has the *S* configuration due to the difference in Cahn-Ingold-Prelog priorities of the two systems. Our interpretation of these observations with regard to the chiral recognition models[10] is as follows: (i) although both chiral amides and chiral benzylic alcohols may interact with the chiral stationary phase,[1] the binding of the amide appears to predominate over binding of the benzylic alcohol; (ii) there may be some secondary effects due to the benzylic alcohol, as evidenced by the changes in α in going from erythro to threo, but these effects are minor and unpredictable.[11,12]

Experimental Section

HPLC analysis was performed on a Varian Vista 5000 LC, using a Groton PF1 diode array detector coupled to a Hewlett-Packard 3392A integrator. The stationary phase was a Bakerbond chiral DNBPG covalent Pirkle column,[4] and the flow rate was 2.0 mL/min.

Preparation of the Naphthamides. Naphthoyl chloride (1.5 equiv) was added to a solution of the amino alcohol and triethylamine (1.5 equiv) in methylene chloride at 0 °C. The reaction mixture was allowed to warm to room temperature and stirred for 4 h. The solution was washed with 10% HCl and brine, dried over magnesium sulfate, filtered, and concentrated in vacuo. The product was purified by radial chromatography eluting with 50:50 hexane and ethyl acetate.

Acknowledgment. K.S.R. thanks the University of Miami for a Maytag Fellowship. This work was supported by the National Institutes of Health (GM-37985).

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(11) Note that for **1-2a** vs **3-4a** (unoxygenated erythro vs threo), α decreases, whereas for **1-2b** vs **3-4b** (methylenedioxy erythro vs threo), α increases.

(12) For a study of the separation of enantiomeric and diastereomeric di- and tripeptides that also showed primary dependence only on the absolute configuration of the stereocenter nearest the chiral binding sites, see: Pirkle, W. H.; Alessi, D. M.; Hyun, M. H.; Pochapsky, T. C. *J. Chromatogr.* **1987**, *398*, 203-209.

On the Hydroxide Ion as a One-Electron Reductant in Organic Chemistry

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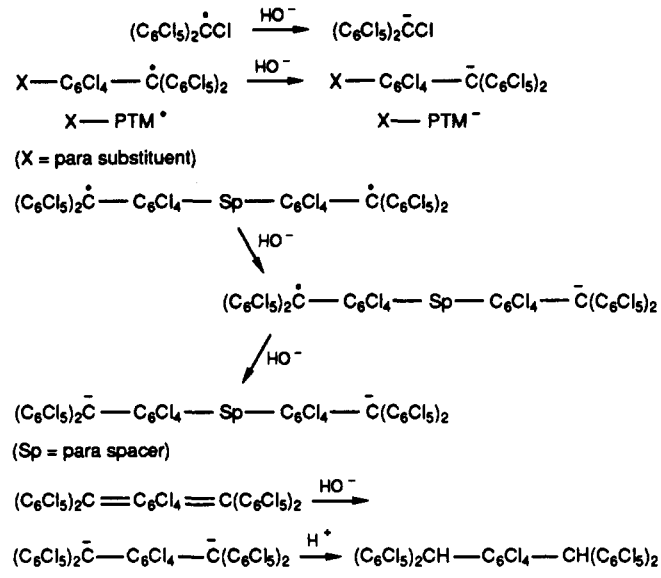
In 1967 it was announced[1a,2] that in certain polar solvents hydroxide ion converts perchlorotriphenylmethyl radical (PTM•), the paradigm of an "inert free radical",[1,3-5] rapidly and quantitatively into perchlorotriphenylmethyl anion (PTM⁻). This is a simple, clear-cut, unambiguous example of one-electron donation to radical PTM•, i.e., a genuine single-electron transfer (SET).

Scheme I



In recent years, strong evidence supporting HO^- as a one-electron donor in other areas of organic chemistry has been reported.[6-9] ESR spectroscopy has shown the involvement of radical-anions in the Cannizzaro reaction of substituted benzaldehydes with NaOH in THF/HMPT.[10] However, evidence for the formation of extremely reactive HO• radical remains either ambiguous or circumstantial. A review on general and fundamental aspects of HO^- as one-electron reducing agent in displacement, addition, and single-electron transfer reactions has recently been published.[11]

It is quite surprising that for a species so familiar as the HO^- so little experimental evidence on its reductive character had been reported, this being due to various factors: (1) The vast majority of reactions with HO^- were, and still are, carried out in water or protic solvents because of insolubility of the alkali-metal hydroxides in other organic solvents. In water and in aqueous solvents, HO^- is highly stabilized by hydration (about 100 kcal/mol),[12] and therefore its reactivity in simple SET processes is either very low or practically nonexistent. (2) The overwhelming majority of potential organic SET acceptors cannot provide a drive (positive redox potential) to offset the HO^- hydration free energy. (3) The complexity of the mechanisms going from substrate to product often masks the nature of the processes involved. (4) The awkwardness of alternative (to ionic) radical mechanisms proposed. (5) The low thermodynamic stability and chemical reactivity of the relevant reaction intermediates and products. (6) The lack of appropriate experimental techniques, such as advanced ESR spectrometry.

Nevertheless, polar solvents, such as DMSO, HMPT, and THF, in which alkali-metal hydroxides are at least somewhat soluble, particularly in the presence of water, diminish dramatically the HO^- solvation,[13] and so they may

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Scheme II

$$(C_6Cl_5)_3C^{\bullet} + HO^- \longrightarrow (C_6Cl_5)_2C^- + HO^{\bullet}$$

PTM• PTM⁻

allow reactions which would not take place otherwise. Because of the cumulative electron-attracting effect of the chlorines, perchloroorganic chemistry embodies chemical species which possess enhanced electron affinity which eventually may be good SET acceptors. Also, perchlorination reduces sharply the number of potential reaction sites, and consequently, it often eliminates mechanistic and structural ambiguities. Furthermore, since within that domain the reacting species, including reaction intermediates, are often thermally stable and unusually unreactive, the experimental results may be interpreted in an unambiguous, straightforward manner.[4]

The one-electron reduction by HO^- (Scheme I) has profusely been used to convert in excellent yields perchlorinated diphenylmethyl,[3a,14,15] triphenylmethyl,[1a,2,14,16-18] and 9-phenylfluorenyl[19] radicals into their anions, as well as related diradicals and paraquinodimethanes[3b,5a,20] to their stable dianions.[21] The perchlorinated triphenylmethides can easily be isolated when tetra-*n*-butylammonium hydroxide in aqueous THF is used.[18] Therefore, the one-electron reduction of radical PTM• may be interpreted as shown in Scheme II.[1a,5b,22,23]

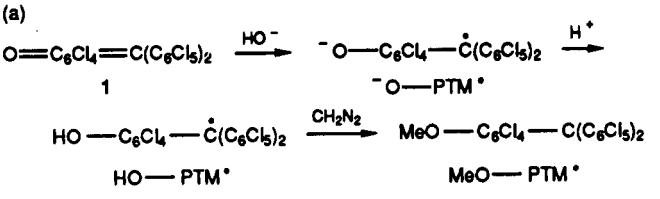
In order to acquire additional information on the role of HO^- as a reductant, the reaction of $(n\text{-Bu})_4N^+ HO^-$ with PTM•, at room temperature, using purissimum, peroxide-free THF, has been performed in the rigorous absence of oxygen, i.e., by degassing the reaction components and using a sealed vacuum line (0.02 mmHg) filled with oxygen-free argon (1 atm). UV–vis spectrometry shows that the resulting mixture, consisting exclusively of the PTM^- salt, remains absolutely unaltered for months.

Instead of using a trivalent-carbon free radical as a SET acceptor, it was decided to attempt the reaction with nonradical substrates such as perchlorofuchsone (1). The reaction of the latter with $(n\text{-Bu})_4N^+ HO^-$ in aqueous THF at room temperature has been investigated, using a great excess of the base, both in an ESR cell and in semimicropreparative scale. The yellowish solution of fuchsone 1 turns deep-green immediately due to the formation of feudal[5c,21] radical-anion $^-$O–PTM•, which, by addition of aqueous HCl, is converted into bright-red radical-phenol HO-PTM•. HO-PTM•, which had earlier been synthesized by reduction of fuchsone 1 with aqueous HI/I_2 in benzene,[17] has been identified by conversion into methyl ether MeO-PTM• with diazomethane.[17] The intermediate radical-anion $^-$O-PTM• (Scheme IIIa) had also been obtained by treating radical-phenol HO-PTM• with aqueous $NaHCO_3$.[17] The $^-$O-PTM• is formed extensively by ionization of HO-PTM• in DMSO.[17] The UV–vis spectra of these two radicals have been reported.

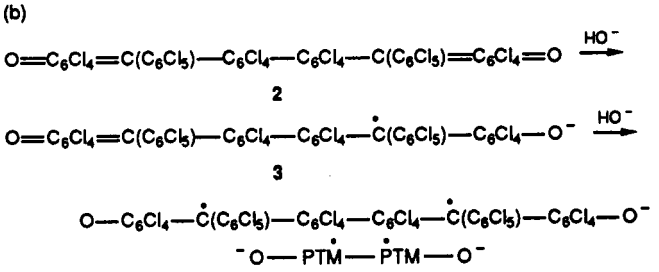
According to their ESR ^{13}C hyperfine coupling constants (hcc) and main-line width[21,23] of allodial[5c,21] perchloro radical-anions, such as $(C_6Cl_5)_2\dot{C}\text{-}C_6Cl_4\text{-}C_6Cl_4\text{-}\bar{C}(C_6Cl_5)_2$ (•PTM-PTM⁻), display an extremely rapid spin–charge exchange, and consequently their apparent spin densities on their molecular moieties are halved with respect to those of the radicals of the PTM series (Figure 1, Table I).[5c,14] The ESR spectrum of $^-$O-PTM• consists of a single main line, and low-intensity ^{13}C satellite line pairs (Table I). Its ^{13}C hcc values are intermediates between those of monoradical PTM•[14] and radical-anion •PTM-PTM⁻,[21] (Table

Scheme III

(a)



(b)



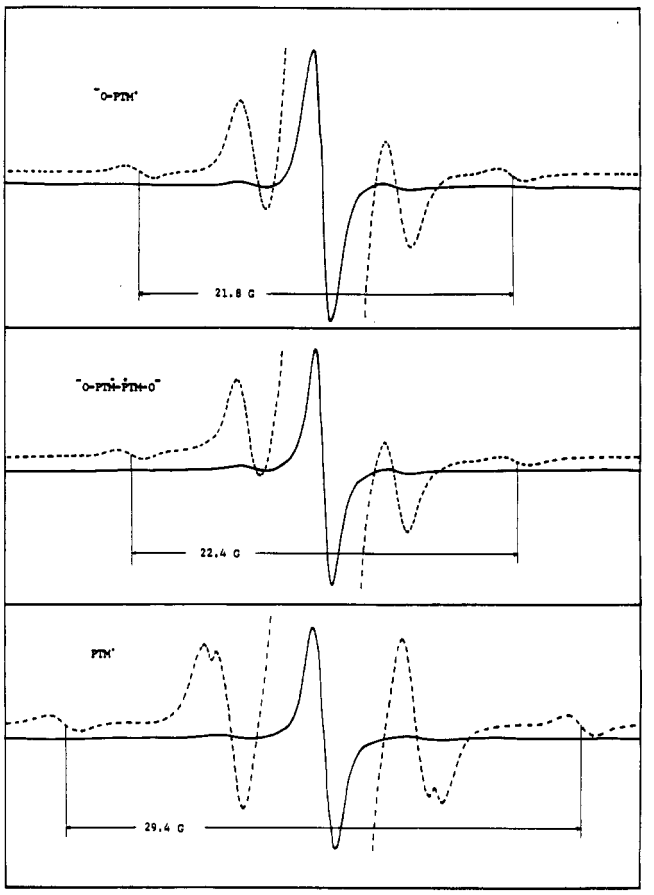


Figure 1. ESR spectra of radical-anions $^-$O-PTM•, $^-$O-PTM•-PTM•-O⁻ vs radical PTM•, including ^{13}C hyperfine coupling line pairs (Table I).

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(23) Ballester, M.; Pascual, I. *Tetrahedron Lett.* **1985**, *26*, 5589.

I) this being attributed to either an asymmetric rapid spin–charge exchange, $^{-}$O-PTM$^{\bullet}$ ⇔ $^{\bullet}$O-PTM^{-}, the equilibrium lying on the left-hand side, or to resonance, $^{-}$O-PTM$^{\bullet}$ ↔ $^{\bullet}$O-PTM^{-}, the negative charge mainly on the electronegative oxygen atom. Since the ESR linewidth in highly chlorinated triphenylmethyl radicals arises mainly from unresolved hyperfine couplings with the chlorine nuclei,[5c,21,24] its value in the $^{-}$O-PTM$^{\bullet}$ is also lower: 1.0 G (PTM$^{\bullet}$, 1.3 G) (Table I). The $^{-}$O-PTM$^{\bullet}$/PTM$^{\bullet}$ ratios for the α, bridgehead, and ortho ^{13}Cs hcc, and the linewidth are coincident (0.74, 0.75, 0.74, and 0.76, respectively), showing that the apparent spin density diminishes in the same proportion all over the molecule. Therefore, it appears that in the ESR frequency scale, about a 25% of the odd electron resides on the oxygen atom. It is emphasized that radical–anion $^{-}$O-PTM$^{\bullet}$ is a phenylene analogue of a benzophenone ketyl.

The UV–vis spectrum of radical–anion $^{-}$O-PTM$^{\bullet}$ [17] is quite different from that of the PTM radicals (λ (max), ≈750 nm vs 500–560 for PTM$^{\bullet}$ [14]), indicating that extensive odd-electron delocalization occurs, as in ketyl radicals.[25,26]

In view of the preceding results, it was decided to attempt the reaction between $(n\text{-Bu})_4N^+$ HO$^-$ and perchlorodifuchsone **2**, under the conditions employed with fuchsone **1**. This reaction not only does take place but affords valuable information as well. An intense ESR line appears which is similar to that of $^{-}$O-PTM$^{\bullet}$, its linewidth being 1.0 G ($^{-}$O-PTM$^{\bullet}$, 1.0 G). Also, two low-intensity ^{13}C (natural abundance, 1.1%) satellite line pairs are observed, their coupling constants being practically coincident with those of $^{-}$O-PTM$^{\bullet}$ (α, 22.4 G; bridgehead, 9.4; ortho, 8.0 vs 21.8 G, 9.5, 7.9, respectively) (Figure 1, Table I). Such coincidences suggest that diradical–dianion $^{-}$O-PTM-$\dot{P}$TM-O$^-$ is formed and that it displays no spin–spin exchange, as the perchloro-$\alpha,\alpha,\alpha',\alpha'$-tetraphenylbi-*p*-toluene-α,α'-diyl diradical ($^{\bullet}$PTM-PTM$^{\bullet}$).[27]

Equal initial weights of fuchsone **1** and difuchsone **2** give about the same ESR signal oscillation (first derivative) amplitude. This confirms that the reduction product of difuchsone **2** is diradical-dianion $^{-}$O-PTM-$\dot{P}$TM-O$^-$, ruling out radical–phenoxide **3**.[27]

Under the same and even harder reaction conditions (addition of DMSO to THF), HO$^-$ fails to reduce other ketones, such as benzophenone, fluorenone, and perchlorobenzophenone, as ascertained by product isolation and the absence of ESR signal. Anthracene in THF or THF/DMSO does not give any ESR signal either. It is noted, however, that perchlorobenzophenone, with $(n\text{-Bu})_4N^+$ HO$^-$ in aqueous THF, gives an intense blue solution which displays no ESR signal.

The reaction of perchlorofluorenone (**4**) with $(n\text{-Bu})_4N^+$ HO$^-$ in aqueous THF at room temperature, in the absence of oxygen, does not give any ESR signal either. After 3 days, 2*H*-2′-carboxyoctachlorobiphenyl acid (**6**) is obtained (76.5% yield), showing that here the HO$^-$ does not act as a reducing species but as a nucleophile, causing ring opening (Scheme IV).[5d]

Remarks and Conclusions

On account of the powerful electron-withdrawing effect of the chlorines, perchlorination assists the formation of organic charge-transfer complexes.[5e] Consequently, the one-electron donation from HO$^-$ to PTM$^{\bullet}$ has been assumed to take place through a radical–anion p-π CT complex between those two species (Scheme V).[1a,5b,22,33] Such a complex would either decompose, giving anion PTM$^-$ and radical HO$^{\bullet}$ (path a),[2] or react somehow as the latter would, leaving anion PTM$^-$ behind (path b).[1a,23]

A SET process involving an initial reaction of HO$^-$ with the solvent to give the actual reducing anion was also proposed when using DMSO (formation of anion MeSOCH$_2^-$).[3c,14] However, as mentioned earlier, it was found that reduction proceeds very fast in polar solvents of quite dissimilar structure (DMSO, HMPT, DMF, AN, acetone, ethanol) some of which, under the usual reaction conditions (strong hydroxides, room temperature), cannot afford anions.

From the preceding results it is concluded that in THF the HO$^-$ acts as a reductant when (1) the solvent is of polar character; (2) the SET acceptor character of the substrate is enhanced by powerful electron-attracting substituents, as in some perchlorinated substrates; (3) the one-electron donation from HO$^-$ is assisted by the formation of an additional bond or by bond strengthening, as in the SETs with substrates such as perchlorofuchsone **1** and perchlorodifushsone **2**, where aromatization supplies a significant part of the energy required for the process to occur. Otherwise, either no SET takes place, as indicated above, or nucleophilic aromatic attack results, as in perchlorofluorenone.

Experimental Section

General Methods and Equipment. The IR, UV–vis, and ESR spectra have been recorded with Perkin-Elmer Model 682, Beckman Acta M-VI, Perkin-Elmer Model Lambda array 3840, and Varian Model E109 spectrometers, respectively. The ESR ^{13}C coupling constants have been calculated by computer simulation.[18] Since the IR spectra differ markedly from their nonchlorinated counterparts, those of the species dealt with here are included.

The formation of radical–anions have been carried out in the dark. To prevent any contamination the air was replaced by purified argon.

Perchlorofuchsone (1). This ketone, which had already been synthesized by hydrolysis of perchlorotriphenylcarbenium hexachloroantimonate in wet CH_2Cl_2,[17] was obtained (1.65 g; 65% yield) by hydrolytic treatment in situ of a mixture of PTM$^{\bullet}$ (2.6 g) and $SbCl_5$ (3 mL) in CH_2Cl_2 (200 mL), at room temperature. Some radical PTM$^{\bullet}$ was obtained (0.70 g; 27%[21]).

Reduction of Perchlorofuchsone with Tetra-*n*-butylammonium Hydroxide: Radicals HO-PTM$^{\bullet}$ and MeO-PTM$^{\bullet}$, and Radical–Anion $^{-}$O-PTM$^{\bullet}$. To a solution of fuchsone **1** (0.033 g) in THF (8 mL) was added aqueous (40%) $(n\text{-Bu})_4N^+$ HO$^-$ (0.8 mL), a deep green color appearing immediately. After 0.5 h, the resulting solution was acidified with aqueous HCl until wine-red, and the ESR spectrum of the solution was recorded. The reaction mixture was poured into water and extracted with $CHCl_3$, and the extract was evaporated to dryness. Its IR spectrum was that of a mixture of HO-PTM$^{\bullet}$ [17] and fuchsone **1**.[17]

A solution of perchlorofuchsone (**1**; 0.64 g) and aqueous (40%) $(n\text{-Bu})_4N^+$ HO$^-$ (2.5 mL) in pure THF (50 mL) was let stand at room temperature for 1 h under argon. A concentrated aqueous HCl was added, and then a solution of diazomethane in ethyl ether was added. The resulting mass was washed with water, dried with anhydrous Na_2SO_4, and evaporated to dryness. The solid residue was dissolved in CCl_4/hexane (1:1) and flash chromatographed on silica gel, eluting first with the same solvent mixture, and then with $CHCl_3$ giving, respectively, MeO-PTM$^{\bullet}$ (0.26 g) and **1** (0.25 g). Total yield, 80%. This radical was identified by IR and R_f (TLC).[17]

In an argon atmosphere, a drop (a great excess) of concentrated (40%) aqueous solution of $(n\text{-Bu})_4N^+$ HO$^-$ was added to a solution of fuchsone **1** (0.005 g) in THF) (1.25 mL) at room temperature.

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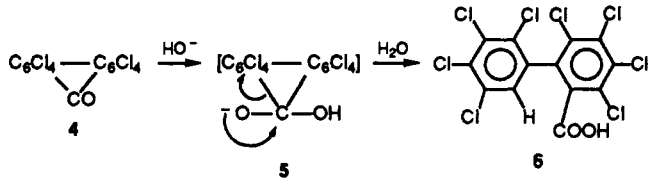
(27) Ballester, M.; Pascual, I.; Carreras, C., forthcoming publication.

Table I. ESR Data on Radical-Anions (THF)

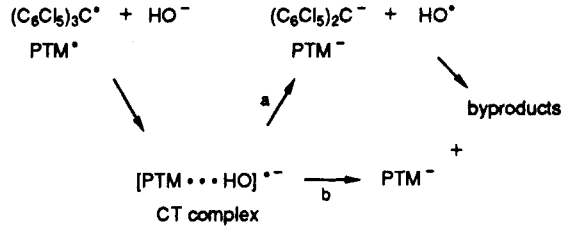
radical	linewidth, G	hyperfine coupling constants, G		
		α	bridgehead	ortho
PTM• (CCl_4)[a]	1.3	29.4	12.7[b]	10.7[b]
$^-$PTM-PTM•[c]	1.1	14.8[d]	5.5[d]	
$^-$O-PTM•	1.0	21.8	9.5[b]	7.9[b]
$^-$O-PTM•-P•TM-O$^-$	1.0	22.4	9.4[b]	8.0[b]

[a] Reference 12. [b] Data obtained from computer simulation. [c] Reference 22. [d] Hyperfine coupling constant halving.

Scheme IV



Scheme V



The ESR spectrum was taken from 0.5 to 25 h. The $^-$O-PTM• signal increased gradually up to 2 h, remaining constant thereafter (complete conversion of 1).

Perchlorodifuchsone (2). This diketone was obtained by hydrolysis of perchloro-α,α,α′,α′-tetraphenylbi-*p*-toluene-α,α′-diyliumhexachloroantimonate ($^+$PTM-PTM$^+$ $2SbCl_6^-$) in wet CH_2Cl_2.[21]

In an argon atmosphere, a drop (a great excess) of concentrated aqueous solution of $(n\text{-Bu})_4N^+$ HO^- was added to a solution of difuchsone **2** (0.007 g) in THF (1.5 mL) at room temperature. The ESR spectrum was also taken from 0.5 to 25 h, the ESR signal increasing gradually up to 2 h, and remaining constant thereafter (complete conversion of 2).

Reaction of Perchlorofluorenone (4) with $(n\text{-Bu})_4N^+$ HO^-. The perchlorofluorenone (4) was prepared from perchlorofluorene as described.[14] To a solution of 4 (0.152 g) in THF (35 mL) was added aqueous (40%) $(n\text{-Bu})_4N^+$ HO^- (3 mL) at room temperature in an argon atmosphere. The original deep-yellow solution became colorless immediately. After letting it stand (72 h), it was poured into diluted aqueous HCl, the mass was extracted with $CHCl_3$, and the organic layer washed with water, dried over anhydrous Na_2SO_4, and evaporated. The residue (0.154 g) was passed through silica gel in $CHCl_3$ containing a 2% of HCOOH, and by evaporation under vacuum and recrystallization of the residue (0.132 g), 2*H*-2′-carboxyoctachlorobiphenyl (**6**) was obtained (0.107 g; 77% yield): white solid; mp 191–193 °C; UV-vis (C_6H_{12}) 198 nm, 220 (sh), 285, 294 (ε 100000, 78000, 1265, 1270); IR (KBr) 3300–2700, 1720, 1535, 1435, 1415, 1375, 1345, 1335, 1265, 1232, 1180, 1120, 1078, 845, 655, 645, 620, 592, 525, 470 cm^{-1}. Anal. Calcd for $C_{13}H_2Cl_8O_2$: C, 32.9; H, 0.4; Cl, 59.9. Found: C, 33.2; H, 0.4; Cl, 60.0.

Acknowledgment. This research has been supported by the DGICYT (Ministerio de Educación y Ciencia, Spain) through Project PB87-0388. Thanks are due to Mrs. A. Diez for the ESR spectra, to Mr. A. Llebaria and Mr. J. Vidal for their experimental assistance, and to Drs. C. Rovira, J. Riera, and J. Castañer for their support. I.P. wishes to express her gratitude to the Spanish Ministry of Education and Science for a grant.

Synthesis of the 6-Benzoyl Derivative of 1-Deoxy-1-oxo-7-desacetylforskolin and an Unambiguous Assignment of the Absolute Stereochemistry of Forskolin

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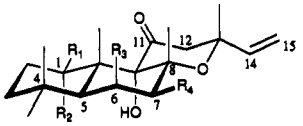
Received June 6, 1990

Forskolin (1), isolated from the Indian mint *Coleus forskohlii*,[2] has attracted considerable interest due to its unique properties as an activator of adenylate cyclase to produce cyclic AMP in various eukaryotic systems.[3,4] In addition to its use as a tool in biochemical research, positive preclinical test results have led to scheduling of the clinical trial of forskolin as an antihypertensive agent.[5] The compound is also being studied as a possible bronchodilator, as an antithrombotic and antimetastatic agent, as a drug for the treatment for glaucoma, and as a cardiovascular agent.[3,6]

The absolute stereochemistry of forskolin was originally postulated as shown in 1 in 1977[1] by the application of the empirical Mills rule[7] to its 5-ene derivatives. This stereochemical proposal was subsequently corroborated through the statistical analysis of the X-ray data obtained for 7-desacetyl-7-bromoisobutyrylforskolin.[8,9] However, the calculated R_2 values[10] of the enantiomers (7.9 and 8.4%) used in this analysis might be deemed as being comparatively large for drawing an unequivocal conclusion. Therefore, in light of extreme biological significance of forskolin and its analogues, an independent, nonempirical validation of the absolute stereochemistry of forskolin was undertaken. We describe a novel, highly efficient method for the synthesis of a 6-benzoylated forskolin (5) involving the regioselective hydrolysis of the 6,7-cyclic orthoester intermediate 4 and an unambiguous assignment of the absolute stereochemistry of forskolin (1) by the use of the exciton chirality circular dichroism (CD) method[11] on the 6,7-dibenzoate derivative of forskolin (6).



1 R_1 = H; R_2 = R_3 = OH; R_4 = OAc
2 R_1, R_2 = O; R_3 = OH; R_4 = OAc
3 R_1, R_2 = O; R_3 = R_4 = OH
4 R_1, R_2 = O; R_3, R_4 = O-C(OCH$_3$)Ph (O)
5 R_1, R_2 = O; R_3 = OBz; R_4 = OH
6 R_1, R_2 = O; R_3 = R_4 = OBz

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