Table I. Extractability of OH^- in the Organic Phase as $(C_6H_{13})_4N^+OH^-$ with Tetrahexylammonium Salts 1a-c in Chlorobenzene-Aqueous NaOH Two-Phase Systems[a] at 25 and 60 °C

$(C_6H_{13})_4N^+X^-$			extractability of 1d,[b] %			
compd	X^-	T, °C	15% NaOH	30% NaOH	40% NaOH	50% NaOH
1a	Cl^-	25	19	13	10	8
		60	28	22	17	10 (48)[c]
1b	$MeSO_3^-$	25	14	5	3	3
		60	18	12	6	4 (33)[c]
1c	Br^-	25	2.5	1.5		≤0.5
		60	5	4	3	≤1 (9)[c]

[a] 40 mL of a chlorobenzene solution of 1a-c (4×10^{-2} M) and 40 mL of an aqueous solution of NaOH (15-50% w/w). [b] Evaluated via acid-base titration of the organic phase.[10] Percent expressed as $[Q^+OH^-]/([Q^+X^-] + [Q^+OH^-]) \times 100$, $Q^+ = (C_6H_{13})_4N^+$. Average of at least three determinations. [c] Values obtained from the selectivity constants, $K_{OH/X}^{sel}$, evaluated in the system PhCl-15% aqueous NaOH (see Table II).

Table II. Effect of the Aqueous Base Concentration on Both the Selectivity Constants $K_{OH/X}^{sel}$ (X = Cl, $MeSO_3$, Br) and Decomposition Percent (Hofmann Elimination) of Quaternary Salts 1a-c in Chlorobenzene-Aqueous NaOH Two-Phase Systems,[a] at 60 °C

	1a		1b		1c	
NaOH, %	$10^5K_{OH/Cl}$[b]	dec after 2 h, %[c]	$10^5K_{OH/MeSO_3}$[b]	dec after 7 h, %[c]	$10^5K_{OH/Br}$[b]	dec after 7 h, %[c]
15	91	2	33	7	2.2	1
30	25	17	6.5	36	0.67	15
40	9.3	76	1.0	65	0.25	
50	2.2	100	0.33	94	0.02	40

[a] For reaction conditions see footnote a, Table I. [b] Calculated values according to the equilibrium constant 2, see text. [c] Percents evaluated by following the disappearance of quaternary salt.

bility of OH^- was found to diminish (2.4-5 times) for all the anions. The percent of quaternary hydroxide **1d** found at 60 °C in the system PhCl-50% aqueous NaOH (10%, 4%, and ≤ 1% for Cl^-, $MeSO_3^-$, and Br^-, respectively)[9] is noticeably lower than that expected by a mass effect on the equilibrium 1 (i.e., 48%, 33%, and 9%)[11] (Table I). $K_{OH/X}^{sel}$ values so obtained dramatically diminish in the same sense (41, 100, and 110 times for Cl^-, $MeSO_3^-$, and Br^-, respectively) (Table II).

It is well-known[1,10] that, under PTC conditions in the presence of strongly alkaline aqueous solutions, lipophilic quaternary ammonium salts such as **1a-c** undergo Hofmann decomposition via OH^- extraction in the organic phase.[10] Degradation measurements, carried out in the PhCl-aqueous NaOH two-phase system at 60 °C, show that the decomposition extent[12] of **1a-c** is strongly enhanced by increasing the base concentration from 15% to 50% (Table II). These data are in striking contrast with the effect of aqueous base concentration on selectivity constants $K_{OH/X}^{sel}$. As shown in Table II, the highest degradation rates are indeed observed in the PhCl-50% aqueous NaOH system, where the lowest values of extracted OH^- are found.

This apparent discrepancy can be explained on the basis of the different hydration state of the hydroxide ion transferred in the organic phase at various aqueous base concentrations.

Indeed we found[13] that by increasing the aqueous NaOH concentration from 15% to 50% the specific hydration of $(C_6H_{13})_4N^+OH^-$ (**1d**) dissolved in chlorobenzene is progressively reduced from 11 to 3.5 molecules of water.[14] The higher anion destabilization, due to the lower hydration, produced dramatic enhancements of OH^- reactivity (up to 10^4 times)[13] and is likely the main reason for its reduced extractability in the organic phase.

These results, to the best of our knowledge, provide the first quantitative evaluation of the effect produced by the aqueous base concentration both on the selectivity coefficients $K_{OH/X}^{sel}$ and reactivity of OH^- under liquid-liquid PTC conditions.

Registry No. OH^-, 14280-30-9; $(CH_3(CH_2)_5)_4N^+Cl^-$, 5922-92-9; $(CH_3(CH_2)_5)_4N^+Br^-$, 4328-13-6; $(CH_3(CH_2)_5)_4N^+CH_3SO_3^-$, 105140-20-3.

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Received May 2, 1986

(10) Landini, D.; Maia, A.; Rampoldi, A. *J. Org. Chem.* **1986**, *51*, 3187.
(11) These data are calculated by the selectivity constants evaluted in the system PhCl-15% aqueous NaOH (see Table II).
(12) Unfortunately, it was impossible to determine the decomposition rate constants due to the complexity of the system.
(13) Landini, D.; Maia, A. *J. Chem. Soc., Chem. Commun.* **1984**, 1041.
(14) The specific hydration of $(C_6H_{13})_4N^+OH^-$ was determined by Karl Fischer analysis of the organic phase following a previously described procedure.[13]

Discorhabdin C, a Highly Cytotoxic Pigment from a Sponge of the Genus *Latrunculia*

Summary: The cytotoxic sponge pigment discorhabdin C (1) was shown, by a single-crystal X-ray diffraction study, to contain a new tetracyclic iminoquinone chromophore with a spiro 2,6-dibromocyclohexadienone.

Sir: The strong cytotoxicity of extracts from various sponges of the genus *Latrunculia* du Bocage was detected in our wide-scale screening of New Zealand's marine invertebrates for antiviral and antitumor activity.[1] Bioassay-directed analysis of one such extract led to the isolation of a compound named discorhabdin C (1).[2] This compound, the major pigment of the red-brown sponge, is toxic

(1) Presented in part at the PAC CHEM 84 Congress, Honolulu, HI, Dec., 1984.
(2) One characteristic of the family Latrunculiidae Topsent is the possession of discorhabd microscleres: Bergquist, P. R. *Sponges*; Hutchinson: London, 1978.

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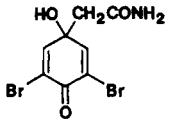
toward L1210 tumor cells at very low levels (ED_{50} < 100 ng/mL).

1



2

Percolation of MeOH/toluene (3:1) through the freeze-dried sponge led to an extract which was crudely partitioned by reverse-phase flash chromatography.[3] The cytotoxic fractions were combined and purified by two further stages of RPLC to give discorhabdin C (1), which was characterized as its hydrochloride: mp >360 °C; $[\alpha]_D$ 0°; IR (KBr) 3700–2500, 1675, 1585, 1540, 1325, 1020, 695 cm^{-1}; UV (MeOH) 245 (ϵ 28500), 351 (10000), 545 nm (500); UV (MeOH/KOH) 337 (ϵ 13000), 481 nm (1500). Low-resolution FABMS gave a complex collection of ions around m/z 464, MH^+, interpreted as a dibromo isotope pattern complicated by reduction in the FABMS matrix (as observed for quinones).[4] The molecular formula of the free base, $C_{18}H_{13}Br_2N_3O_2$, was determined by high-resolution FABMS.[5] Discorhabdin C hydrochloride was slightly soluble in MeOH and H_2O and soluble in Me_2SO. The ^1H NMR spectra indicated 11 nonexchangeable and three exchangeable protons.[6] The ^{13}C NMR spectrum showed 16 carbon signals, two of which each represented two equivalent carbons, and an SFORD experiment confirmed the presence of 11 protons attached to carbons.[7]

The complex heterocyclic framework of discorhabdin C (1) was determined by a single-crystal X-ray diffraction study. Precession photography of a small crystal of the trifluoroacetate salt indicated a triclinic crystal system. Accurate cell constants, determined by a least-squares fit of 23 high angle reflections, were a = 8.470 (2) Å, b = 10.562 (2) Å, c = 13.810 (2) Å, α = 67.84 (1)°, β = 78.53 (1)°, and γ = 88.38 (2)°, in space group $P\bar{1}$. Two molecules per unit cell gave a calculated density of 1.87 g cm^{-3}. All unique diffraction maxima with 2θ < 50° were collected, at 150 K, on a Nicolet R3m four-circle diffractometer using a variable speed ω scan technique and graphite monochromated Mo Kα radiation (0.7107 Å). A total of 3356 unique reflections were measured and, after correction for background, Lorentz, and polarization effects, the 2878 reflections with values of $F_0^2 > 3\sigma$ were used for the structure solution and for the refinement of structural parameters, by standard heavy atom methods.[8] The bromine positions were located from the Patterson synthesis and the remaining non-hydrogen atoms were located in subsequent Fourier calculations. The initial ambiguities in the scattering factor assignments were resolved with the aid of the spectroscopic data, and by analysis of the behavior of the temperature factors during the refinement calculations. Six water molecules were found in the unit cell. Hydrogen atoms were included in calculated positions. After applying an empirical absorption correction, a full least-squares refinement with anisotropic non-hydrogen atoms and isotropic hydrogens converged to a standard crystallographic R factor of 0.055.

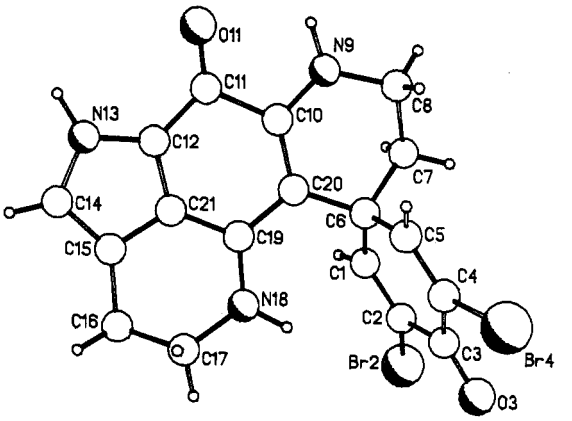


Figure 1. Computer-generated perspective drawing of discorhabdin C.

Figure 1 is a computer-generated perspective drawing of protonated discorhabdin C. The chromophore is approximately planar, with the two six-membered heterocyclic rings in half-chair conformations: C7 above and C17 below the plane. The N9–C10 and N18–C19 bond lengths are both about 1.33 Å, demonstrating similar double-bond character and delocalization of the positive charge between these two nitrogens. The free base is arbitrarily represented as the 1,4-iminoquinone tautomer (1). The cyclohexadienone ring is planar, tilted at an angle of 76° to the plane of the chromophore. There is considerable strain at C6, the spiro ring junction, with bond angles ranging from 104° to 113° and the C6–C7 bond unusually long at 1.58 Å. Also, the cyclohexadienone ring is "pushed away" from N18, as the angle C3–C6–C20 is 23° larger than the C3–C6–C7 angle. Conformational exchange must occur in solution since the NMR signals of C1 and C5 and of C2 and C4 are equivalent.

Discorhabdin C (1) has a new molecular skeleton, and we can find no previous reports of the pyrrolo[1,7]-phenanthroline skeleton of the iminoquinone chromophore. There is only one other report of metabolites (apart from sterols and fatty acids) from a *Latrunculia* species: the latrunculins are also toxins but are 2-thiazolidinone-bearing macrolides.[9] The 2,6-dibromocyclohexadienone portion of discorhabdin C (1) is clearly related to compound **2**, isolated from another sponge as a product of tyrosine metabolism.[10] Discorhabdin C (1) could well be derived from some such tyrosine derivative (C1 to C8, N9) and from a tryptamine derivative (C10 to C21, N13, and N18).

(3) Blunt, J. W.; Calder, V. L.; Fenwick, G. D.; Lake, R. J.; McCombs, J. D.; Munro, M. H. G.; Perry, N. B., submitted for publication in *J. Nat. Prod.*

(4) Cooper, R.; Unger, S. *J. Antibiot.* **1985**, *38*, 24.

(5) MH^+, m/z 461.9451, $C_{18}H_{14}{}^{79}Br_2N_3O_2$ requires 461.9452.

(6) ^1H NMR (MeOH-d_4, 300 MHz) δ 7.73 (s, 2 H, H1 + H5), 7.22 (s, 1 H, H14), 3.79 (t, J = 7 Hz, 2 H, H17), 3.73 (t, J = 6 Hz, 2 H, H8), 2.90 (t, J = 7 Hz, 2 H, H16), 2.12 (t, J = 6 Hz, 2 H, H7); ^1H NMR (Me_2SO-d_6, 80 MHz) δ 13.3 (s, 1 H, H13), 10.3 (s, 1 H, H9), 8.3 (s, 1 H, H18), 7.8 (s, 2 H, H1 + H5), 7.5 (s, 1 H, H14), 4.0–3.6 (m, 4 H, H8 + H17), 3.0 (t, J = 7 Hz, 2 H, H16), 2.1 (br s, 2 H, H7).

(7) ^{13}C NMR (Me_2SO-d_6, 20 MHz) 171.5 (s, C3), 165.5 (s, C11), 153.3 (s), 151.9 (s), 151.4 (2 × d, C1 + C5), 127.8 (d, C14), 123.7 (s), 123.3 (s), 122.7 (2 × s, C2 + C4), 120.0 (s), 91.8 (s, C20), 44.8 (s, C6), 43.8 (t, C17), 38 (t, C8), 33.8 (t, C7), 18.2 (t, C16).

(8) All calculations (including diagrams) were done on a Nova 4X computer by using SHELXTL: Sheldrick, G. M. "SHELXTL User Manual"; Nicolet XRD Corporation: Cupertino, CA, 1983; Revision 4.

(9) Kashman, Y.; Groweiss, A.; Lidor, R.; Blasberger, D.; Carmely, S. *Tetrahedron* **1985**, *41*, 1905.

(10) Tymiak, A. A.; Rinehart, K. L., Jr. *J. Am. Chem. Soc.* **1981**, *103*, 6763.

Discorhabdin C (1) represents a new class of potential antitumor agents and is being tested further. Related compounds, isolated from another *Latrunculia* species, are also being studied.

Acknowledgment. This work was supported by the Harbor Branch Oceanographic Institution, Princeton, NJ, the Canterbury Medical Research Foundation, and the New Zealand University Grants Committee. Sponge identification was by Dr. Graham Fenwick, and bioassays were made by Vicky Calder, both of this Department. Low-resolution FABMS results were provided by Dr. Pat Holland, Soil Research Institute, Ruakura. High-resolution FABMS measurements were provided by J. C. Cook, Jr., University of Illinois. Low-temperature X-ray work was done in this Department with the help of Dr. Ward T. Robinson.

Registry No. 1, 105372-81-4; 1·HCl, 105372-82-5.

Supplementary Material Available: Tables of fractional coordinates, thermal parameters, bond distances and bond angles (5 pages). Ordering information is given on any current masthead page.

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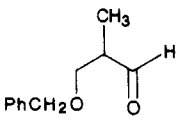
Dramatic Effects of Oxygen Substituents on 1,3-Asymmetric Induction in Additions of Allyltriphenylstannane to β-Alkoxy Aldehydes: A Chemical and Spectroscopic Investigation

Summary: The level of stereoselectivity realized in the Lewis acid mediated additions of allyltriphenylstannane to β-alkoxy aldehydes chiral by virtue of substitution at C_3 depends critically upon the choice of the β-oxygen substituent as well as the choice of Lewis acid. The chemical behavior seen in such addition reactions correlates very well with the solution structures of the Lewis acid complexes formed from such aldehydes and various Lewis acids, as determined by variable-temperature ^1H and ^{13}C NMR spectroscopy.

Sir: Recently we reported the results of an NMR investigation of the structures resulting from exposure of the β-alkoxy aldehydes 1 and **2a** to $TiCl_4$, $SnCl_4$, and $MgBr_2$.[1]



1

The results clearly showed that both $TiCl_4$ and $MgBr_2$ afforded a bidentate chelate with **2a** in which the methyl substituent occupied an axial (or pseudoaxial) position, which nicely rationalizes the stereoselectivity realized in nucleophilic additions to such chelates. We now report that the choice of O-substituent plays a critical role in determining the conformation of chelates derived from aldehydes such as **2** in solution and that the stereoselectivity realized in the addition of allylstannanes to such chelates is consistent with predictions based upon the preferred solution conformation of such chelates. Moreover, the reluctance of certain combinations of substrate and Lewis acid to yield conformationally rigid bidentate chelates is also consistent with the chemistry observed with such compounds.

Variable-temperature ^1H and ^{13}C NMR spectroscopy provides a sensitive assay for chelation of aldehydes of general structure **2** with Lewis acids. In this study, we examined via both spectroscopy and reaction chemistry (vide infra) the species derived from reaction of β-alkoxy aldehydes **2a–e** with $MgBr_2$, $TiCl_4$, and $SnCl_4$—Lewis acids that have shown stereoselectivities in Lewis acid mediated nucleophilic additions to β-alkoxy aldehydes consistent with "chelation control".[2] Information regarding solution conformation is available simply by examination of the coupling constants between protons at C_2 and C_3 for cases where bidentate chelation is established. The most pertinent NMR data is summarized in Table I.[3]

The β-benzyloxy aldehyde **2a** with a methyl substituent at C_3 affords a well-behaved bidentate chelate with $MgBr_2$ over the temperature range of 0–20 °C in which the methyl group occupies an axial position. With $TiCl_4$, chelation is again observed (−93 to −70 °C) and the methyl group is again axial. Parallel behavior is observed with **2b**, where the methyl substituent is replaced by *n*-hexyl.[4] However, simply changing the O-substituent to methyl (**2c**) results in a dramatic change in the preferred conformation of such chelates: the *n*-hexyl group at C_3 now occupies an *equatorial* position in the chelates formed by reaction with $MgBr_2$ or $TiCl_4$. With the *O*-ethyl compound **2d**, the *n*-hexyl substituent reuturns to an essentially axial position in the chelates derived from both Lewis acids. Thus steric effects resulting from the nature of the *O*-substituent are very important in determining the preferred solution conformation of such chelates. The preferred solution conformations as determined by NMR spectroscopy are shown in Figure 1.

A variety of observations suggest that both temperature and steric congestion at and around the ether oxygen are also very important in determining the extent to which chelation can be realized in such systems, particularly with $SnCl_4$. While formation of a well-defined bidentate chelate is observed from **1a** (in which no alkyl substituent is present at C_3) and $SnCl_4$ by ^1H NMR between −80 and −60 °C, the results obtained with the C_3 substituted materials **2a–c** are rather different. The ^1H spectrum from the more sterically demanding *O*-methyl derivative **2c** and $SnCl_4$ at −80 °C contains slightly broadened lines in which the loss of resolution prevents a direct extraction of the solution conformation.[5] The broadened lines suggest the presence

(1) Keck, G. E.; Castellino, S. *J. Am. Chem. Soc.* **1986**, *108*, 3847.

(2) (a) Keck, G. E.; Boden, E. P. *Tetrahedron Lett.* **1984**, *25*, 265. (b) Keck, G. E.; Boden, E. P. *Tetrahedron Lett.* **1984**, *25*, 1879. (c) Keck, G. E.; Abbott, D. E. *Tetrahedron Lett.* **1984**, *25*, 1883. (d) Keck, G. E.; Abbott, D. E.; Wiley, M. R. *Tetrahedron Lett.*, in press. (e) Reetz, M. T.; Kesseler, K.; Jung, A. *Tetrahedron Lett.* **1984**, *25*, 729. (f) Kiyooka, S.; Heathcock, C. H. *Tetrahedron Lett.* **1983**, *23*, 4756. (g) Reetz, M. T.; Jung, A. *J. Am. Chem. Soc.* **1983**, *105*, 4833. (h) Reetz, M. T. *Angew. Chem., Int. Ed. Engl.* **1984**, *23*, 556.

(3) All NMR spectra were recorded on a Varian XL 300 NMR spectrometer operating at 300 MHz for ^1H and 75 MHz for ^{13}C by using 0.1 M solutions of substrates in CD_2Cl_2. Decomposition of the substrate occurs in the presence of $TiCl_4$ at temperatures greater than −50 °C. Compound **2b**, however, decomposes at temperatures greater than −65 °C. The $MgBr_2$ chelates were studied between 0 and 20 °C due to the insolubility of some of the chelates at lower temperatures.

(4) In the case of **2b** with $TiCl_4$, the solution conformation cannot be extracted directly from the observed ^1H spectrum or by decoupling. In this case, the diastereotopic methylenes at C_2 appear as a broad singlet with $w_{1/2}$ = 13.4 Hz. Lineshape analysis in conjunction with spin simulation reveals that no large vicinal coupling to the C_3 methine can be present in this case.

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