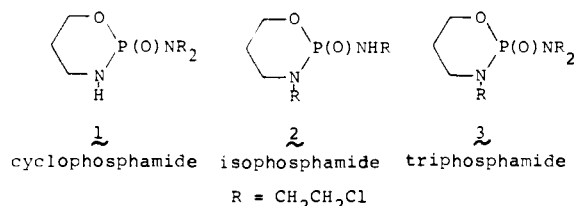


# Communications to the Editor

## Resolution of Triphosphamide

Sir:

The presence of a chiral phosphorus atom in the potent antitumor agents **1**–**3** has prompted several recent studies directed at the optical resolution of **1**<sup>1,2</sup> and **2**.<sup>3</sup> The (+) enan-



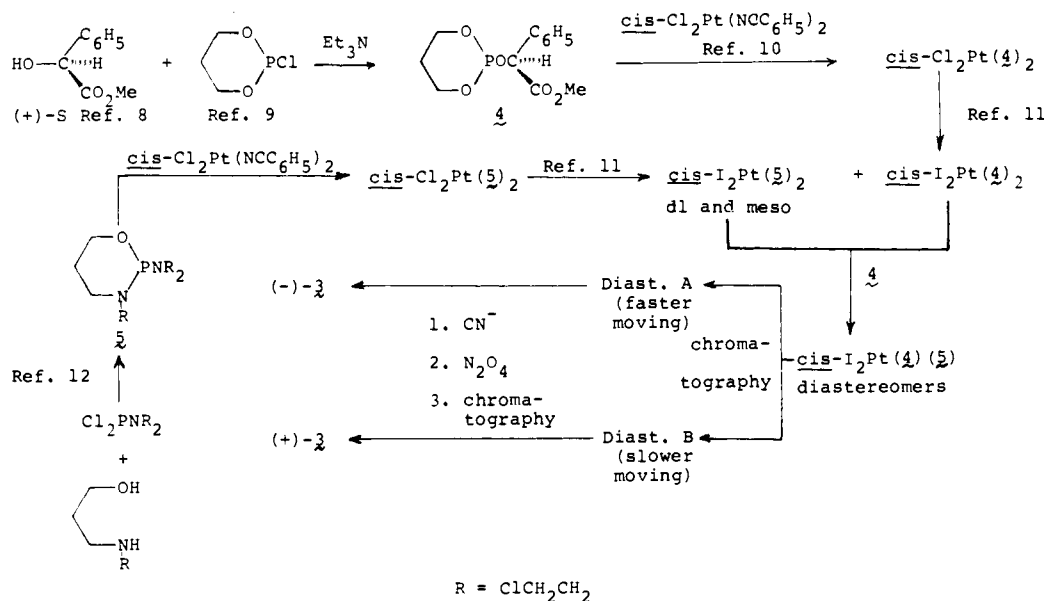
tiomer of **1** is of *R* absolute configuration<sup>4</sup> and is more readily metabolized in human patients,<sup>5</sup> while the (–) enantiomer, which has been shown to have the *S* configuration,<sup>6</sup> is more active against PC6 mouse tumors.<sup>7</sup>

Here we report the optical resolution of triphosphamide (**3**). As outlined in Scheme I, commercially available (+)-(*S*)-mandelic acid was converted into the methyl ester,<sup>8</sup> which was then condensed with an equimolar amount of 2-chloro-1,3,2-dioxaphosphorinane<sup>9</sup> in benzene at 3 °C in the presence of triethylamine. Following filtration of the Et<sub>3</sub>NHCl, the crude phosphite in benzene solution was added dropwise to a 5 °C CH<sub>2</sub>Cl<sub>2</sub> solution containing the stoichiometric amount of *cis*-Cl<sub>2</sub>Pt(NCC<sub>6</sub>H<sub>5</sub>)<sub>2</sub>.<sup>10</sup> After the solution stirred for 30 min at room temperature, the solvent and benzonitrile were evaporated under vacuum, the solids were dissolved in a minimum amount of CH<sub>2</sub>Cl<sub>2</sub>, and the solution was chromatographed on silica gel to give *cis*-Cl<sub>2</sub>Pt(**4**)<sub>2</sub> as a colorless oil:  $[\alpha]^{25}_{589} +79.2^\circ$  (*c* 2.0, CH<sub>2</sub>Cl<sub>2</sub>); <sup>1</sup>H NMR (CDCl<sub>3</sub>) 1.7–2.4 m, 4 H, CCH<sub>2</sub>C), 3.75 (s, 6 H, CH<sub>3</sub>), 3.8–4.9 (m, 8 H, CH<sub>2</sub>OP), 6.4 (br d, 2 H, CH, <sup>3</sup>J<sub>PH</sub> = 11.5 Hz), 7.3–7.7 ppm (m, 10 H, C<sub>6</sub>H<sub>5</sub>); <sup>31</sup>P NMR (C<sub>6</sub>D<sub>6</sub>) 69.1 ppm (<sup>1</sup>J<sub>PPi</sub> = 5742 Hz). Halogen metathesis<sup>11</sup> gave the yellow, solid diiodide complex and the

product was purified by chromatography on a silica gel column (CH<sub>2</sub>Cl<sub>2</sub> eluant) in 61% overall yield based on methyl mandelate:  $[\alpha]^{25}_{589} 62.0^\circ$  (*c* 2.0, CH<sub>2</sub>Cl<sub>2</sub>). *cis*-I<sub>2</sub>Pt(**5**)<sub>2</sub> was obtained from the corresponding chloride<sup>11,12</sup> in 96% yield as a yellow solid (<sup>1</sup>H NMR (CD<sub>2</sub>Cl<sub>2</sub>) 1.5–2.3 (m, 4 H, CCH<sub>2</sub>C), 2.8–4.7 ppm (m, 16 H, CH<sub>2</sub>N, CH<sub>2</sub>Cl, CH<sub>2</sub>O)) and the *dl* and *meso* diastereomers were separated by silica gel column chromatography using a 10:1 MeC<sub>6</sub>H<sub>5</sub>–CHCl<sub>3</sub> eluant mixture (<sup>31</sup>P NMR (CH<sub>2</sub>Cl<sub>2</sub>–C<sub>6</sub>D<sub>6</sub>): *dl*, 70.9 ppm (<sup>1</sup>J<sub>PPi</sub> = 5071 Hz); *meso*, 73.6 ppm (<sup>1</sup>J<sub>PPi</sub> = 4989 Hz)). A suspension of equimolar quantities of the two platinum iodide complexes in benzene in the presence of a catalytic amount (1.0 mol %) of **4** was refluxed for 7 h. After evaporation of the solvent, the products were chromatographed on silica gel with CH<sub>2</sub>Cl<sub>2</sub> to give a 22% yield of diastereomer A as yellow needles ( $[\alpha]^{25}_{589} 42.2^\circ$  (*c* 2.15, CH<sub>2</sub>Cl<sub>2</sub>); <sup>1</sup>H NMR (CD<sub>2</sub>Cl<sub>2</sub>) 1.6–2.1 (m, 4 H, CCH<sub>2</sub>C), 3.0–5.0 (m, 20 H, CH<sub>2</sub>O, CH<sub>2</sub>N, CH<sub>2</sub>Cl), 3.7 (s, 3 H, CH<sub>3</sub>O<sub>2</sub>C), 6.4 (br d, H, HC, <sup>3</sup>J<sub>PH</sub> = 12.2 Hz), 7.2–7.7 ppm (m, 5 H, C<sub>6</sub>H<sub>5</sub>); <sup>31</sup>P NMR (CH<sub>2</sub>Cl<sub>2</sub>–C<sub>6</sub>D<sub>6</sub>) 72.6 (<sup>1</sup>J<sub>PPi</sub> = 4677 Hz, **5**), 74.4 ppm (<sup>1</sup>J<sub>PPi</sub> = 5846 Hz, **4**) and an identical yield of diastereomer B ( $[\alpha]^{25}_{589} 11.85^\circ$  (*c* 5.205, CH<sub>2</sub>Cl<sub>2</sub>); <sup>1</sup>H NMR (CD<sub>2</sub>Cl<sub>2</sub>) 1.6–2.2 (m, 4 H, CCH<sub>2</sub>C), 3.2–5.2 (m, 20 H, CH<sub>2</sub>O, CH<sub>2</sub>N, CH<sub>2</sub>Cl), 3.7 (s, 3 H, CH<sub>3</sub>O<sub>2</sub>C), 6.4 (br d, 1 H, HC, <sup>3</sup>J<sub>PH</sub> = 12.5 Hz); 7.3–7.6 ppm (m, 5 H, C<sub>6</sub>H<sub>5</sub>); <sup>31</sup>P NMR (CH<sub>2</sub>Cl<sub>2</sub>–C<sub>6</sub>D<sub>6</sub>) 71.5 (<sup>1</sup>J<sub>PPi</sub> = 4690 Hz, **5**), 73.6 (<sup>1</sup>J<sub>PPi</sub> = 5859 Hz, **4**)).

Addition of a CH<sub>2</sub>Cl<sub>2</sub> solution of diastereomer A or B to eight times the molar amount of NaCN suspended in methanol at –50 °C was followed by stirring for 1–2 h and filtration of all of the inorganic salts. Gaseous N<sub>2</sub>O<sub>4</sub> was passed through the filtrate at –70 °C to oxidize the phosphorus ligands liberated in the cyanide treatment. After the reaction mixture was poured into 5% aqueous NaHCO<sub>3</sub>, the CH<sub>2</sub>Cl<sub>2</sub> layer was evaporated to give yellow oils in both cases, which were chromatographed on silica gel with CHCl<sub>3</sub> to give (–)-**3** from diastereomer A (64.6% yield based on diastereomer A ( $[\alpha]^{25}_{589} -29.7^\circ$  (*c* 3.535, MeOH); <sup>31</sup>P NMR<sup>13</sup> (C<sub>6</sub>D<sub>6</sub>) 12.4 ppm; <sup>13</sup>C

Scheme I



NMR<sup>14</sup> (C<sub>6</sub>D<sub>6</sub>) 66.48 (d, OCH<sub>2</sub>, <sup>2</sup>J<sub>PC</sub> = 7.33 Hz), 50.34 (d, NCH<sub>2</sub>CH<sub>2</sub>Cl, <sup>2</sup>J<sub>PC</sub> = 2.44 Hz), 49.31 (d, N(CH<sub>2</sub>CH<sub>2</sub>Cl)<sub>2</sub>, <sup>2</sup>J<sub>PC</sub> = 4.89 Hz), 47.57 (s, NCH<sub>2</sub>CH<sub>2</sub>Cl), 42.32 (s, N(CH<sub>2</sub>CH<sub>2</sub>Cl)<sub>2</sub>), 41.48 (d, NCH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>O, <sup>2</sup>J<sub>PC</sub> = 3.66 Hz), 26.04 ppm (d, NCH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>O, <sup>3</sup>J<sub>PC</sub> = 3.66 Hz) and (+)-**3** from diastereomer **B** (64.4% yield; [α]<sub>D</sub><sup>25</sup><sub>589</sub> +30.1° (c 3.535, MeOH)). The <sup>31</sup>P NMR (C<sub>6</sub>D<sub>6</sub>) and <sup>13</sup>C NMR (C<sub>6</sub>D<sub>6</sub>) spectra of (+)-**3** are identical with those of (–)-**3** and both enantiomers are colorless oils. The chemical purity of the enantiomers is demonstrated by the NMR data and a single TLC spot using a 2:1 ratio of CH<sub>2</sub>Cl<sub>2</sub>–Me<sub>2</sub>CO as a development solvent (R<sub>f</sub> 0.53). The enantiomers are optically pure according to FT <sup>31</sup>P NMR spectroscopy. Thus a 1:1 molar ratio of (±)-**3** to EuOpt-I (Willow Brook Laboratories) shift reagent as a 0.2 M solution in C<sub>6</sub>D<sub>6</sub> exhibited two well-defined peaks at –107.21 and –108.73 ppm. Under the same conditions, the enantiomers gave only the –108.73-ppm peak for (+)-**3** and the –107.21-ppm peak for (–)-**3**.

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- (14) <sup>13</sup>C chemical shifts are measured relative to the solvent and calculated relative to tetramethylsilane.
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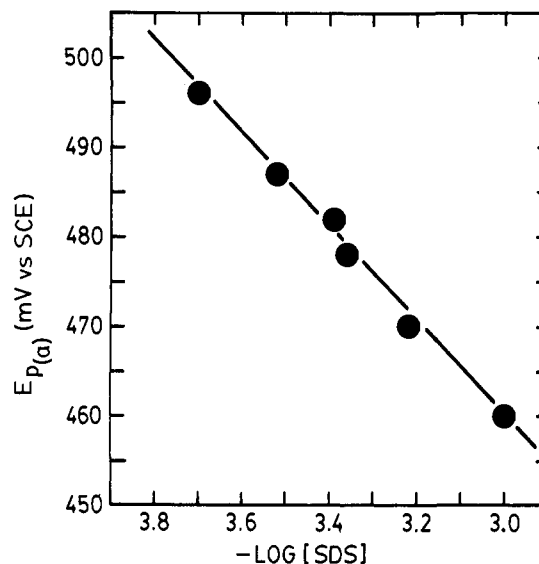
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### Electrochemistry in Ordered Systems. 1. Oxidative Electrochemistry of 10-Methylphenothiazine in Anionic, Cationic, and Nonionic Micellar Systems

Sir:

Electron-transfer reactions of phenothiazine derivatives of interest in physiological<sup>1</sup> and photoionization studies<sup>2</sup> have been examined in both aqueous<sup>3</sup> and nonaqueous<sup>4</sup> media. We report herein the effects on the redox properties of 10-methylphenothiazine (MPTH) resulting from solubilization of this substrate in anionic, cationic, and nonionic surfactants.<sup>5</sup> Relative to voltammetric behavior in aqueous media,<sup>6</sup> the addition of either cationic or nonionic surfactants causes no significant shift in the differential pulse voltammetric (DPV) peak potentials for the one-electron oxidation of MPTH to the corresponding cation radical (MPTH<sup>+</sup>).<sup>7</sup> This invariance of peak potential indicates the absence of preferential interactions<sup>9</sup> between either MPTH or MPTH<sup>+</sup> and surfactant in both cationic and nonionic micellar systems.<sup>10</sup>



**Figure 1.** Dependence of DPV peak potential for the oxidation of 20 μM MPTH on SDS concentration in 0.05 M LiClO<sub>4</sub>: slope = –53 (±3) mV; intercept = 303 (±7) mV; coefficient of correlation = 0.9962.

In anionic SDS systems, however, the DPV peak potential for the oxidation of MPTH to MPTH<sup>+</sup> was found to vary linearly with the logarithm of the SDS concentration up to the cmc (Figure 1) and to remain invariant at surfactant concentrations in excess of this value. Alterations of the peak potential can be expected as a result of preferential interaction between the medium and one member of the redox couple.<sup>9</sup> For an oxidation process, a cathodic shift reflects increased ease of oxidation and is attributable to stabilization of the oxidized member of the couple (i.e., MPTH<sup>+</sup>). Below the cmc, the extent of surfactant aggregation is minimal and such solutions may be viewed as being comprised of free monomeric surfactant species.<sup>8</sup> Hence the variation of peak potential with surfactant concentration below the cmc points to an interaction between monomeric dodecyl sulfate anion (DS<sup>–</sup>) and MPTH<sup>+</sup>. Above the cmc, monomer concentration remains essentially unchanged with newly added surfactant resulting in increased numbers of micelles.<sup>8a</sup> That the DPV peak potential above the cmc is unaltered by added surfactant reflects invariance of the microenvironment experienced by the solubilized MPTH and resulting MPTH<sup>+</sup>.

To assess the relative stability of MPTH<sup>+</sup> in the surfactant systems addressed in this work, the rates of decay of MPTH<sup>+</sup> in H<sub>2</sub>O, H<sub>2</sub>O–LiClO<sub>4</sub>, H<sub>2</sub>O–KBr, SDS–LiClO<sub>4</sub>, Brij–LiClO<sub>4</sub>, and CTAB–KBr were measured. The half-lives for the solvolyses of MPTH<sup>+</sup> in these media (Table I) show that of the cation radical in the anionic surfactant system to be ca. twice that observed in comparable aqueous medium. Grätzel et al.<sup>2c</sup> reported MPTH<sup>+</sup> to be extremely stable in SDS micelles, decaying <20% in 24 h. The more rapid decay of MPTH<sup>+</sup> in SDS described here may be a manifestation of supporting electrolyte (LiClO<sub>4</sub>) on micelle structure.<sup>8a</sup> Indeed, in the

**Table I.** Half-Life of MPTH<sup>+</sup> in Media of Interest to This Work<sup>a</sup>

| medium  | t <sub>1/2</sub> , h <sup>b</sup> |
|---|-----------------------------------|
| H <sub>2</sub> O                                | 8.8 (±0.3) <sup>c</sup>           |
| LiClO <sub>4</sub> (0.05 M)                     | 9.9 (±0.6)                        |
| KBr (0.05 M)                                    | 7.2 (±0.8)                        |
| CTAB (4.9 mM)–KBr (0.05 M)                      | 1.4 (±0.2)                        |
| Brij-35 (2020 mg %)-LiClO <sub>4</sub> (0.05 M) | 2.5 (±0.5)                        |
| SDS (20 mM)-LiClO <sub>4</sub> (0.05 M)         | 17.2 (±0.6)                       |

<sup>a</sup> [MPTH<sup>+</sup>]<sub>0</sub> ≈ 5 × 10<sup>–5</sup> M, introduced as perchlorate salt.<sup>11</sup> Decay kinetics monitored spectrophotometrically at 516 nm. <sup>b</sup> Mean of triplicate determinations at 25 °C. <sup>c</sup> Average deviation.