(4) Wrighton, M. S.; Ginley, D. S. *J. Am. Chem. Soc.* **1975**, *97*, 2065.
(5) (a) Giannotti, C.; Merle, G. *J. Organomet. Chem.* **1976**, *105*, 97. (b) Abrahamson, H. B.; Palazzotto, M. C.; Reichel, C. L.; Wrighton, M. S., *J. Am. Chem. Soc.* **1979**, *101*, 4123.
(6) Bond, G. C.; Hellier, M. *J. Catal.* **1965**, *4*, 1.
(7) Putnik, C. F.; Welter, J. J.; Stucky, G. D.; D'Aniello, M. J., Jr.; Sosinsky, B. A.; Kirner, J. F.; Muetterties, E. L. *J. Am. Chem. Soc.* **1978**, *100*, 4107.
(8) (a) Wrighton, M. *Chem. Rev.* **1974**, *74*, 401. (b) Hoyano, J. K.; Graham, W. A. G. *Inorg. Chem.* **1972**, *11*, 1265.
(9) Byers, B. H.; Brown, T. L. *J. Am. Chem. Soc.* **1975**, *97*, 947 and 3260; **1977**, *99*, 2527.
(10) Evidence for 15-e$^-$–Co species from 17-e$^-$ fragments has been provided: Absi-Halabi, M.; Brown, T. L. *J. Am. Chem. Soc.* **1977**, *99*, 2982.
(11) The oxidative addition of H_2 to Co(0) in the equilibrium $H_2 + N_2Co(PPh_3)_3 \rightleftarrows N_2 + H_2Co(PPh)_3$ may be via 15-e$^-$ species: Speier, G.; Marko, L. *Inorg. Chim. Acta* **1969**, *3*, 126. However, direct abstraction of H· from $HSiEt_3$ by the 17-e radical *may* be possible if there is ligand redistribution to produce $[Co(CO)_nL_{4-n}]$ species. See also Kidd, D. R.; Brown, T. L. *J. Am. Chem. Soc.* **1978**, *100*, 4103.
(12) For discussion of various catalytic reactions of alkenes using cobalt carbonyl precursors, see Taqui Khan, M. M.; Martell, A. E. "Homogeneous Catalysis by Metal Complexes"; Academic Press: New York, 1974; Vol. II.
(13) (a) Hieber, W.; Lindner, E. *Chem. Ber.* **1961**, *94*, 1417. (b) Wender, I.; Pino, P. "Organic Syntheses via Metal Carbonyls"; Interscience: New York, 1968; pp 188–189. (b) Piacenti, F.; Bianchi, M.; Benedetti, E. *Chim. Ind. (Milan)* **1967**, *49*, 245.
(14) A reviewer suggested that $[CoL_4(olefin)]^+$ may represent an actual catalyst involved here. Small quantities of very active species are of course difficult to rule out, but $[CoL_4]^+$, though a reactive species, has a short lifetime and gives decomposition to $[CoL_5]^+$ and Co(0) under catalytic conditions: Muetterties, E. L.; Watson, P. L. *J. Am. Chem. Soc.* **1978**, *100*, 6978. Note too that we find photocatalytic formation of 3,3-dimethylpentane when $[Co_2(CO)_6(P(OPh)_3)_2]$ is irradiated in the presence of $HSiEt_3$–3,3-dimethyl-1-pentene, evidencing catalytic activity for alkenes incapable of easy π-allyl–hydride formation believed to be important in the $[CoL_4]^+$ catalyzed isomerization. Use of $DSiEt_3$ results in the formation of $HSiEt_3$ and deuterated hydrocarbon alkane and alkene product.

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α-Hydroxynitrosamines: Transportable Metabolites of Dialkylnitrosamines

Sir:

We report herein evidence demonstrating that α-hydroxynitrosamines (**1**), the proposed critical metabolites in dialkylnitrosamine carcinogenesis,[1] (a) decompose via an alkyldiazotic acid (**2**), as previously postulated;[1] and (b) may be the "transportable" metabolic forms[2] responsible for alkylation of nuclear DNA upon in vivo administration of nitrosamines.[3] The instability of **1** has to date prevented their isolation and spectroscopic characterization; however, they can be studied by in situ preparation via the alkaline- or enzyme-catalyzed hydrolyses of the corresponding α-acetoxynitrosamine (**3**).[2,4]

$$\underset{\mathbf{1}}{RN(NO)CH_2OH} \quad \underset{\mathbf{2}}{RN{=}NOH} \quad \underset{\mathbf{3}}{RN(NO)CH_2OAc}$$

$$\underset{\mathbf{4}}{RN(NO)CO_2Et} \quad \underset{\mathbf{5}}{RNHCO_2Et}$$

a, R = $PhCH(CH_3)$
b, R = $CH_2{=}CHCH_2$
c, R = CH_3CH_2
d, R = $PhCH_2$

To elucidate the decomposition pathway of **1**, *l*-(−)-acetoxymethyl(1-phenylethyl)nitrosamine (**3a**)[5] was prepared by the method of Saavedra,[4] and the stereochemical outcome of its alkaline (pH 8.5) and esterase hydrolyses was studied. These results were compared with the alkaline (pH 8.5) hydrolysis of *l*-(−)-ethyl *N*-(1-phenylethyl)nitrosocarbamate (**4a**), a compound, which under basic conditions reacts via **2a**.[6] The results shown in Table I demonstrate that the optical purity of the product, 1-phenylethanol, is virtually identical in all three hydrolyses.[7] Thus **2a** is an intermediate in the hydrolysis of **1a**, as expected.[1]

Table I. Hydrolysis of **3a** and **4a**

compd	reaction conditions[a]	$t_{1/2}$, h	α°_D (temp, °C)[b]	% net[c,d] inversion
3a	ph 7.0	41		
4a	pH 7.0	13		
3a	pH 7 + esterase[e]	0.25	+13.60 (25)[f]	31.2[i]
3a	pH 8.5	8.3	+12.75 (25)[g]	29.2[j]
4a	pH 8.5	5.0	+12.50 (24)[h]	28.6[j]

[a] All reactions were carried out at 37 °C in 0.05 M phosphate buffer, at ~2 mM concentration of nitroso compounds. [b] Reaction product 1-phenylethanol was diluted with pure racemic alcohol to obtain optical measurements. [c] Initial 1-phenylethylamine used in syntheses has α_D (26 °C) of −38.95°, 99% optically pure. [d] Optically pure 1-phenylethanol has α_D (25 °C) of +43.70°: Burwell, Jr., R. L.; Shields, A. D.; Hart, H. *J. Am. Chem. Soc.* **1954**, *76*, 908–909. Control experiments show that the 1-phenylethanol is stereochemically stable to reaction conditions. [e] Hog liver esterase concentration = 2.53×10^{-7} M; molar ratio of **3a**:esterase, 4400. [f] Dilution factor, 4.75. [g] Dilution factor, 5.30. [h] Dilution factor, 5.43. [i] Yield of alcohol, 80%. [j] Yield of alcohol, 90%.

Table II. Inhibition of Hog Liver Esterase Activity

compd[a]	mole ratio of compd:esterase[b]	% inhibition[c]
3a	10:1	0
4a	11:1	95
	10:1	90[d,e]
	6:1	64
	3:1	48
	1:1	30
4b	10:1	51[d]
4c	10:1	28[d]
4d	10:1	100[d]
4a + 5d	10:10:1	52[f,g]
5a	10:1	80[f]
5b	10:1	79[f]
5d	10:1	88[f]

[a] Note 5. [b] Mole ratios are based on enzyme molecular weight of 164 000: Krisch, K. *Enzymes* **1971**, *5*, 43–69. Esterase concentration, 9×10^{-6} M. [c] *N*-Acetyl-L-tyrosine ethyl ester assay method: Birk, Y. *Methods Enzymol.* **1976**, *45*, 716–718. Phosphate buffer of pH 7.0 (0.05 M) was used. [d] After extensive dialysis against pH 7.0 (0.05 M) phosphate buffer, the esterase activity remained inhibited to the same extent. [e] Control experiments were carried out to demonstrate that the product(s) of reaction were not responsible for the observed inhibition. [f] Control experiments with the unnitrosated carbamates showed that these compounds all reversibly inhibit the esterase at a level of ~80%. This inhibition, which is readily removed by dialysis, is attributed to formation of a carbamyl-enzyme (ENZ-OH → ENZ-OCONHR) which is slowly hydrolyzed back to free enzyme: Erlanger, B. F.; Cohen, W., *J. Am. Chem. Soc.* **1963**, *85*, 348–349. [g] Conditions: preincubation with **5d** for 2 h (footnote *f*) followed by incubation with **4a** for 2 h, followed by extensive dialysis.

The results of the enzymatic hydrolysis of **3a** also indicate that the collapse of **1a** to **2a** occurs away from the enzymic environment. If the collapse takes place within the enzyme's active site we would expect (a) a difference in the stereochemistry of the 1-phenylethanol product caused by a change in the solvation of **2a** compared with that in free solution;[6,7] and (b) the irreversible inhibition of the esterase due to alkylation at, or near, the active site.[8,9]

0002-7863/79/1501-6772$01.00/0

In comparison with **3a**, which has no effect on the esterase's activity (Table I), **4a** is an efficient suicide-type inhibitor[8,10] of the enzyme (Table II). This result is attributed to the direct hydrolysis of **4a** to highly reactive **2a** within, and subsequent binding to, the enzyme's active site.[8] The irreversible inhibition of esterase activity effected by **4a** is markedly diminished by preincubation with a reversible inhibitor (**5d**), demonstrating involvement of the active site in the inhibition process (Table II). Incubation of ethyl *N*-allylnitrosocarbamate (**4b**) and ethyl *N*-ethylnitrosocarbamate (**4c**) with esterase under identical conditions afforded 51 and 28% irreversible inhibition, respectively. The lower levels of inhibition observed for **4b** and **4c** (Table II) are attributed to an increase in the partitioning of their hydrolysis intermediates, **2b** and **2c**, to stable diazoalkanes.[11,12] The benzyl analogue (**4d**) gives 100% inhibition as anticipated, because of the predominant diversion of its hydrolysis product **2d** to a "carbonium-ion"-type intermediate. We interpret these results to mean that the enzymatically formed α-hydroxynitrosamine is sufficiently stable to diffuse away from the site of its formation before further decomposition and, therefore, may be considered a "transportable" metabolite. Further elaboration of the concept of transportable metabolites using in vitro experiments is ongoing.

Acknowledgment. This work was supported by Public Health Service contract N01 CP33278.

References and Notes

(1) Druckrey, H.; Preussmann, R.; Schmähl, D.; Muller, M. *Naturwissenschaften* **1961**, *48*, 134–135. Magee, P. N.; Nicoll, J. W.; Pegg, A. E.; Swann, P. F. *Trans Biochem. Soc.* **1975**, *3*, 62–65. Keefer, L. K.; Lijinsky, W.; Garcia, H. *J. Natl. Cancer Inst.* **1973**, *51*, 299–303. Weissler, M.; Schmähl, D. *Z. Krebsforsch.* **1976**, *85*, 47–49. Althoff, J.; Grandjean, C.; Pour, P.; Gold, B. *Ibid.* **1977**, *90*, 127–140.

(2) Baldwin, J. E.; Branz, S. E.; Gomez, R. F.; Kraft, P. L.; Sinskey, A. J.; Tannenbaum, S. R. *Tetrahedron Lett.* **1976**, 333–336. This term, first used by Baldwin, is meant to describe a somewhat stabilized form of a potential alkylating agent. Such a species is required in nitrosamine carcinogenesis, as the initial enzymic α-hydroxylation takes place in the cytoplasm, while the eventual alkylation of interest occurs in the nucleus: Farber, E. *J. Clin. Pharmacol.* **1975**, *15*, 24–28. Arcos, J. C.; Bryant, G. M.; Pastor, K. M.; Argus, M. F. *Z. Krebsforsch.* **1976**, *86*, 171–183. The possibility that nitrosamines can be activated within the nucleus has been explored, but the results, which do show that isolated nuclei can activate nitrosamines, are difficult to put into perspective relative to the total amount of activation that takes place in vivo: Grandjean, C.; Gold, B.; Knepper, S.; Morris, N., unpublished results.

(3) Swann, P. F.; McGee, P. N. *Biochem. J.* **1968**, *110*, 39–47. O'Connor, P. J.; Capps, M. J.; Craig, A. W. *Br. J. Cancer* **1973**, *27*, 153–166. Margison, G. P.; Margison, J. M.; Montesano, R. *Biochem. J.* **1976**, *157*, 627–634.

(4) Weissler, M. *Angew. Chem.* **1974**, *86*, 817–818. Roller, P. O.; Shimp, D. R.; Keefer, L. K. *Tetrahedron Lett.* **1975**, 2065–2068. Saavedra, J. E. *Ibid.* **1978**, 1923–1926.

(5) All compounds used in this study exhibit satisfactory spectral (^{1}H NMR, ^{13}C NMR, IR, UV) and analytical characteristics.

(6) Moss, R. A.; Lane, S. M. *J. Am. Chem. Soc.* **1967**, *89*, 5655–5660. Moss, R. A.; Landon, M. J. *Ibid.* **1970**, *92*, 5755–5756. White, E. H.; Ryan, T. J.; Field, K. W. *Ibid.* **1972**, *94*, 1360–1361. Moss, R. A.; Talkowski, C. J. *Ibid.* **1972**, *94*, 4767–4768. Moss, R. A., Talkowski, C. J.; Reger, D. W.; Powell, C. E. *ibid.* **1973**, *95*, 5215–5229.

(7) Our results (Table I) show higher stereochemical inversion of products than observed by Moss,[6] whose results are based on the hydrolysis of the potassium salt of **2** under a variety of reaction conditions.

(8) White, E. H.; Roswell, D. F.; Politzer, I. R.; Branchini, B. R. *J. Am. Chem. Soc.* **1975**, *97*, 2290–2291. White, E. H.; Jelinski, L. W.; Perks, H. M.; Burrows, E. P.; Roswell, D. F. *Ibid.* **1977**, *99*, 3171–3173. White, E. H.; Perks, H. M.; Roswell, D. F. *Ibid.* **1978**, *100*, 7421–7423.

(9) A reviewer has raised the possibility that 1 decomposes to the corresponding anti diazotate, whereas it has been demonstrated that nitrosocarbamates afford the syn isomer.[6] The significance of the possible formation of the anti isomer is that it is less reactive than the syn isomer (Thiele, J. *Chem. Ber.* **1908**, *41*, 2806–2811; *Justus Liebigs Ann. Chem.* **1910**, *376*, 239–268) and could account for the failure of **3** to inhibit the enzyme. Although, this possibility cannot be unambiguously discounted, there is evidence that indicates that the syn diazotate arises from the hydrolysis of **3**. First, we have decomposed acetoxymethylmethylnitrosamine in diethyl ether using KO-*t*-Bu and the $CH_3N_2O^-K^+$ isolated shows the syn geometry according to ^{1}H NMR (Suhr, H. *Chem. Ber.* **1963**, *96*, 1720–1725). Secondly, Moss has shown that *syn*- and *anti*-1-phenylethane diazotate do not give the same percent net retention upon ethylation. In fact the results show almost a 10-fold increase in percent net retention of the ether produced with the syn isomer compared with the anti isomer (Moss, R. A.; Powell, C. E. *J. Am. Chem. Soc.* **1976**, *98*, 283–285).

(10) Abeles, R. H.; Maycock, A. L. *Acc. Chem. Res.* **1976**, *9*, 313–319. Rando, R. R. *Ibid.* **1975**, *8*, 281–288.

(11) White, E. H.; Woodcock, D. J. "The Chemistry of the Amino Group", Patai, S., Ed.; Wiley Interscience: New York, 1968; pp 440–483.

(12) Hart, H.; Brewbaker, J. L. *J. Am. Chem. Soc.* **1968**, *91*, 716–718.

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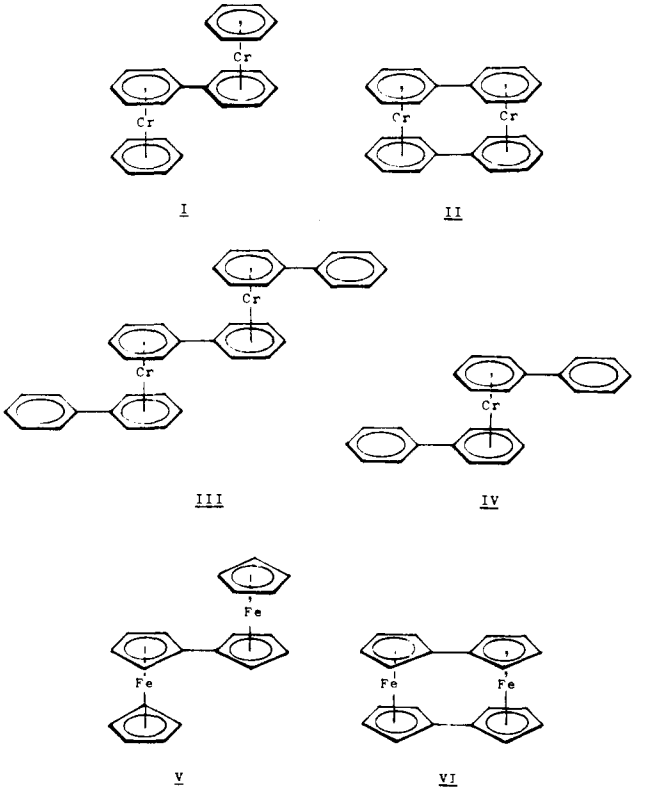
Received June 7, 1979

μ-(η^6:η^6-Biphenyl)-bis[(η^6-benzene)chromium] and Bis[μ-(η^6:η^6-biphenyl)]-dichromium. Novel Species to Explore Mixed-Valence Sandwich Complex Chemistry[1]

Sir:

At present there exists a profound interest in mixed-valence species in general[2,3] as well as in binuclear mixed-valence metallocenes in particular.[4–9] Although a multitude of spectroscopic techniques have been applied in the study of the latter systems, certain controversial points concerning intervalence transfer in the monocations and the nature of spin–spin interaction in the dications remain.[8] Since we have recently investigated the kinetics of electron exchange in solutions containing bis(η-arene)chromium(0) and the corresponding bis(η-arene)chromium ($I^{+\cdot}$) radical cations,[1] favoring a head-on disposition of the exchange partners in the transition state, we attempted the synthesis of bis[μ-(η^6:η^6-biphenyl)]-dichromium monocation (II^+), where the two-sandwich complex moieties would be fixed in a rigid side-on arrangement. In this communication we report on the preparation of II and of μ-(η^6:η^6-biphenyl)-bis[(η^6-biphenyl)chromium]



(III).[10] Since bis(η-arene)chromium (d^5) complexes possess a nondegenerate $^2A_{1g}$ ground state,[11] yielding well-resolved ESR spectra in solution as well as in glassy media, it was expected that proton hyperfine structure would supply information pertaining to spin distribution in the monocations I^+ and II^+ and to spin–spin interaction in the dications I^{2+} and II^{2+}.

0002-7863/79/1501-6773$01.00/0