Table I

nucleic acid	Na^+(M)	K_{EB}	K_{BMSp}
calf thymus	0.075	2×10^5 M^{-1} [b]	$\geq 2 \times 10^{11}$ M^{-1}
calf thymus	1.0	4.2×10^4 M^{-1}	1.5×10^7 M^{-1}
(dG-dC)·(dG-dC)	1.0	2.0×10^4 M^{-1}	7.5×10^7 M^{-1}
dA·dT	1.0	2×10^3 M^{-1} [a]	4.4×10^4 M^{-1}
rA·dT	1.0	2.3×10^5 M^{-1} [a]	2.3×10^8 M^{-1}

[a] From Bresloff and Crothers.[9] [b] Data of LePecq[4c] reanalyzed in terms of von Hippel-McGhee equations.

trolyte theory of Manning.[16] As shown by Record et al.,[10] the observed binding affinity, K_{obsd}, of a ligand at a monovalent cation concentration equal to M^+ can be estimated by the equation $K_{obsd} = K_0[M^+]^{n\psi}$, where K_0 is the binding affinity at 1 M Na^+, n is the number of ion pair interactions which the ligand makes with nucleic acid, and ψ is the charge density parameter which is known for a variety of nucleic acids. For example, from Table I, at 1 M Na^+ the binding affinity of BMSp is 1.5×10^7 M^{-1} or 3.6×10^2 times greater than EB. At low salt, 0.075 M, where electrostatic contributions become more important, the estimated affinity of BMSp for calf thymus is 1×10^{11} M^{-1} or 10^6 times greater than EB. This estimate compares favorably with the estimated affinity, $K \geq 2 \times 10^{11}$ M^{-1}, determined experimentally from spectrophotometric titrations.[17]

In addition, the binding specificity of BMSp compared to EB is substantially increased. From the work of Crothers,[9] it is known that the binding of the monomer EB to the RNA-DNA hybrid rA·dT is favored over the DNA-DNA duplex dA·dT by a factor of 100. This 100-fold specificity exhibited by EB increases to 5200 for BMSp. Since the only difference between rA·dT and dA·dT is the presence of the 2′-hydroxyl group on the sugar ring and not base sequence, these results indicate that the specificity which BMSp and EB[9] exhibit for certain nucleic acids can arise from *preferential recognition of different nucleic acid conformations.*

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References and Notes

(1) (a) Gate, E. F.; Cundliffe, E.; Reynolds, P. E. "The Molecular Basis of Antibiotic Action"; Wiley: New York, 1972. (b) Corcoran, J. W.; Hahn, F. E., Eds. "Mechanism of Action of Antimicrobial and Antitumor Agents"; Springer-Verlag: New York, 1975. (c) Hahn, F. E., Ed. "Progress in Molecular and Subcellular Biology", Vol. 2; Springer-Verlag: New York, 1971. (d) Sartorelli, A. C., Ed. "Cancer Chemotherapy", ACS Symposium Series No. 30; American Chemical Society: Washington, D.C., 1976. (e) Conners, T. A.; Roberts, J. J., Ed. "Platinum Coordination Compounds in Cancer Chemotherapy"; Springer-Verlag: Heidelberg, 1974.
(2) Lerman, L. S. *J. Mol. Biol.* **1961**, *3*, 18.
(3) (a) Waring, M. J.; Wakelin, F. P. G. *Nature (London)* **1974**, *252*, 653. (b) Waring, M. J. *Biochem. J.* **1976**, *157*, 721. (c) LePecq, J. B.; Bret, M. L.; Barbet, J.; Roques, B. *Proc. Natl. Acad. Sci. U.S.A.* **1975**, *72*, 2915. (d) Canellakis, E. S.; Shaw, Y. H.; Hammers, W. E.; Schwartz, R. A. *Biochim. Biophys. Acta* **1976**, *418*, 277. (e) Fico, R. M.; Chem, T. K.; Canellakis, E. S. *Science* **1977**, *198*, 53. (f) Dervan, P. B.; Becker, M. M. *J. Am. Chem. Soc.* **1978**, *100*, 1968. (g) Kuhlmann, K. F.; Charbeneau, N. J.; Mosher, C. W. *Nucleic Acids Res.* **1978**, *5*, 2629.
(4) (a) Bresloff, J. L.; Crothers, D. M. *J. Mol. Biol.* **1975**, *95*, 103. (b) Bauer, W.; Vinograd, J. *J. Mol. Biol.* **1968**, 33, 141. (c) LePecq, J. B.; Paoletti, C. *ibid.*, **1967**, *27*, 87. (d) Waring, M. J., in ref 1b, pp 141–165.
(5) (a) Hirschman, S. Z.; Leng, M.; Felsenfeld, G. *Biopolymers* **1967**, *5*, 277. (b) Stevens, L. *Biol Rev.*, **1970**, *45*, 1.
(6) Becker, M. M.; Dervan, P. B. California Institute of Technology, unpublished work.
(7) D. Straus, California Institute of Technology, unpublished work.
(8) The unwinding angle of BMSp increases from 1.5 to twice that of EB when the salt concentration is raised from 0.075 to 1 M Na^+.[6]
(9) J. L. Bresloff, Ph.D. Dissertation, Yale University, 1974. We thank Dr. D. M. Crothers for informing us of these results. This data was readjusted by a factor of 2.3 to correct for solvent differences.
(10) Record, M. T.; Lohman, T.; DeHaseth, P. *J. Mol. Biol.* **1976**, *107*, 145.
(11) LePecq, J. B. *Methods Biochem. Anal.* **1971**, *20*, 41.
(12) Scatchard, G. *Ann. N. Y. Acad. Sci.* **1949**, *51*, 660.
(13) McGhee, J. D.; von Hippel, P. H. *J. Mol. Biol.* **1974**, *86*, 469. See also Crothers, D. M. *Biopolymers* **1968**, *6*, 515.
(14) The binding of BMSp to poly(dA)·poly(dT) involves more than one BMSp-DNA complex. An alternative approach was necessary to analyze this data.[6]
(15) Müller, W.; Crothers, D. M.; Waring, M. J. *Eur. J. Biochem.* **1973**, *39*, 223; Müller, W.; Crothers, D. M. *ibid.*, **1975**, *54*, 267.
(16) Manning, G. *J. Chem. Phys.* **1969**, *51*, 924.
(17) See footnote 32 in ref 3f. Spectrophotometric data revealed the percent bound BMSp at BMSp/BP = 0.25 to be ≥97% at 0.075 M Na^+.
(18) National Institutes of Health Trainee (GM-01262).
(19) Alfred P. Sloan Research Fellow, 1977–1979. Camille and Henry Dreyfus Teacher-Scholar Grant Recipient, 1978–.

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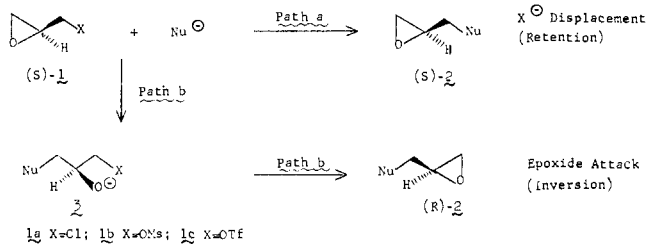
Mode of Nucleophilic Addition to Epichlorohydrin and Related Species: Chiral Aryloxymethyloxiranes

Sir:

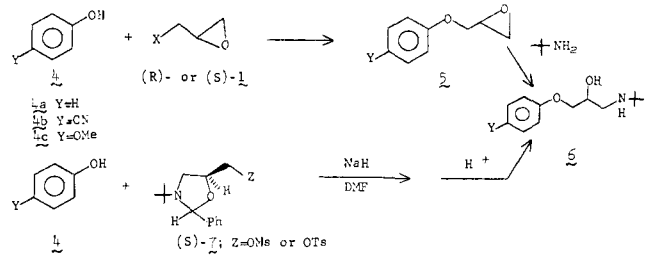
Nucleophilic attack on epichlorohydrin (**1a**) or a related methyloxirane (**1**) generally results in the formation of a new methyloxirane **2**.[1-8] In principle, **2** may be derived from **1** via two distinct processes: (1) direct displacement of the leaving



group (path a) or (2) initial epoxide attack (**3**) followed by extrusion of the leaving group (path b). In spite of considerable effort, the mechanism of such a nucleophilic addition has yet to be conclusively established.[4-7]

Since the stereochemistry of the products obtainable from chiral **1**[9,10] according to paths a or b would not be identical, a determination of the absolute configuration and chiral purity of **2** would establish the mode of nucleophilic addition. Our results from the reactions of chiral **1**[9,10] with various phenols to give chiral aryloxymethyloxiranes reported herein indicate that the mode of nucleophilic addition depends on the leaving group involved and the conditions used.

The reactions of (*R*)- and/or (*S*)-**1** with phenols **4a–c** have been examined using two sets of conditions: (1) refluxing in acetone or CH_2Cl_2 in the presence of K_2CO_3 and (2) stirring **1** with the preformed phenoxide in DMF or THF. The *S*/*R* ratios presented were determined by an examination of the ^1H NMR spectra of **5** in the presence of a chiral shift reagent, Eu(hfbc)$_3$,[9,12,13] and by optical rotation.



The absolute configuration of **5** obtained from (*R*)-**1a** under acetone-K_2CO_3 conditions was established by the reaction with *tert*-butylamine to give **6**, which was then compared with chirally pure (*S*)-**6** synthesized from (*S*)-**7**.[14] The unambiguous assignment of the predominant configuration of **5** and **6** derived from (*R*)-**1a** as (*S*)[15] was thus possible. The *S*/*R* ratios

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Table I. Chirality of Aryloxymethyloxiranes **5** from Chiral **1**

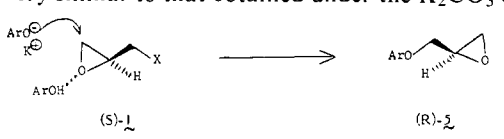
entry	**1** (no. of equiv)[a]	**4**	condn,[b] time (h)	% yield	**5**	*S*/*R* ratio[c]	% retention
1	(*R*)-**1a** (2)	**4a**	A, 40	73	**5a**	95/5	5
2	(*R*)-**1a** (2)	**4b**	A, 40	70	**5b**	92/8	8
3	(*R*)-**1a** (2)	**4c**	A, 60	88	**5c**	91/9	9
4	(*R*)-**1a** (2)	**4a**	A, 40	60	**5a**	87/13	13
5	(*S*)-**1a** (2)	**4a**	A, 48	65	**5a**	5/95	5
6	(*S*)-**1a** (2)	**4b**	A, 40	74	**5b**	10/90	10
7	(*S*)-**1a** (2)	**4c**	A, 60	80	**5c**	3/97	3
8	(*R*)-**1a** (2)	**4a**	D, 18	65	**5a**	50/50	50
9	(*R*)-**1a** (2)	**4b**	D, 18	35	**5b**	70/30	30
10	(*R*)-**1a** (2)	**4c**	D, 18	83	**5c**	50/50	50
11	(*S*)-**1a** (2)	**4a**	D,[d] 18	70	**5a**	50/50	50
12	(*S*)-**1a** (2)	**4b**	D, 18	32	**5b**	30/70	30
13	(*S*)-**1b** (2)	**4a**	A, 20	80	**5a**	20/80[g]	20
14	(*S*)-**1b** (1)	**4a**	D, 18	53	**5a**	85/15	85
15	(*S*)-**1b** (1)	**4b**	D, 18	37	**5b**	80/20	80
16	(*S*)-**1b** (1)	**4c**	D, 18	84	**5c**	85/15	85
17	(*S*)-**1c** (1)	**4a**	C, 0.2	91	**5a**	≥98/2	≥98
18	(*S*)-**1c** (1)	**4b**	C, 0.2	97	**5b**	≥98/2	≥98
19	(*S*)-**1c** (1)	**4c**	C, 0.2	96	**5c**	≥98/2	≥98
20	(*S*)-**1c** (1)	**4a**	B, 40	93	**5a**	≥98/2	≥98
21	(*S*)-**1c** (1)	**4b**	B, 40	82	**5b**	≥98/2	≥98
22	(*S*)-**1c** (1)	**4c**	B, 110	80	**5c**	≥98/2	≥98
23	(*S*)-**1a** (2)	**4a**	E,[e] 40	50	**5a**	15/85	15
24	(*S*)-**1b** (1)	**4a**	E,[e] 20	70	**5a**	70/30	70
25	(*S*)-**1a** (2)	**4a**	F,[f] 40	90	**5a**	7/93	7

[a] **1** (2 equiv) was used in some instances to diminish the importance of the reaction of product **5** with additional phenol. [b] Reaction conditions: A, K_2CO_3–refluxing acetone; B, K_2CO_3–refluxing CH_2Cl_2; C, NaH–THF used to form phenoxide, and then (*S*)-**1c** was added in CH_2Cl_2; D, NaH–DMF. [c] Purification of all samples was accomplished by thick layer chromatography on silica gel GF (Analtech, 2000 μ) eluting with 0.5–2% CH_3OH–CH_2Cl_2 prior to the analysis of chiral purity. Enanthiomeric ratios were determined from the ^1H NMR spectra in the presence of Eu(hfbc)$_3$ and from optical rotation. Errors are generally ±2–3%. [d] KH was used in the place of NaH for this experiment. [e] Preformed potassium phenoxide, formed in THF (the THF was evaporated), was reacted with (*S*)-**1a** or (*S*)-**1b** in refluxing acetone. [f] Preformed potassium phenoxide (as in *e*) was reacted with (*S*)-**1a** in refluxing acetone in the presence of 1 equiv of phenol. [g] Product **5a** was converted to the corresponding **6a** prior to the analysis of the enantiomeric ratio.

for **5** prepared under the other experimental conditions could then be ascertained.

Racemization of the starting materials or products under any of the reaction conditions was not observed[16] with the exception of (*R*)-**1a** in acetone.[17] Gas chromatographically purified (*R*)-**1a**[9] exhibited no such racemization. Since (*S*)-**1a** also showed no racemization in control experiments, the preference for path b under the acetone–K_2CO_3 conditions was found to fall in the range of 90–97% (entries 5–7).

In all cases, the ratio of direct displacement (path a) to epoxide attack (path b) increased as expected for the series (**1a** < **1b** < **1c**).[18] Upon reaction with preformed phenoxides in DMF or acetone, chiral **1a** and **1b** gave less selectivity for path b when compared with the acetone–K_2CO_3 conditions.[20] Therefore, another mechanism leading to this higher selectivity for epoxide attack under the acetone–K_2CO_3 conditions was implicated.[20] A reasonable pathway involving a facilitation via complexation is shown below. In support of this mechanism, a ratio very similar to that obtained under the K_2CO_3 conditions resulted from the reaction of (*S*)-**1a** with potassium phenoxide in the presence of 1 equiv of phenol. In the absence of this activating complexation, the epoxide was an effective leaving group only when it was in competition with the relatively poor Cl^- leaving group.



(S)-1 (R)-2

A pathway involving direct displacement (path a) was the only one observed in the reaction of nucleophiles **4a–c** with the triflate (*S*)-**1c**. The results obtained under refluxing CH_2Cl_2–K_2CO_3 conditions suggest that phenols may be nucleophilic enough to react with **1** provided that a very good leaving group is involved.

Our results indicate that these three carbon chiral units may react via either mode of nucleophilic addition depending on the leaving group involved and the reaction conditions used. Synthetically, (*S*)-**1c** is extremely useful for the preparation of the corresponding (*S*)-**5** in good yield and in chirally pure form. Alternatively, (*R*)-**5** having a high chiral purity may be obtained from (*S*)-**1a** under the acetone–K_2CO_3 conditions.

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References and Notes

(1) Fabris, H. J. *J. Org. Chem.* **1967,** *32,* 2031. Koelsch, C. F.; McElvain, S. M. *J. Am. Chem. Soc.* **1930,** *52,* 1164. Gilman, H.; Hofferth, B.; Honeycutt, J. *ibid.* **1952,** *74,* 1594. Normant, H. *C. R. Acad. Sci.* **1944,** *219,* 163. Kwart, H.; Goodman, A. L. *J. Am. Chem. Soc.* **1960,** *82,* 1947. Mouzin, G.; Cousse, H.; Bonnaud, B. *Synthesis* **1978,** 304.
(2) Ross, J. H.; Baker, D.; Coscia, A. T. *J. Org. Chem.* **1964,** *29,* 824. Landor, S. R.; Pepper, E. S. *J. Chem. Soc. C* **1966,** 2283. Mesropynan, E. G.; Bunyatyan, Yu, A.; Aliev, R. K. *Khim. Geterotsikli Soedin* **1974,** 22; Knunyanz, I. L. *Chem. Ber.* **1935,** *68B,* 397. Heywood, D. L.; Phillips, B. *J. Am. Chem. Soc.* **1958,** *80,* 1257.
(3) Augstein, J.; Green, S. M.; Monro, A. M.; Potter, G. W. H.; Worthing, C. R.; Wrigley, T. I. *J. Med. Chem.* **1965,** *8,* 446. Howe, R.; Rao, B. S.; Chodnekar, M. S. M. *ibid.* **1970,** *13,* 169. Wasson, B. K.; Gibson, W. K.; Stuart, R. S.; Williams, H. W. R.; Yates, C. H. *ibid.* **1972,** *15,* 651. Crowther, A. F.; Smith, L. H. *ibid.* **1968,** *11,* 1009.
(4) Eliel, E. L.; Rerick, M. N. *J. Am. Chem. Soc.* **1960,** *82,* 1362. Van Zyl, G.; Zack, J. F.; Huyser, E. S.; Cook, P. L. *ibid.* **1954,** *76,* 707. Leuchs, H. *Chem. Ber.* **1905,** *38,* 1937. Culvenor, C. C. J.; Davies, W.; Haley, F. G. *J. Chem. Soc.* **1950,** 3123. Vander Werf, C. A.; Heisler, R. Y.; McEwen, W. E. *J. Am. Chem. Soc.* **1954,** *76,* 1231.
(5) Haynes, L. J.; Heilbron, I.; Jones, E. R. H.; Sondheimer, F. *J. Chem. Soc.* **1947,** 1583.
(6) Maerker, G.; Carmichael, J. F.; Port, W. S. *J. Org. Chem.* **1961,** *26,* 2681.
(7) Hiskey, C. F.; Slates, H. L.; Wendler, N. L. *J. Org. Chem.* **1956,** *21,* 429. Waters, R. C.; Vander Werf, C. A. *J. Am. Chem. Soc.* **1954,** *76,* 709. Rowton, R. L.; Russell, R. R. *J. Org. Chem.* **1958,** *23,* 1057.
(8) Nakabayashi, N.; Masuhara, E.; Iwakura, Y. *Bull. Chem. Soc. Jpn.* **1966,** *39,* 413.
(9) Baldwin, J. J.; Raab, A. W.; Mensler, K.; Arison, B. H.; McClure, D. E. *J. Org. Chem.* **1978,** *43,* 4876.
(10) The triflate (*S*)-**1c** was prepared from (*R*)-glycidol[9] following procedures described by Vedejs:[11] bp 35–39 °C (0.2 mm). Chiral shift NMR analysis of (*S*)-**1b** and (*S*)-**1c**[9] indicated an enantiomeric purity of ≥98%.
(11) Vedejs, E.; Engler, D. A.; Mullins, M. J. *J. Org. Chem.* **1977,** *42,* 3109.
(12) Fraser, R. R.; Pettit, M. A.; Saunders, J. K. *Chem. Commun.* **1971,** 1450.
(13) Eu(hfbc)$_3$ = tris[3-heptafluorobutyryl-*d*-camphorato]europium(III). The use of 0.1–0.3 molar equiv of Eu(hfbc)$_3$/mol of **5** or **6** resulted in a 10–30-Hz separation of the enantiomeric signals under analysis.
(14) Weinstock, L. M.; Mulvey, D. M.; Tull, R. *J. Org. Chem.* **1976,** *41,* 3121. Baldwin, J. J.; Hirschmann, R.; Lumma, P. K.; Lumma, W. C., Jr.; Ponticello, G. S.; Sweet, C. S.; Scriabine, A. *J. Med. Chem.* **1977,** *20,* 1024.
(15) This correlation was carried out with **5** from the first three entries of Table I. The *S*/*R* ratios for **6** agreed with those observed for the precursors **5** within experimental error (±2–3%).
(16) No decrease in optical rotation resulted when solutions of (*R*)-**1a**, (*S*)-**1a**, or (*S*)-**1b** were stirred in DMF for periods of time longer than those used for the reactions; the addition of the nucleophilic product, NaCl or NaOMs, to these reactions caused no detectable racemization. There was no decrease in optical rotation of (*S*)-**1a** or (*S*)-**1b** in refluxing acetone; upon recovery of (*S*)-**1a** or (*S*)-**1b**, specific rotations comparable with those of the starting materials were also observed. Since (*S*)-**1c** produced enantiomerically pure **5** under either set of conditions, the racemization of (*S*)-**1c** was clearly unimportant. No decrease in optical rotation was observed with (*R*)-**5a** in either DMF or acetone.
(17) The slow racemization of (*R*)-**1a** in the presence or absence of K_2CO_3 appears to be due to a trace nucleophilic impurity and may be responsible for the somewhat variable results exemplified by entries 1 and 4.
(18) The hardness[19] of the leaving group also increases in the order **1a** < **1b** < **1c** and is consistent with the increase in the amount of direct displacement with relatively hard nucleophiles like phenoxides. The preference shown by the softer **4b** for epoxide attack when compared with **4a** or **4c** (entries 8–12) may indicate a trend in which softer nucleophiles favor epoxide attack over direct displacement in reactions with **1a**.

(19) Ho, T.-L. *Chem. Rev.* **1975**, *75*, 1; R. G. Pearson, Ed. "Hard and Soft Acids and Bases", Dowden, Hutchinson & Ross: Stroudsburg, Pa., 1973.
(20) Potassium phenoxide in refluxing acetone showed a greater preference for path b than potassium or sodium phenoxide in DMF; therefore, a solvent effect is also operating in addition to this proposed complexation with phenol.
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A Manganese Phthalocyanine–Dioxygen Molecular Adduct

Sir:

In 1959, Elvidge and Lever[1] reported the ability of manganese(II) phthalocyanine (**1**) to bind molecular oxygen in pyridine solution, finally to yield[2] μ-oxo-bis(pyridinemanganese(III) phthalocyanine) (**2**) (L = pyridine) whose formation proceeds through an intermediate proposed[1] to be an oxygen adduct. Calvin and co-workers[3,4] subsequently proposed that the intermediate is $(HO)Mn^{III}Pc$ (**3**).[5] Clarification of this system is of considerable importance because of relevance to the role played by manganese in photosynthesis[6] and in certain dismutases.[7] The adduct[8] is now shown to be $(O_2)MnPc$ (**4**), as independently proposed by Uchida and co-workers,[9] who, however, presented little supporting evidence.

Oxygenation proceeds more readily in *N,N*-dimethylacetamide (DMA) because of a weaker manganese solvent interaction. Reaction of oxygen with $Mn^{II}Pc$ (**1**) in spectroquality DMA affords the sparingly soluble adduct **4** which precipitates from solution.[10] The infrared spectrum of **4** was recorded after preparation from both $^{16}O_2$ and $^{18}O_2$. Figure 1 illustrates the region near 1100 cm^{-1} where an additional band at 1094 cm^{-1} in the oxygen-18 spectrum appears to correspond with a pronounced shoulder in the oxygen-16 spectrum at ~1154 cm^{-1}. These bands may be tentatively assigned as the ν(O–O) stretching vibrations of a coordinated *terminal* superoxide ion.[11] Bridging superoxides do not absorb in this region in the infrared.[12] No absorption near 800–950 cm^{-1} attributable to coordinated peroxide could be identified in these spectra.

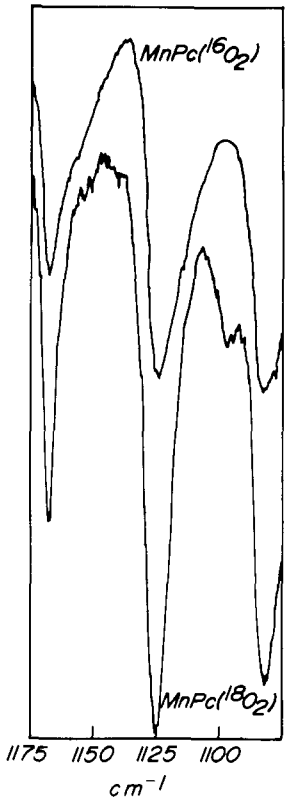

Figure 1. The infrared spectra of $(O_2)MnPc$ incorporating oxygen-16 and oxygen-18 in the region 1075-1175 cm^{-1} (Nujol mull).

The solid (**4**) is paramagnetic, the magnetic moment declining from ~3.9 μ_B at 300 K to ~2.6 μ_B at 84 K. In frozen DMA solution the adduct **4** exhibits a complex X-band, ~18-line, ESR spectrum[13] distinct from that of the other species involved. The frozen solution Q-band spectrum shows two species, a free manganese impurity and the oxygen adduct. A seven-line multiplet may be shown to correspond exactly

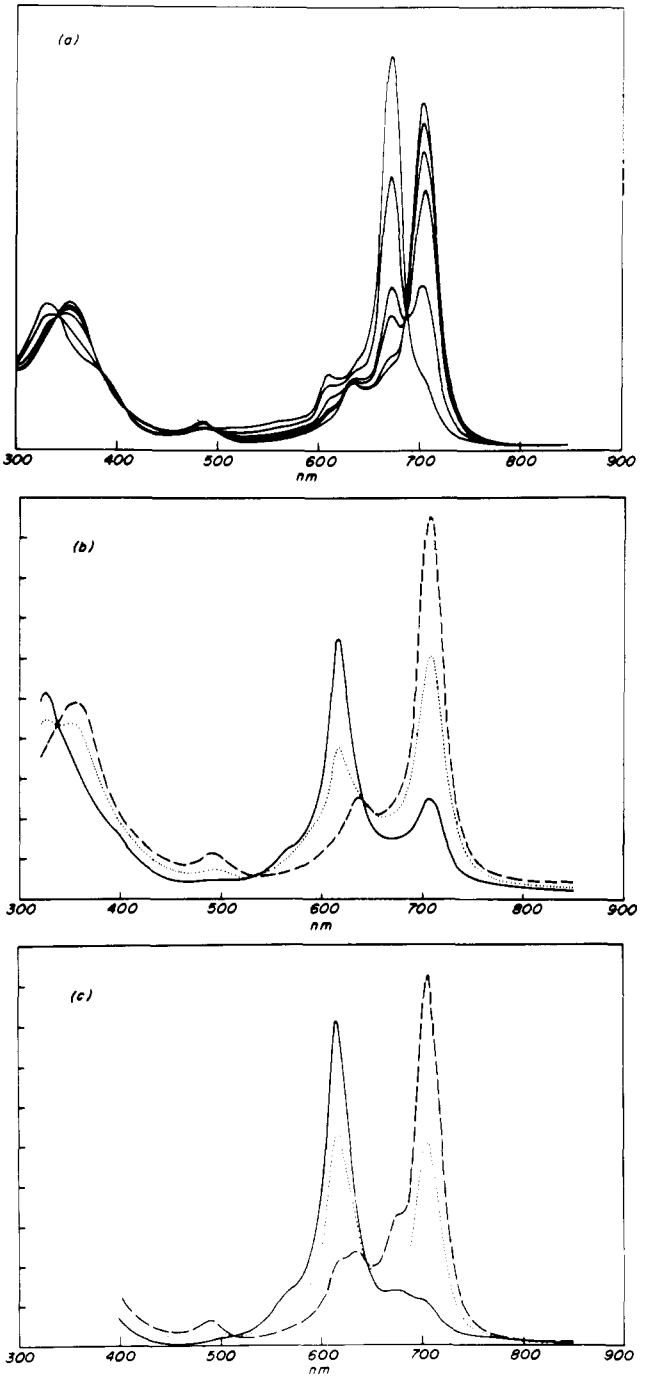

Figure 2. Solution spectra in DMA at ~5×10^{-4} M concentration: (a) equilibrium conversion of PcMn(II) (λ_{max} 674) into $PcMn(O_2)$ under various oxygen pressure; (b) conversion of pure $PcMn(O_2)$ into (DMA)-PcMn-O-MnPc(DMA) using imidazole (~10^{-3} M) at t = 0 (- - -), t = 3 h (···), and t = 20 h (—) (the reaction had not gone to completion under these conditions); (c) conversion of (DMA)PcMn-O-MnPc(DMA) into $PcMn(O_2)$ with oxygen (1 atm) at t = 0 (—), t = 50 min (···), t = 12 h (- - -).

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