of ion stability in solution. The distinctly greater sensitivity of the correlation of the styrenes 1 ($\rho^+ = -10.9$[16]) than for the methylstyrenes 2 ($\rho^+ = -9.4$) also fits the general expectations for solution-phase reactions. In solution the most recent values for the reaction of 1 in H_2SO_4 ($\rho^+ = -3.6$)[10i] and in $HClO_4$ ($\rho^+ = -3.6$)[10c] and the value for 2 in H_2SO_4 ($\rho^+ = -2.9$)[10a,b] follow a similar trend but with a significantly reduced magnitude. An earlier value for 1 in H_2SO_4 ($\rho^+ = -2.9$)[10b] is somewhat different, however there are several of the data points for the H_2SO_4 rates that show noteable deviations from these correlations, so that the overall reliability of the ρ^+ value is not great. We have suggested elsewhere[10g] that one cause of these deviations might be hydrogen-bonding interactions of the acidic solvents with some of substituents diminishing the electron-donating ability of the substituents. This complication does not occur in the gas phase, and similar deviations from the correlation are not observed. The successful correlation of the protonation of the styrenes by σ^+ in both the solution and the gas phase indicates that the difference in solvation energies of the reactants and transition state ($\Delta G°_{solv} - \Delta G‡_{solv}$) are either constant or proportional to the substituent stabilization of the cations.

The fact that system 1 has a greater sensitivity to substituent effects than does 2 is in accord with the trends in the gas-phase basicities of methylamines, which show a diminishing ability of methyl groups to stabilize the cation as the cation becomes more stable. Thus, the reported basicities of NH_3, CH_3NH_2, $(CH_3)_2NH$, and $(CH_3)_3N$ reveal successive methyl-stabilizing increments of 9.3, 6.6, and 4.2 kcal mol^{-1}. While the stabilizing effect of the methyl group in the styrenes is similar in magnitude to that observed in the methylamines, it is considerably less than that observed in aliphatic alkenes. Thus, recent values reported[17] for the proton affinities of $CH_2{=}CH_2$, $CH_3CH{=}CH_2$, and $(CH_3)_2C{=}CH_2$ are 162.3, 178.7, and 195.5 kcal mol^{-1}, respecively, corresponding to methyl stabilization increments of 16.4 and 16.8 kcal mol^{-1}, respectively. (It should be noted, however, that earlier proton affinities [13] of 163.5, 184.9, and 196.9 kcal mol^{-1} lead to mehyl stabilization increments of 21.4 and 12.0 kcal mol^{-1}, respectively.) No matter which set of data are used, comparison of these data with GB($PhCMe{=}CH_2$) - GB($PhCH{=}CH_2$) = 4.5 kcal mol^{-1} clearly shows a diminished methyl stabilizing effect in the aromatic system due to extensive delocalization of the charge in the aromatic ring in the protonated species.

Acknowledgment. We are indebted to the Natural Sciences and Engineering Research Council of Canada and the Fonds National Suisse de la Récherche Scientifique for financial support. A.G.H. gratefully acknowledges a sabbatical leave from the University of Toronto during which this work was carried out.

Registry No. *p*-$MeOC_6H_4CH{=}CH_2$, 637-69-4; *p*-$MeC_6H_4CH{=}CH_2$, 622-97-9; *p*-$FC_6H_4CH{=}CH_2$, 405-99-2; $HC_6H_4CH{=}CH_2$, 100-42-5; *p*-$ClC_6H_4CH{=}CH_2$, 1073-67-2; *p*-$BrC_6H_4CH{=}CH_2$, 2039-82-9; *m*-$BrC_6H_4CH{=}CH_2$, 2039-86-3; *m*-$CF_3C_6H_4CH{=}CH_2$, 402-24-4; *p*-$CF_3C_6H_4CH{=}CH_2$, 402-50-6; *p*-$MeOC_6H_4CMe{=}CH_2$, 1712-69-2; *p*-$MeC_6H_4CMe{=}CH_2$, 1195-32-0; *p*-$FC_6H_4CMe{=}CH_2$, 350-40-3; $HC_6H_4CMe{=}CH_2$, 98-83-9; *p*-$ClC_6H_4CMe{=}CH_2$, 1712-70-5; *p*-$BrC_6H_4CMe{=}CH_2$, 6888-79-5; *m*-$BrC_6H_4CMe{=}CH_2$, 25108-58-1; *m*-$CF_3C_6H_4CMe{=}CH_2$, 368-79-6; *p*-$CF_3C_6H_4CMe{=}CH_2$, 55186-75-9.

(16) The slope, *m*, of the GB - σ^+ correlation gives ρ^+ from the relation $\rho^+ = 1000\ m/2.303RT$.

(17) Traeger, J. C.; McLoughlin, R. G. *J. Am. Chem. Soc.* **1981**, *103*, 3647-3652.

2-Chloro-4(*R*),5(*R*)-dimethyl-2-oxo-1,3,2-dioxaphospholane, a New Chiral Derivatizing Agent

Robert C. Anderson* and Michael J. Shapiro*

Preclinical Research, Sandoz, Inc., East Hanover, New Jersey 07936

Received November 1, 1983

The utility of chiral derivatizing agents (CDAs) in the study of enantiomeric purity by NMR is well documented.[1] Two of the major problems associated with using CDAs are the observation and resolution of appropriate signals in complex NMR spectra and the potential for asymmetric induction during the preparation of the derivatized substrate. While Mosher's reagent[1] and others[2] eliminate the first concern by utilizing ^{19}F NMR, asymmetric induction can still be a problem.[3] Additionally, ^{19}F NMR is not routinely available to most synthetic chemists.

With these problems in mind, the new CDA 1 has been developed, which has a distinct advantage over those presently available. It is easy to use, and analysis of enantiomeric purity is performed by ^{31}P NMR,[4] a nucleus readily available in NMR systems having broad-band capabilities. The reagent is unique in that either retention or inversion at phosphorus during derivatization[5] of an enantiomerically pure alcohol yields a single diastereomer due to the C_2 symmetry of the chiral glycol ligand on phosphorus.

The synthesis of racemic dioxaphospholane 1 has been reported[6] and was followed here by using (*R*,*R*)-(-)-2,3-butanediol,[7] as shown in Scheme I, to produce the enantiomerically pure CDA 1.[8]

We have used this new CDA on a variety of alcohols and the results are shown in Table I. The ^{31}P chemical shift range of all of the derivatized alcohols studies is between 12 and 15 ppm while CDA 1 can be found at 17.4 ppm. With slower reacting alcohols such as 12, an uncharacterized byproduct from reaction of CDA 1, triethylamine, and DMAP was observed at 1.2 ppm.[9] Except for menthol (10), all studies were performed with racemic mixtures to test the extent of asymmetric induction during derivatization and to determine the degree of ^{31}P NMR nonequivalence. The results appear quite good over a range of alcohols, especially in light of the ease of the experimental technique. In spite of the fact that CDA 1 produces diastereomers wherein the interacting asymmetric centers are further apart than those in the diastereomers created by using Mosher's reagent, the ^{31}P NMR nonequivalences using CDA 1 are comparable to those obtained with ^{19}F

(1) (a) Dale, J. A.; Dull, D. L.; Mosher, H. S. *J. Org. Chem.* **1969**, *34*, 3543-2147. (b) Sullivan, G. r.; Dale, J. A.; Mosher, H. S. *Ibid.* **1973**, *38*, 2143-2147. (c) Dale, J. A.; Mosher, H. S. *J. Am. Chem. Soc.* **1973**, *95*, 512-519.

(2) Pirkle, W. H.; Simmons, K. A. *J. Org. Chem.* **1981**, *46*, 3239-3246.

(3) Dutcher, J. S.; MacMillan, J. G.; Heathcock, C. H. *J. Org. Chem.* **1976**, *41*, 2663-2669.

(4) Mikolayczyk, M.; Omelanczuk, J.; Leitloff, M.; Drabowicz, J.; Ejchart, A.; Jurczak, J. *J. Am. Chem. Soc.* **1978**, *100*, 7003-7008.

(5) Wadsworth, W. S.; Larsen, S.; Horten, H. L. *J. Org. Chem.* **1973**, *38*, 256-263.

(6) Shagidullin, R. R; Shakirov, I. Kh.; Plyamovatyi, A. Kh.; Gurarii, L. I.; Mukmenev, E. T. *Zh. Obsch. Khim.* **1976**, *46*, 1021-1026.

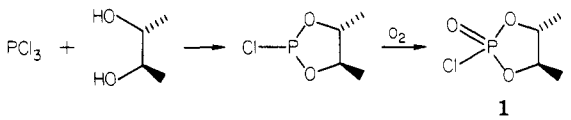
(7) Aldrich Chemical Co.

(8) Reagent 1 and, to a lesser extent, the phosphorylated alcohols are susceptible to moisture. Appropriate precautions are, therefore, warranted. To the NMR tube of derivatized alcohol 11 was added a few drops of water. The tube was shaken vigorously for several minutes and then the ^{31}P NMR was monitored for 15 min. No change in the ratio of the diastereomers was observed.

(9) CDA 1 (1.0 equiv), triethylamine (1.5 equiv), and DMAP (0.1 equiv) were combined and spectra taken. The peak for CDA 1 at 17.4 ppm disappeared completely within 15 min and a new peak at 1.2 ppm appeared.

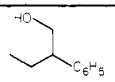
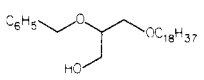
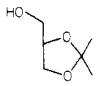
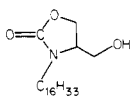
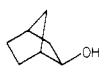
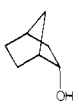
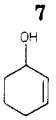
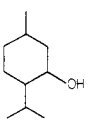
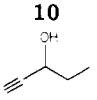
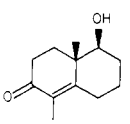
0022-3263/84/1949-1304$01.50/0

Scheme I



1

Table I. ^{31}P NMR Nonequivalences and Enantiomeric Ratios

structure	$\Delta\delta$,[a] Hz	ratio of enantiomers[b]
 2	5.5	51:49
 3	2.40	50:50
 4	0	
 5	5.61	48:52
 6	6.11	50:50
 7	0	
 8	3.7	48:52
 9	0.5	*c*
 10	12.2	68.43:31.57[d] (68.38:31.62)[e]
 11	10.13	51:49
 12	8.3	48:52

[a] 88.9 mHz. [b] Determined from ratio of peak intensities or by integration of peak area and are believed to be accurate to ±1%. [c] Base-line resolution not obtained. [d] Preweighed from pure (+) and (−) enantiomers. [e] Calculated value.

NMR and Mosher's reagent. Furthermore, the potential for asymmetric induction is in principle diminished due to decreased interactions between asymmetric centers during derivatization using CDA 1. In this regard, racemic **12** is reported in the literature[3] as yielding a 63:37 ratio upon use of Mosher's reagent, whereas the results obtained by using CDA 1 are considerably better. The utility of CDA 1 for the direct analysis of primary alcohols such as **2**, **3**, and **5** is also demonstrated. In the past, enantiomeric purity of primary alcohols *has required the use of lanthanide shift reagents in conjunction with the CDA.*[10]

In conclusion, it has been shown that **1** is capable of the direct in situ determination of enantiomeric purity by ^{31}P NMR spectroscopy without the use of auxillary agents for both primary and secondary alcohols.

Experimental Section

2-Chloro-4(*R*),5(*R*)-dimethyl-2-oxo-1,3,2-dioxaphospholane (1). Literature synthesis for the racemic dioxaphospholane[6] was followed by using (*R*,*R*)-(−)-2,3-butandiol[7] to produce enantiomerically pure **1**. This material was stored at 5 °C in a tightly sealed flask within a jar containing a dessicant and showed no signs of decomposition over an 8-month period: bp 105–110 °C at 500 mT; ^{31}P NMR δ 17.4, d = 1.5 g/mL.

^{31}P NMR spectra were obtained on a JEOL FX-200 spectrometer system with the following spectral conditions. A 5-mm NMR tube in a 15-mm broad-band probe tuned to ^{31}P and internal C_6D_6 lock, sweep width of 1 kHz, pulse width of 45°, 16K real data points with no exponential window processing. All shifts obtained are reported by using external H_3PO_4 as reference standard, δ = 0.0.

A typical NMR experiment is as follow: the substrate to be derivatized (1.0 equiv) was dissolved in dry benzene[8] (1.0 mmol/mL) in a vial, and then dry triethylamine (1.5 equiv) and 4-(dimethylamino)pyridine (DMAP) (~0.1 equiv) were added. Then the CDA **1** (1.05 equiv) was added and the vial was shaken for 30 s. After standing for about 15 min, a small amount of C_6D_6, for NMR locking purposes, was added, and the mixture was filtered through cotton into a NMR tube and spectra were taken.

Acknowledgment. We thank Mr. M. X. Kolpak for obtaining the ^{31}P NMR spectra and Professor R. Boeckman for helpful discussions and for compound **12**.

Registry No. **1**, 89104-48-3; (±)-**2**, 89104-46-1; (*R*)-**2** (1 deriv), 89065-35-0; (*S*)-**2** (1 deriv), 89104-36-9; (±)-**3**, 89104-47-2; (*R*)-**3** (1 deriv), 89065-36-1; (*S*)-**3** (1 deriv), 89104-37-0; (±)-**4**, 22323-83-7; (±)-**5**, 89065-43-0; (*R*)-**5** (1 deriv), 89065-37-2; (*S*)-**5** (1 deriv), 89104-38-1; (±)-**6**, 60133-16-6; (*R*)-**6** (1 deriv), 89065-38-3; (*S*)-**6** (1 deriv), 89104-39-2; (±)-**7**, 24325-44-8; (±)-**8**, 62860-38-2; (*R*)-**8** (1 deriv), 89065-39-4; (*S*)-**8** (1 deriv), 89104-40-5; (±)-**9**, 15892-23-6; (*R*)-**9** (1 deriv), 89104-41-6; (*S*)-**9** (1 deriv), 89104-42-7; (1*R*)-**10**, 2216-51-5; (1*S*)-**10**, 15356-60-2; (1*R*)-**10** (1 deriv), 89065-40-7; (1*S*)-**10** (1 deriv), 89104-43-8; (±)-**11**, 65253-21-6; (*R*)-**11** (1 deriv), 89065-41-8; (*S*)-**11** (1 deriv), 89104-44-9; (±)-**12**, 24138-10-1; (*R*)-**12** (1 deriv), 89065-42-9; (*S*)-**12** (1 deriv), 89104-45-0; PCl_3, 7719-12-2; (*R*,*R*)-2,3-butanediol, 24347-58-8; (4*R*,5*R*)-2-chloro-4,5-dimethyl-1,3,2-dioxaphospholane, 89104-49-4.

(10) (a) Yasuhara, F.; Yamaguchi, S. *Tetrahedron Lett.* **1977**, 4085–4088. (b) Merck, E. M.; Lepoiuse, J. A.; Lemiere, G. L.; Alderweireldt, F. C. *Org. Magn. Reson.* **1983**, *21*, 380–387.

Methotrexate Analogues. 22. Selective Cleavage of 2-(Trimethylsilyl)ethyl Esters in the Presence of *N*-*tert*-Butyloxycarbonyl Groups during the Synthesis of Protected Dilysine and Trilysine Derivatives of Methotrexate

Ronald A. Forsch and Andre Rosowsky*

Dana-Farber Cancer Institute and the Department of Pharmacology, Harvard Medical School, Boston, Massachusetts 02115

Received September 29, 1983

In connection with a larger project involving γ-substituted derivatives of the antitumor agent methotrexate

