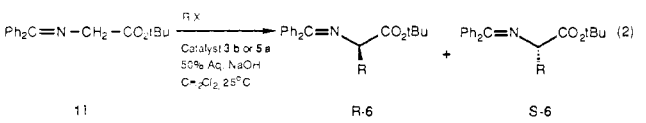
**Table II.** Asymmetric PTC Alkylation of **1i** with Various Alkyl Halides[a]

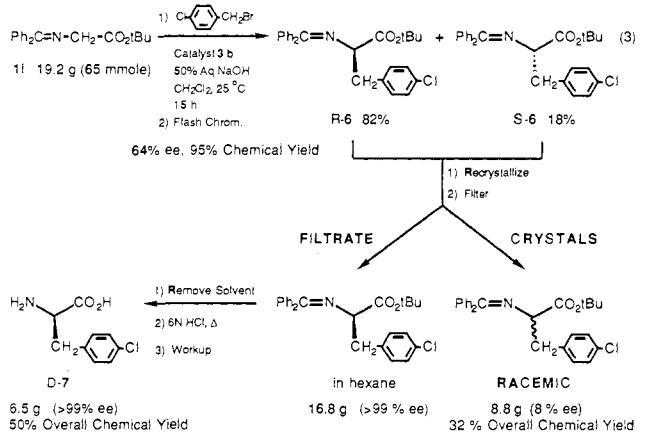
| RX | equiv | 6 | major enantiomer | % ee (% R, % S) | chemical yield (%) | time (h) |
|---|---|---|---|---|---|---|
| $CH_2$=$CHCH_2Br$ | 5 | **6a** | R | 66 (83, 17) | 75 | 5 |
| $CH_2$=$CHCH_2Br$[b] | 5 | **6b** | S | 62 (19, 81) | 78 | 5 |
| $PhCH_2Br$ | 1.2 | **6c** | R | 66 (83, 17) | 75 | 9 |
| $PhCH_2Br$[b] | 1.2 | **6d** | S | 64 (18, 82) | 85 | 9 |
| MeBr | 5 | **6e** | R | 42 (71, 29) | 60[c] | 24 |
| *n*-BuBr | 5 | **6f** | R | 52 (76, 24) | 61 | 14 |
| 4-Cl-$C_6H_4CH_2Br$ | 1.2 | **6g** | R | 66 (83, 17) | 81 | 12 |
| 4-Cl-$C_6H_4CH_2Br$[b] | 1.2 | **6h** | S | 62 (19, 81) | 82 | 12 |
| 2-naphthyl$CH_2Br$[d] | 1.2 | **6i** | R | 54 (77, 23) | 82 | 18 |
| 2-naphthyl$CH_2Br$[b,d] | 1.2 | **6j** | S | 48 (26, 74) | 81 | 18 |

[a] Unless otherwise noted, all reactions were conducted using catalyst **3b** (0.1 equiv).[10] [b] Reactions using catalyst **5a** (0.1 equiv). [c] Quantitative yield of a 60:40 mixture (TLC) of product **6** and starting material **1i**. [d] Product hydrolyzed to amino acid and induction determined by HPLC of GITC derivative.[15]

products are formed in up to 66% ee and either enantiomer is available by simply changing the PTC catalyst.




Methods for the separation of product enantiomers are important in any asymmetric synthesis which is less than 100% stereoselective. Known methods of resolution, either enzymatic[16] or classical,[17] could be employed on derivatives of a particular $\alpha$-amino acid. We are, however, interested in a *general* method by which one or the other enantiomer of a product such as **6** could be purified directly following asymmetric alkylation. A single example illustrates the potential of such methodology. Stereoselective alkylation of **1i** (19.2 g) with 4-chlorobenzyl bromide and catalyst **3b**, followed by removal of racemic product [(±)-**6**] by a single recrystallization,[18] and then deprotection gave 4-chloro-D-phenylalanine (D-**7**, 6.5 g) in >99% ee![19]




In summary, a systematic study of substrate, catalyst, reagents, and reaction conditions has led to a simple, stereoselective synthesis of $\alpha$-amino acid derivatives using chiral phase-transfer catalysis. Research continues toward increasing optical yields and understanding the origin of the optical induction in this important reaction.

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**Supplementary Material Available:** Full experimental details and HPLC spectra for the conversion of **1i** to 4-chloro-D-phenylalanine (D-**7**) in >99% ee (5 pages). Ordering information is given on any current masthead page.

(15) Nimura, N.; Ogura, H.; Kinoshita, T. *J. Chromatogr.* **1980**, *202*, 375-379.
(16) Yamada, H.; Shimizu, S. *Angew. Chem., Int. Ed. Engl.* **1988**, *27*, 622-642.
(17) Jacques, J.; Collet, A.; Wilen, S. H. *Enantiomers, Racemates and Resolutions*; Wiley-Interscience: New York, 1981.
(18) (a) "...racemic compound crystals are generally more stable than enantiomer crystals." Reference 17, p 28. (b) For a recent example, see: Bhattacharya, A.; Dolling, U.-H.; Grabowski, E. J. J.; Karady, S.; Ryan, K. M.; Weinstock, L. M. *Angew. Chem., Int. Ed. Engl.* **1986**, *25*, 476-477.
(19) Products **6h**, **6i**, and **6j** can also be prepared in high % ee using this technique.

## Phenyl- and Mesitylynol: The First Generation and Direct Observation of Hydroxyacetylenes in Solution

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Hydroxyacetylenes or ynols, **1**, are the triple bond analogues of enols, **2**, and, like enols, are tautomers of carbonyl compounds, in this case ketenes, **3**. Unlike enols, however, whose chemistry

RC≡COH RCH=CHOH RCH=C=O
**1** **2** **3**

is currently undergoing vigorous exploration,[1] very little is known about ynols. The first direct observation of an ynol was in fact made only 3 years ago: the parent substance, hydroxyacetylene was generated in the gas phase and was characterized by its mass spectrum.[2,3] Very recently, it was prepared again, in an argon matrix, by photodecarbonylation of hydroxycyclopropenone, and was identified there by its infrared spectrum.[4] We now report that this reaction may also be employed to generate ynols in

(1) See, e.g.: (a) Kresge, A. J. *L' Actualitē Chim.* **1988**, 233-240. CHEMTECH **1986**, *16*, 250-254. (b) Capon, B.; Guo, B.; Kwok, F. C.; Siddhanta, A.; Zucco, C. *Acc. Chem. Res.* **1988**, *21*, 137-140. Rappoport, Z.; Biali, S. E. *Acc. Chem. Res.* **1988**, *21*, 442-449. Toullec, J. *Adv. Phys. Org. Chem.* **1982**, *18*, 1-77.
(2) von Baar, B.; Weiske, T.; Terlouw, J. K.; Schwarz, H. *Angew. Chem., Int. Ed. Engl.* **1986**, *25*, 282-284.
(3) Hydroxyacetylene has also been characterized by high level ab initio MO calculations, see: Bouma, W. J.; Nobes, R. H.; Radom, L.; Woodward, C. E. *J. Org. Chem.* **1982**, *47*, 1869-1875, and references cited therein.
(4) Hochstrasser, R.; Wirz, J. *Angew. Chem.* **1989**, *101*, 183-185.

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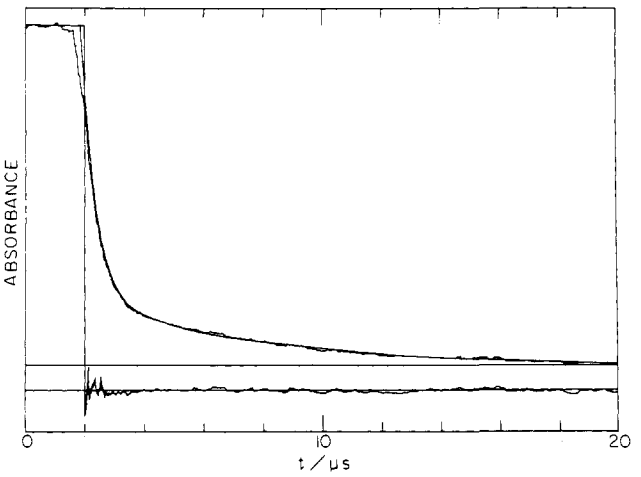
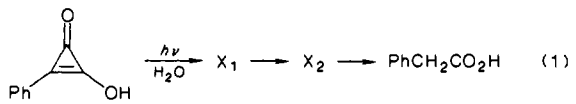



**Figure 1.** Absorbance change following flash photolysis of phenylhydroxycyclopropenone in 0.10 M aqueous sodium hydroxide solution at 25 °C. Least-squares fitting to a biexponential expression gave $\tau_1$ = 0.50 μs, $\tau_2$ = 6.2 μs, and the deviations shown in the lower trace.

solution under conditions where their reaction kinetics can be monitored directly, and we have used this to begin exploring ynol chemistry in an aqueous medium.[5]

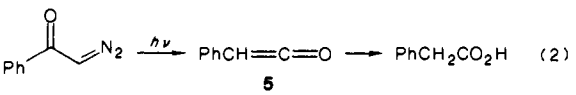
We have found that flash photolysis of phenylhydroxycyclopropenone, **4**,[6] in aqueous solution produces phenylacetic acid and that two successively formed transient species may be detected in the course of this reaction, Figure 1, eq 1.[7] The second one




(1)

**4**

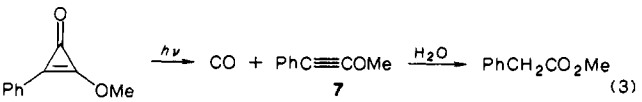
of these transients, $X_2$, decays with a rate law, $k_{obsd}/s^{-1}$ = (4.22 ± 0.27) × $10^3$ + (1.18 ± 0.06) × $10^6$ [$HO^-$] at 25 °C, which is identical with that determined before for the hydration of phenylketene, **5**, generated independently by a photo-Wolff reaction of diazoacetophenone (eq 2): $k_{obsd}/s^{-1}$ = (4.65 ± 0.14) × $10^3$ +




(2)

**5**

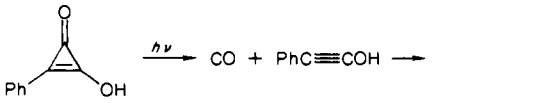
(1.22 ± 0.05) × $10^6$ [$HO^-$];[8] this identifies the second transient as phenylketene. We also found that flash photolysis of phenylmethoxycyclopropenone, **6**,[9] gives phenylmethoxyacetylene, **7**, eq 3, which we again identified by its rate of hydration.[10] This,



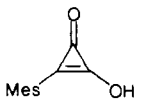

(3)

**6** **7**

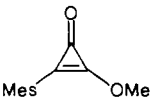
plus the fact that photodecarbonylation of cyclopropenones is known to give acetylenes,[4,12] indicates that the first of these transient species, $X_1$, is phenylhydroxyacetylene and that the transformation of eq 1 proceeds as shown in eq 4. Mesitylhydroxycyclopropenone, **8**,[6] and its methyl ether, **9**, behave in an entirely analogous manner.




(4)




**8**




**9**

Disappearance of both ynols is catalyzed by the hydronium ion and shows general acid, but not general base, catalysis; it also gives a hydronium ion isotope effect in the normal direction, $k_{H^+}/k_{D^+} > 1$. This is classic evidence for rate-determining proton transfer and suggests that conversion of the ynol to ketene occurs by simple protonation of the substrate on acetylenic carbon. The rates of reaction, however, are much too fast for carbon protonation of the ynols themselves and suggest that the species undergoing reaction are the ynolate ions. For example, $k_{H^+}$ = 1–10 $M^{-1}$ $s^{-1}$ may be estimated for rate-determining proton transfer to the acetylenic carbon atom of phenylynol, eq 5, from $k_{H^+}$ = 0.09 $M^{-1}$ $s^{-1}$ for the corresponding reaction of phenylmethoxyacetylene, eq 6,[11] and the fact that enols are usually one or two orders of magnitude more reactive than the corresponding methyl enol ethers.[13] This estimate is nine orders of magnitude less than $k_{H^+}$ = 1.4 × $10^{10}$ $M^{-1}$ $s^{-1}$ determined here for the reaction of phenylynol. Enolate ions, on the other hand, are much more reactive than enols—by factors of the order of $10^8$ [1a]—and the rate constant determined here is thus consistent with a mechanism involving rate-determining protonation of the ynolate ion on acetylenic carbon, eq 7.

$$PhC{\equiv}COH + H^+ \rightarrow PhCH{=}COH^+ \quad (5)$$

$$PhC{\equiv}COMe + H^+ \rightarrow PhCH{=}COMe^+ \quad (6)$$

$$PhC{\equiv}COH \rightleftharpoons PhC{\equiv}CO^- + H^+ \xrightarrow[r.d.]{} PhCH{=}C{=}O \quad (7)$$

This mechanism requires the rate of reaction to be proportional to $H^+$ concentration when the position of the ynol–ynolate equilibrium lies on the side of ynolate and to be independent of $H^+$ concentration when the equilibrium lies over to the side of ynol. We found observed first-order specific rates of decay to be accurately proportional to $H^+$ concentration over the range [$H^+$] = 0.0002–0.002 M; above this upper limit, the rates became too fast for us to measure. This implies that ynolate is the predominant species present in all of the solutions we used, and it sets an upper limit $pK_a \leq 2.8$ on the acid dissociation constant of phenylynol. This is a remarkable result: it makes phenylynol at least 7 p$K$ units more acidic than its double bond analogue, the enol of phenylacetaldehyde, PhCH=CHOH, for which $pK_a$ = 9.5.[14] With hindsight, such a $pK_a$ difference seems quite reasonable; it is reminiscent of the well-known greater acidity of acetylenic C–H bonds over ethylenic C–H bonds. Enols, moreover, are many orders of magnitude more acidic than corresponding saturated

(5) Ynolate anions have been generated, but not observed directly, in aprotic organic solvents, where they promise to be useful synthons, see: Stang, P. J.; Roberts, K. A. *J. Am. Chem. Soc.* **1986**, *108*, 7125–7127. Kowalski, C. J.; Lal, G. S.; Haque, M. S. *J. Am. Chem. Soc.* **1986**, *108*, 7127–7128.

(6) Chickos, J. S.; Patton, E.; West, R. *J. Org. Chem.* **1974**, *39*, 1647–1650.

(7) Three different flash systems were used: (1) a conventional apparatus with excitation flash produced by capacitor discharge through a pair of xenon flash lamps, 50 μs pulse width, $\lambda_{monitor}$ = 230 or 250 nm, (2) a laser system using a KrF excimer laser, $\lambda_{excit}$ = 248 nm, 25 ns pulse width, 200 mJ per pulse, $\lambda_{monitor}$ = 270 or 295 nm, and (3) a laser system using a Nd-YAG laser, $\lambda_{excit}$ = 266 nm, 10 ns pulse width, 60 mJ per pulse, $\lambda_{monitor}$ = 240 or 280 nm; consistent results were obtained with all three systems. The photodecomposition of **4** is highly efficient with quantum yield ~0.7.

(8) Allen, A. D.; Kresge, A. J.; Schepp, N. P.; Tidwell, T. T. *Can. J. Chem.* **1987**, *65*, 1719–1723.

(9) Farnum, D. G.; Chickos, J.; Thurston, P. E. *J. Am. Chem. Soc.* **1966**, *88*, 3075–3081.

(10) $k_{H^+}$ = (8.69 ± 0.09) × $10^{-2}$ $M^{-1}$ $s^{-1}$, which is identical with $k_{H^+}$ = (8.81 ± 0.18) × $10^{-2}$ $M^{-1}$ $s^{-1}$ determined for the acid-catalyzed hydration of independently prepared phenylmethoxyacetylene.[11]

(11) Banait, N.; Hojatti, M.; Findlay, P.; Kresge, A. J. *Can. J. Chem.* **1987**, *65*, 441–444.

(12) See, e.g.: Sander, W.; Chapman, O. L. *Angew. Chem., Int. Ed. Engl.* **1988**, *27*, 398–399.

(13) Dubois, J. E.; El-Alaoui, M.; Toullec, J. *J. Am. Chem. Soc.* **1981**, *103*, 5393–5401. Capon, B.; Zucco, C. *J. Am. Chem. Soc.* **1982**, *104*, 7567–7572. Chiang, Y.; Kresge, A. J.; Wirz, J. *J. Am. Chem. Soc.* **1984**, *106*, 6392–6395.

(14) Chiang, Y.; Kresge, A. J.; Walsh, P. A.; Yin, Y., submitted to *J. Chem. Soc., Chem. Commun.*

alcohols; this difference is traditionally assigned to cooperative inductive (s-character of carbon) and mesomeric (charge delocalization) effects, both of which should indeed come to play a second time in going from enols to ynols.

**Acknowledgment.** We thank the Center for Fast Kinetics Research at the University of Texas, Austin, where some of this work was done, and we are also grateful to the Natural Sciences and Engineering Research Council of Canada, the donors of the Petroleum Research Fund, administered by the American Chemical Society, the Swiss National Science Foundation, and the Ciba Stiftung for financial support of this work.

**Registry No. 1** (R = Ph), 104170-24-3; **1** (R = Mes), 119111-60-3; **4**, 1600-39-1; **5**, 3496-32-0; **6**, 6460-83-9; **8**, 51212-56-7; **9**, 119111-59-0; $D_2$, 7782-39-0.

## Electrical Communication between Redox Centers of Glucose Oxidase and Electrodes via Electrostatically and Covalently Bound Redox Polymers

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Electrical communication between redox centers of enzymes and metal electrodes is of essence in amperometric biosensors and in electrodes for selective electrosynthesis of biochemicals. Direct electrical communication between the centers and electrodes is prevented by thick insulating protein layers that surround the centers. Thus, for example, the two $FADH_2$ redox centers of reduced glucose oxidase [E.C. 1.1.3.4] are prevented from transferring electrons to metal electrodes by an insulating glycoprotein shell. Transfer of electrons has, nevertheless, been effectively mediated by low molecular weight, fast redox couples that diffuse into and out the enzyme. Mediators employed in amperometric glucose sensors include ferrocenes,[1a] quinones,[1b] components of organic metals,[1c] octacyanotungstates,[1d] and ruthenium complexes.[1e] Recently, direct, unmediated electrical communication has been established between electrodes and glucose oxidase to which electron relays were covalently or coordinately bound.[2]

Here we show that the redox centers of glucose oxidase can be readily electrooxidized via a high molecular weight (MW ~ 60000) polycationic redox polymer. The polymer forms an electrostatic complex with the polyanionic enzyme, wherein the electron-transfer distance is reduced (Figure 1a). The complex forms at low ionic strength, where the polycation is "stretched" by internal electrostatic repulsion. At high ionic strength, screening

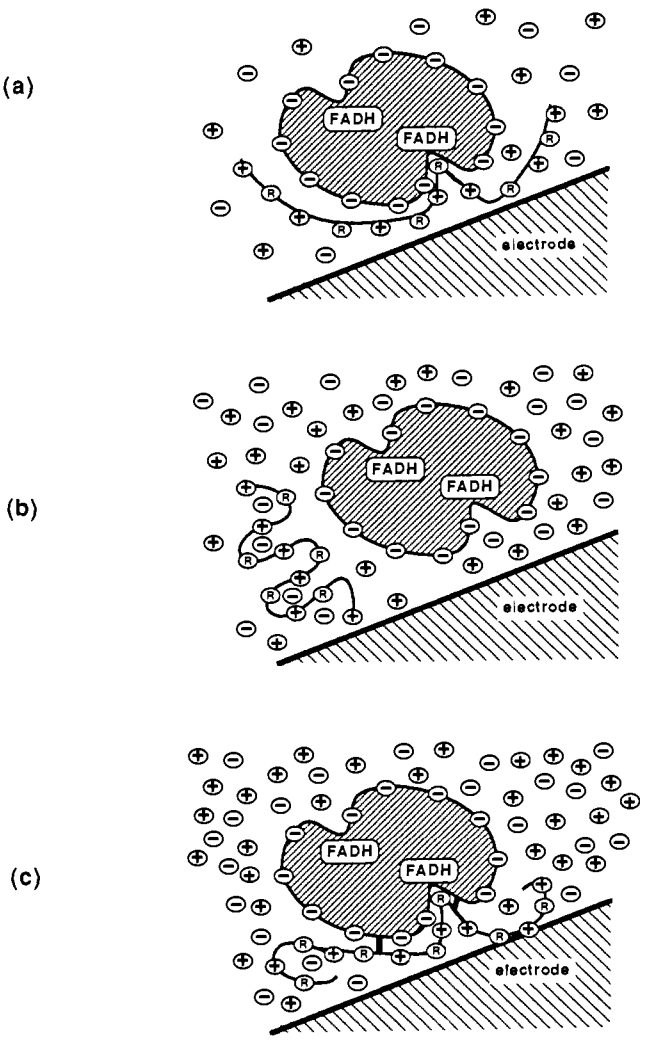


**Figure 1.** (a) Electrostatic bonding of a polycationic redox polymer to a polyanionic enzyme at low ionic strength brings redox centers of the two within range for electron transfer. Electrons are transferred to the electrode via the polymer. (b) Charge screening and coiling of the redox polymer at high ionic strength leads to dissociation of the electrostatic complex, stopping electron transfer, and thereby electrooxidation of glucose. (c) After covalent bonding of the redox polymer to the enzyme, the complex does not dissociate at high ionic strength, and electrooxidation of glucose persists.

of the polymer and enzyme charges by counterions and probably coiling of the polymer (through bonding of pairs of cationic sites to an anion) prevent formation of the complex[3] and electron transfer does not take place (Figure 1b). The redox polymer enzyme complex is, however, preserved even at high ionic strength if the polymer is covalently bound to the enzyme. Upon such bonding, the electrooxidation of glucose persists even at high ionic strength (Figure 1c).

The two polymers employed in this study were (1) a copolymer of poly(*N*-methylvinylpyridinium chloride) and of poly(vinylpyridine $Os(bpy)_2Cl$) and (2) the same with ~1/20th of the vinylpyridine/pyridinium replaced by 4-aminostyrene. Diazoti-

(1) (a) Cass, A. E. G.; Davis, G.; Francis, G. D.; Hill, H. A. O.; Aston, W. J.; Higgins, I. J.; Plotkin, E. V.; Scott, L. D. L.; Turner, A. P. F. *Anal. Chem.* **1984**, *56*, 667. (b) Ikeda, T.; Katasho, I.; Kamei, M.; Senda, M. *Agric. Biol. Chem.* **1984**, *48*, 1969. Ikeda, T.; Hamada, H.; Miki, K.; Senda, M. *Agric. Biol. Chem.* **1985**, *49*, 541. (c) Kulys, J. J.; Samalius, A. S.; Swirmickas, J. S. *FEBS Lett.* **1980**, *114*, 7. Cenas, N. K.; Kulys, J. J. *Bioelectrochem. Bioenergy* **1981**, *8*, 103. Kulys, J. J.; Cenas, N. K. *Biochim. Biophys. Acta* **1983**, *744*, 57. Albery, W. J.; Bartlett, P. N.; Cass, A. E. G.; Craston, D. H.; Haggett, B. G. D. *J. Chem. Soc., Faraday Trans. 1* **1986**, *82*, 1033. Albery, W. J.; Bartlett, P. N. *J. Electroanal. Chem.* **1985**, *194*, 211. Albery, W. J.; Bartlett, P. N.; Craston, D. H. *J. Electroanal. Chem.* **1985**, *194*, 223. (d) Taniguchi, I.; Miyamoto, S.; Tomimura, S.; Hawkridge, F. M. *J. Electroanal. Chem.* **1988**, *240*, 33. (e) Crumbliss, A. L.; Hill, H. A. O.; Page, D. J. *J. Electroanal. Chem.* **1986**, *206*, 327.

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