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USE OF OSMATE(VI) ESTER trans-N,N,N',N'-TETRAMETHYL-1,2-CYCLOHEXANEDIAMINE COMPLEXES FOR DETERMINATION OF GLYCOL STEREOCHEMISTRY

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Abstract: Osmate(VI) esters chelated with optically active trans-N,N,N',N'-tetramethyl-1,2-cyclohexanediamine are useful derivatives for enantiomeric identification of sub-milligram quantities of glycols by ^{1}H NMR spectroscopy.

The recognition or determination of the chirality of vicinal glycols has received considerable attention, in part as a consequence of the importance of this functionality in natural products chemistry. Derivatization with chiral acyl halides[1] or isocyanates,[2] useful with primary and secondary alcohols, becomes a more complex process with hindered alcohols or with glycols which may react to give mixtures of singly and doubly derivatized products. Chiroptical methods requiring no explicit substrate derivatization have also been developed. Particularly valuable is the complexation of a glycol with Ni(acetylacetonate)$_2$ or Pr(dipivalomethanato)$_3$, followed by the observation of the induced circular dichroism (CD) originating in the inorganic ligands.[3] The sign of the resultant Cotton effect can be correlated with the absolute configuration of the glycol. The exciton chirality method,[4] although it does require formation of a diester of the original glycol, is of particular interest because it permits a non-empirical assignment of absolute chirality.

The possibility of determining the configuration of chiral alkenes (as well as the corresponding glycols) on the basis of the optical rotatory dispersion (ORD) curves of osmate esters has been demonstrated in several laboratories.[5] In connection with a study of the alkaloids of Myosotis scorpioides L. (the True Forget-me-not), we became interested in distinguishing between a pair of enantiomeric diols by ^{1}H NMR spectroscopy. To accomplish this, we wanted an easily (and reversibly) prepared derivative which would incorporate additional chirality. The formation of acetals or ketals using chiral carbonyl compounds appeared unsuitable, since mixtures of diastereomers would be expected from each diol enantiomer in most cases. To circumvent this difficulty, we sought a chiral complexing agent with a two-fold rotation axis, which would form a nonparamagnetic cyclic derivative from a 1,2-diol. We required that both enantiomers of this reagent be available, so that either diol enantiomer could be recognized unambiguously, even when only a single diol enantiomer is available as a standard.

Towards this end, we reinvestigated osmate(VI) esters of glycols. In aqueous pyridine the reagent $Os_2O_6(pyridine)_4$ is known to react smoothly and rapidly with glycols to form diamagnetic pyridyl osmate esters (Figure 1) from which the glycol may be recovered by standard procedures.[6] These pyridyl osmate esters readily undergo ligand exchange with an assortment of chelating tertiary nitrogen donor ligands.[7] We chose trans-N,N,N',N'-tetramethyl-1,2-cyclohexanediamine (TMCHD) as the donor ligand because it possesses a two-fold rotation axis and is readily available as either enantiomer in high optical purity.[8]

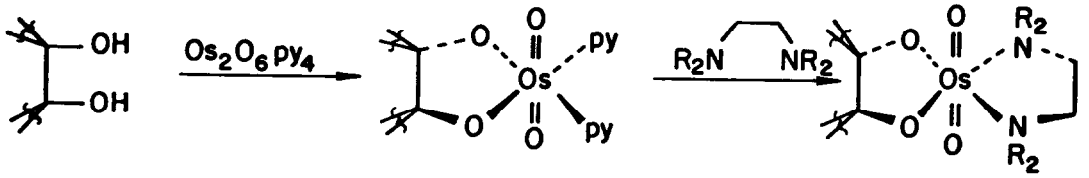


Figure 1.

As a test of this complexing reagent, we treated (R,R)-2,3-butanediol with one-half equivalent of the dimer $Os_2O_6(pyridine)_4$ in 2:1 pyridine:water. After one hour, evaporation of the solvents in vacuo left the osmate complex as brown crystals which were washed with ether and dried. Without further purification, the complex was dissolved in acetone-d_6 and divided equally into two NMR tubes. Treatment of the one sample with (R,R)-TMCHD (slightly over one equivalent) led to immediate displacement of the pyridine ligands, with the appearance of two new N-methyl resonances at δ 2.95 and 2.58 ppm. In contrast, treatment of the other tube with (S,S)-TMCHD produced a complex with N-methyl resonances at δ 3.00 and 2.52. This latter set of signals coincides precisely with that observed for the (R,R)-TMCHD osmate ester of (S,S)-2,3-butanediol, as indeed it must, since these two complexes are themselves enantiomeric. Data for a number of other TMCHD osmate esters are shown in Table 1. We have tentatively assigned the downfield N-methyl resonances to pseudoaxial methyl groups on the five-membered chelate ring, which should experience a deshielding effect from the diamagnetic anisotropy of the Os=O bond. In the general case where the glycol does not possess a two-fold rotation axis, all four of the N-methyl groups become chemically inequivalent, and give rise to separate resonances (Figure 2).

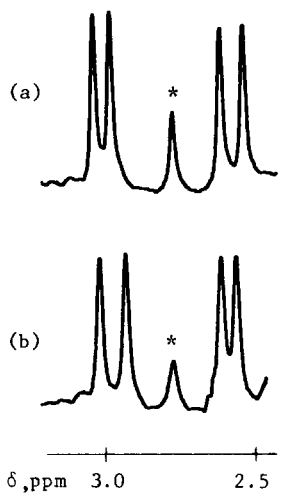
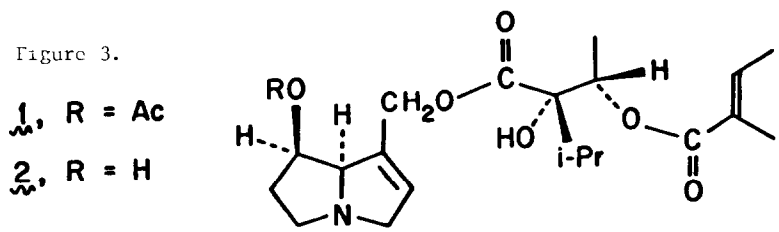


Figure 2. ^1H NMR (acetone-d_6) of diastereomeric osmate esters of (2S,3R)-methyl trachelanthate with (a) (R,R)-TMCHD, (b) (S,S)-TMCHD. (*) indicates HDO.

To demonstrate the utility of this procedure, we have employed TMCHD-chelated osmate esters for the determination of absolute stereochemistry in two pyrrolizidine alkaloids from M. scorpioides L. Alkaline hydrolysis of these compounds afforded, among other products, an α-isopropyl-α,β-dihydroxybutyric acid. Both diastereomers of this acid (trachelanthic and viridifloric acids) occur naturally, with three of the four possible enantiomeric forms reported thus far.[9] The absolute configurations of these enantiomers have been established,[10] but their small optical rotations make identification of unknown samples difficult unless mixture melting point comparisons with authentic samples are possible. Comparison of our material with an authentic sample of viridifloric acid by FT ^{1}H NMR spectroscopy indicated that we had isolated the erythro isomer. To assign an absolute configuration to our unknown, an authentic sample of erythro-(2S,3S) acid was methylated with diazomethane in ether and then transformed int its (R,R)- and (S,S)-TMCHD osmate esters. Similar treatment of a very small sample of our hydrolysis product (500 micrograms) and examination by FT ^{1}H NMR spectroscopy permitted assignment of its absolute stereochemistry as (2S,3S). This, together with other spectral data and hydrogenolysis experiments, led to structures 1 and 2 for the parent alkaloids, with absolute configurations as shown: (Figure 3).[11]

Figure 3.



In conclusion, we expect that TMCHD-chelated osmate esters will find application as versatile derivatives for the enantiomeric identification of glycols, and possibly their resolution, on a sub-milligram scale.

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References and Notes

1. See, for example, Dale, J.A., Dull, D.L., and Mosher, H.S., J. Org. Chem. 1969, 34, 2543-2549.
2. See, for example, Pirkle, W.H. and Hoekstra, M.S., J. Org. Chem. 1974, 39, 3404-3406; Pirkle, W.H. and Adams, P.E., ibid. 1979, 44, 2169-2175; Corey, E.J. and Hashimoto, S., Tetrahedron Lett. 1981, 22, 299-302.
3. Dillon, J. and Nakanishi, K., J. Amer. Chem. Soc. 1975, 97, 5409-5417, 5417-5422, and references cited therein.
4. Harada, N. and Nakanishi, K., Acc. Chem. Res. 1972, 5, 257-263, and references cited therein.
5. Bunnenberg, E. and Djerassi, C., J. Amer. Chem. Soc. 1960, 82, 5953-5955; Scott, A.I. and

Wrixon, A.D., J. Chem. Soc. Chem. Comm. 1969, 1184-1186; Sakota, N. and Tanaka, S., Bull. Chem. Soc. Jpn. 1971, 44, 485-488.
6. Criegee, R., Marchand, B., and Wannowius, H., Justus Liebigs Ann. 1942, 550, 99-133: Subbaraman, L.R., Subbarman, J., and Behrman, E.J., J. Org. Chem. 1973, 38, 1499-1504.
7. Midden, W.R., Chang, C.-H., Clark, R.L., and Behrman, E.J., J. Inorg. Biochem. 1980, 12, 93-105.
8. Whitney, T.A., J. Org. Chem. 1980, 45, 4214-4216. (R,R)-TMCHD is commercially available from Strem Chemicals, Inc., and should be distilled before use.
9. Culvenor, C.C.J. and Smith, L.W., Aust. J. Chem. 1966, 19, 1955-1964.
10. Kochetkov, N.K., Likhosherstov, A.M., and Kulakov, V.N., Tetrahedron 1969, 25, 2313-2323.
11. Details to be published elsewhere; manuscript in preparation.

TABLE 1. ^{1}H NMR Resonances for some (R,R)-TMCHD Osmate Esters*

Glycol	Abs. configuration	N-Me$_{ax}$	N-Me$_{eq}$
EtOOC-CH(OH)-CH(OH)-COOEt	(R,R)	3.07	2.64
	(S,S)	3.05	2.66
H_3C-CH(OH)-CH(OH)-CH_3	(R,R)	2.95	2.58
	(S,S)**	3.00	2.52
threo-MeOOC-C(^{i}Pr)(OH)-CH(OH)-CH_3 (trachelanthate)	(2S,3R)	3.03, 2.97	2.59, 2.51
	(2R,3S)**	3.02, 2.93	2.60, 2.55
erythro-MeOOC-C(^{i}Pr)(OH)-CH(OH)-CH_3 (viridiflorate)	(2S,3S)	3.04, 2.96	2.59, 2.54
	(2R,3R)**	3.02, 2.96	2.62, 2.54

* Chemical shifts are in ppm downfield from internal Me_4Si for 0.034 M solutions in acetone-d_6.
** enantiomeric osmate complex actually observed

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