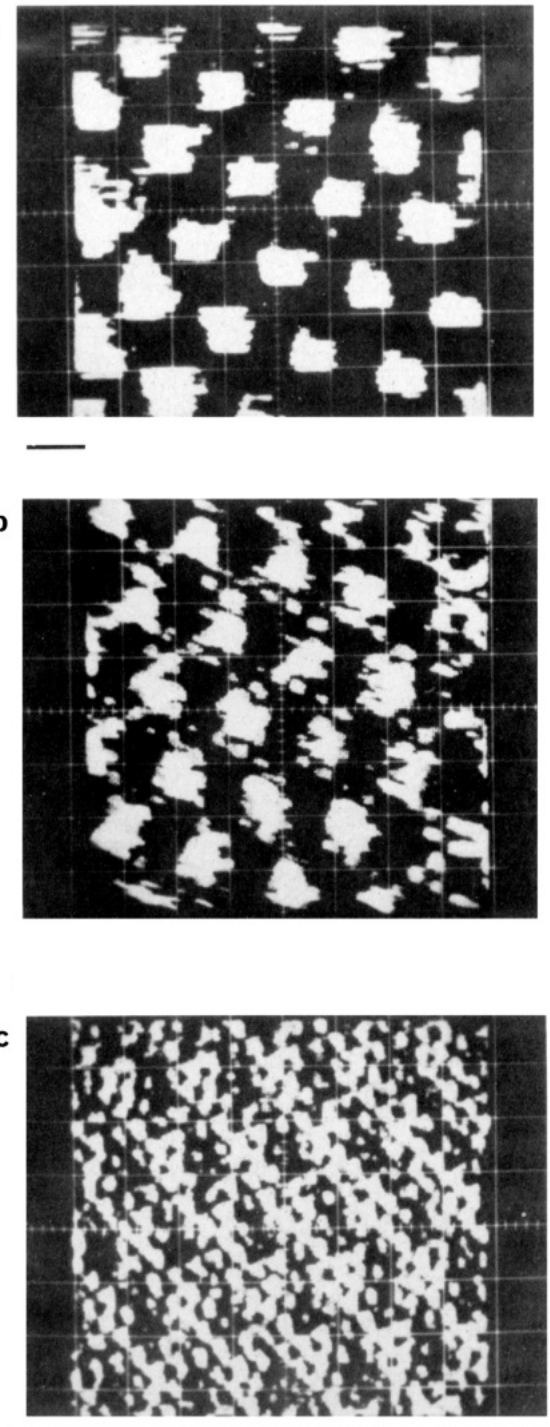

Figure 1. Top-view images of the (a) TaS_2, (b) TaS_2-$^1/_4$EDA, and (c) Li-TaS_2 samples recorded with the following STM parameters: (i) tunneling current = 1.8 nA, (ii) sample-tip bias voltage = 6 mV, and (iii) horizontal and vertical scan frequencies of 31 and 0.12 Hz, respectively. The horizontal and vertical distance scale, black line = 10 Å, is the same for the three images. The white spots correspond to peaks in the tunneling conductivity.

(1) (a) Binning, G.; Rohrer, H. *Angew. Chem., Int. Ed. Engl.* **1987**, *26*, 606–614. (b) Hansma, P. K.; Tersoff, J. *J. Appl. Phys.* **1987**, *61*, R1–R23. (c) Quate, C. F. *Phys. Today* **1986**, *39*, 26–33. (d) Golovchenko, J. A. *Science (Washington, D.C.)* **1986**, *232*, 48–53.

(2) (a) Becker, R. S. *Proc. Natl. Acad. Sci. U.S.A.* **1987**, *84*, 4667–4670. (b) Tromp, R. M.; Hamers, R. J.; Demuth, J. E. *Science (Washington, D.C.)* **1986**, *234*, 304–309.

(3) Park, S.-I.; Quate, C. F. *Appl. Phys. Lett.* **1986**, *48*, 112–114.

(4) (a) Sonnenfeld, R.; Hansma, P. K. *Science (Washington, D.C.)* **1986**, *232*, 211–213. (b) Giambattista, B.; McNairy, W. W.; Slough, C. G.; Johnson, A.; Bell, L. D.; Coleman, R. V.; Schneir, J.; Sonnenfeld, R.; Drake, B.; Hansma, P. K. *Proc. Natl. Acad. Sci. U.S.A.* **1987**, *84*, 4671–4674. (c) Liu, H.-Y.; Fan, F.-R.; Lin, C. W.; Bard, A. J. *J. Am. Chem. Soc.* **1986**, *108*, 3838–3839.

(5) (a) Lev, O.; Fan, F.-R.; Bard, A. J. *J. Electrochem. Soc.* **1988**, *135*, 783–784. (b) Foster, J. S.; Frommer, J. E.; Arnett, P. C. *Nature (London)* **1988**, *331*, 324–326. (c) Schneir, J.; Hansma, P. K. *Langmuir* **1987**, *3*, 1025–1027.

(6) Bryant, A.; Smith, D. P. E.; Binning, G.; Harrison, W. A.; Quate, C. F. *Appl. Phys. Lett.* **1986**, *49*, 936–938.

(7) Spectroscopic tunneling measurements have been used successfully in vacuum to study this problem but are difficult to carry out in air or in liquids.

(8) Wilson, J. A.; DiSalvo, F. J.; Mahajan, S. *Adv. Phys.* **1975**, *24*, 117–201.

(9) DiSalvo, F. J. In *Electron–Phonon Interactions and Phase Transitions*; Riste, T., Ed.; Plenum: New York, 1977; pp 107–136.

(10) (a) Coleman, R. V.; McNairy, W. W.; Slough, C. G.; Hansma, P. K.; Drake, B. *Surf. Sci.* **1987**, *181*, 112–118. (b) Slough, C. G.; McNairy, W. W.; Coleman, R. V.; Drake, B.; Hansma, P. K. *Phys. Rev. B* **1986**, *34*, 994–1005. (c) Coleman, R. V.; Drake, B.; Hansma, P. K.; Slough, G. *Phys. Rev. Lett.* **1985**, *55*, 394–397.

0002-7863/88/1510-5200$01.50/0