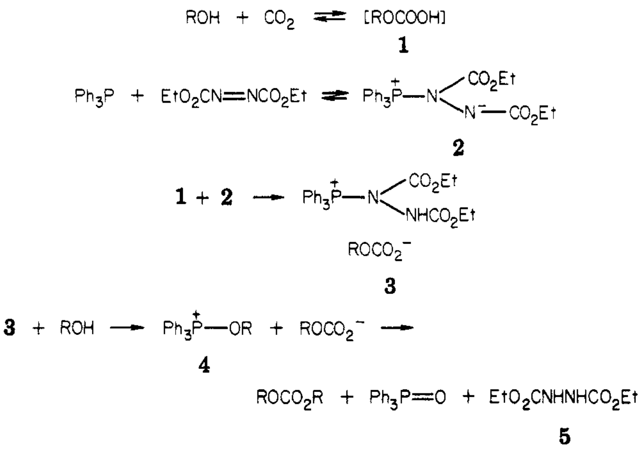
Scheme I

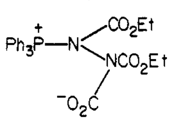


overall reaction is shown in eq 6, and examples listed in Table I.

$$2ROH + CO_2 + Ph_3P + DEADC \rightarrow ROCO_2R + Ph_3P{=}O + EtO_2CNHNHCO_2Et \quad (6)$$

A mechanism which is consistent with that proposed previously for reactions mediated by DEADC/Ph_3P[6] is shown in Scheme I.

An alternative mechanism, involving betaine 6 (from 2



6

and CO_2) was considered. However, production of dialkyl carbonate from 6 would require 1 mol of DEADC and Ph_3P for each mole of alcohol, rather than the 1:1:2 molar ratio used, or would result in a maximum conversion of 50% and recovery of half the charged alcohol. In the present work, very little starting alcohol was observed in the crude product. The high recovery (ca. 90% of theory) of dicarbethoxyhydrazine adds support to the proposed mechanism, as does the absence of ethyl alkyl carbonates, which would be expected if the alternative mechanism were operative.

An interesting prediction may be made, as a consequence of the mechanism in Scheme I: that carbonates of enantiomerically pure alcohols should be *R,S* diastereoisomers. Moreover, 1,2- and 1,3-diols and diols in larger "puckered" rings should undergo regioselective[8] inversions, of potential value in sugar, steroid, macrolide,[9] and prostaglandin work.

Experimental Section

All products were identical (IR, NMR, GC/MS) with authentic samples made by the method of Ball et al.[4] or from the corresponding alcohol and phosgene. GC-determined yields were corrected for response factors. Chromatographic grade THF was sufficiently dry when freshly opened and remained dry when stored over 4A molecular sieves.

Method A. To 100 mL of anhydrous THF in a 250-mL, three-necked, round-bottomed flask equipped with a magnetic stirrer, drying tube, and submerged gas inlet capillary tube were was added 100 mmol of alcohol and 50 mmol (13.1 g) of Ph_3P. Stirring was started, and a slow, steady stream of "Bone-Dry" CO_2 (Matheson) was begun. After 10 min, 50 mmol (8.17 g, 99% of theory) of DEADC was added in two or three portions. After 4–6 h, the CO_2 was shut off and the solution allowed to stir for 18 h. THF was removed on a rotary evaporator and the semisolid residue chromatographed over Brockmann 1 neutral alumina (30 g) by using benzene and monitoring by IR. Careful handling, especially during THF removal, is required for the lower-boiling carbonates.

Method B. To 50-mL of anhydrous THF in a 250-mL Parr bottle equipped with magnetic stirrer and pressure closure were added 5.0 g (38.5 mmol) of 2-ethylhexyl alcohol, 5.6 g (21.4 mmol) of Ph_3P (in 25 mL of anhydrous THF), and 4.35 g (25 mmol) of DEADC (in 25 mL of anhydrous THF). The closure was seated, and the vessel was evacuated (10 mmHg) briefly, weighed, and refilled with "Bone-Dry" CO_2 (1 g, 0.0227 mol). The mixture was vigorously stirred for 18 h and worked up as in method A, yielding 3.4 g of bis(2-ethylhexyl) carbonate (61%) after chromatography.

Acknowledgment. I thank Mr. S. Griff for GC/MS results and comparisons with authentic samples.[10] The technical assistance of Mr. L. Criscione is gratefully acknowledged.

Registry No. Dipentyl carbonate, 2050-94-4; di-*sec*-butyl carbonate, 623-63-2; bis(2-ethylhexyl)carbonate, 14858-73-2; diallyl carbonate, 15022-08-9; 1-pentanol, 71-41-0; allyl alcohol, 107-18-6; CO_2, 124-38-9; Ph_3P, 603-35-0; DEADC, 1972-28-7.

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[8] See ref 6c,d. Axial hydroxyl groups, for example, are frequently not reactive to ester- or ether-forming DEADC/Ph_3P conditions.

[9] See, for example, B. Seuring and D. Seeback, *Justus Liebigs Ann. Chem.*, 2044 (1978).

[10] Previously unreported fragmentation patterns will be presented in a future paper by Mr. Griff.

On the Possibility of New Families of (4*n* + 2)-π-Electron Biradicaloid Hydrocarbons[1]

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Received April 9, 1982

We report evidence, both experimental and from calculations, that anth-fused[2] dibenzannelated [4*n* + 2]-annulenes might exist as biradicaloid hydrocarbons, having either a triplet ground state or a low-lying thermally accessible triplet state.

In 1973, Kolc and Michl[3] used the "biradicaloid hydrocarbon" for a molecule whose ground state has two oribtals which are approximately nonbonding and which are occupied by two electrons, regardless of the actual electronic configuration of this state. They used this term because

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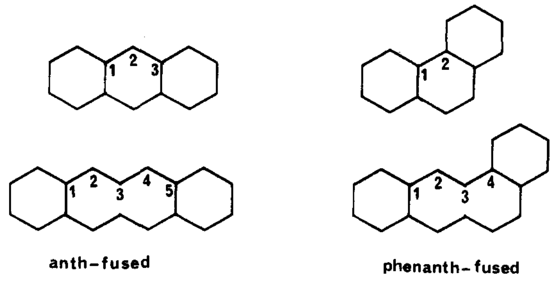
[1] Benzannelated Annulenes. 9. For part 8 see R. H. Mitchell, R. V. Williams, R. Mahadevan, Y. H. Lai, and T. W. Dingle, *J. Am. Chem. Soc.*, 104, 2571 (1982).

[2] We use the term anth-fused to describe molecules like anthracene which are 1,3-, 1,5-, 1,7-, etc. fused as opposed to phenanth-fused, which are 1,2-, 1,4-, 1,6-, etc. fused.



[3] J. Kolc and J. Michl, *J. Am. Chem. Soc.*, **95**, 7391 (1973).

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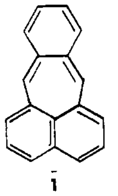
only a minor perturbation separates a pair of singly occupied nonbonding orbitals on the one hand from a doubly occupied high-lying HOMO and a low-lying LUMO on the other. In that and subsequent[4] papers they studied extensively the annelated [4*n* + 1]annulene pleiadene (**1**) and several of its derivatives. Pleiadene can be written with the Kekulé structure **1** or as the biradicaloid canonical structure **1a**. The actual molecule is obtained as a highly reactive hydrocarbon[5] which can be only studied at low temperatures frozen in a glass[3,6] and which dimerizes at normal temperatures. Such behavior is clearly reminiscent of radical reactivity, e.g., **1a**, and is consistent with MO calculations,[3,7] which indicate a small HOMO–LUMO gap.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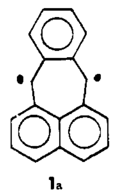
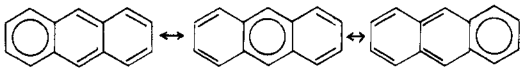

1a

Careful consideration of the structural formula of **1** reveals that it is a benzonaphtho[7]annulene. However, the benzene ring has an intact Kekulé type delocalization only in the discrete radical form **1a**. The naphthalene ring has a naphthalenoid electron distribution in either formulation; hence, there is a driving force for an electronic state better represented by **1a** rather than by **1** in the delocalization energy of the benzene ring. Lo and Whitehead[8] have made extensive calculations on bond lengths, bond energy, and geometry in aromatic hydrocarbons. In most linear polyacene aromatic hydrocarbons optimum aromaticity in one six-membered ring is pitted against that in the other rings. For example, in the trivial example of anthracene **2**, any of the three rings can be benzenoid, but only one may be so at a time (as shown). However, to form two benzene rings, as in **2a**, one ring must be completely localized, in this case to a diradical. Whereas there is little evidence for supposing **2a** as the ground state, an excited state of this form can often be adopted as a formal model in rationalizing much of anthracene's reaction chemistry.[9] However, the extreme reactivity of the polyacenes, e.g., heptacene, can be rationalized in this way, in which to maximize benzenoid rings (or aromatic sextets) some rings become more localized and have more radical character. This is consistent with the formulations of Clar and Robinson on the aromatic sextet and its significance,[9b] in which anth-fused systems are much more reactive than phenanth-fused systems.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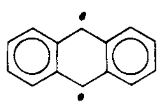

2a

Table I. Calculations of Triplet–Singlet Energies

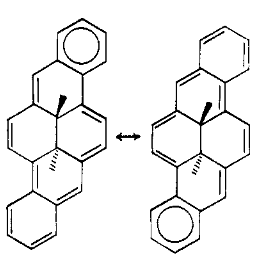
compd	ref	$E_{LUMO} - E_{HOMO}$: HMO, β	$E_{LUMO} - E_{HOMO}$: $E_{\Pi\text{-SCF}}$, eV	$E_{TRIP\text{-}SING}$: Π-SCF, eV	$E_{TRIP\text{-}SING}$: +CI,[a] eV
16		0.2723	3.450	0.1870	−0.270
25		0.2723	3.368	0.2237	(−0.20)
18		0.3196	3.502	0.2014	−0.181
13		0.2723	3.440	0.2643	(−0.16)
20	15	0.3652	3.402	0.2910	−0.128
1	4	0.3635	4.125	0.4613	−0.0158
10		0.4522	4.068	0.5207	0.0977
21	16	0.4522	3.974	0.5640	0.114
3	17	0.4522	4.048	0.5880	0.1267
19		0.4304	4.227	0.6557	(0.20)
8		0.4950	4.262	0.7429	(0.26)
26		0.5274	4.758	1.4143	(0.31)
23	18	0.5546	4.288	1.0366	(0.44)
12		0.5546	4.378	1.0488	(0.45)
17		0.5546			
7	19	0.6500	4.946	1.2460	0.565
6	17, 20	0.6500	4.876	1.2610	(0.58)
9		0.6308	5.026	1.3317	(0.60)
22		0.6308	4.976	1.3703	(0.63)
24		0.6878	4.981	1.5114	(0.69)
15		0.6063	4.904	1.5551	(0.70)
11	17	0.7146	5.154	1.5195	0.713
5	21	0.8900	5.474	1.6300	0.743
14		0.7090	5.052	1.8284	(0.80)
2	8	0.8284	5.810	1.7342	1.0822
4	22	1.210	6.942	2.8382	1.8357

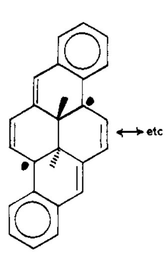
[a] Values in parentheses were obtained by plotting $E_{LUMO} - E_{HOMO}$ (Π-SCF) vs. $E_{TRIP\text{-}SING}$ (Π-SCF + singles I) (see text).

A localized diradical, however, should become much more accessible if the delocalization energy (DE) of the benzannelated ring is rather small relative to the DE for benzene. In pleiadene, where the low DE of a [7]annulene (or a [17]annulene) in **1** is competing with the high DE of benzene in **1a**, the energy of **1a** comes much closer to that of **1** and suggests that the molecule can exist as **1a** at higher temperatures.

It thus seemed reasonable to us that compounds where the energy difference between the two forms is reduced even further, so that they are more nearly equal, might exist.

On such possibility is **3** in which the macroring is a [14]annulene, annelated with two benzene rings *such that delocalization in each benzene ring is opposed by the other*. Moreover, the remaining radicaloid π system has extensive classical delocalization of the "isolated" π electrons still possible. Note that rigid planarity is enforced by the geometric constraints of the dihydropyrene system.[10]


3



3a

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(4) See for example: J. Kolc, J. W. Downing, A. P. Manzara, and J. Michl, *J. Am. Chem. Soc.*, **98**, 930 (1976); R. P. Steiner and J. Michl, *ibid.*, **100**, 6413 (1978); A. Castellan, J. Kolc, and J. Michl, *ibid.*, **100**, 6687 (1978).

(5) M. P. Cava and R. H. Schlessinger, *Tetrahedron*, 21, 3073 (1963); J. W. Lown and A. S. K. Aidoo, *Can. J. Chem.*, **49**, 1848 (1971).

(6) J. Kolc and J. Michl, *J. Am. Chem. Soc.*, **92**, 4147 (1970).

(7) G. Binsch and I. Tamir, *J. Am. Chem. Soc.*, **91**, 2450 (1969).

(8) D. H. Lo and M. A. Whitehead, *Can. J. Chem.*, **46**, 2027, 2041 (1967); *Chem. Commun.* 771 (1968); *Tetrahedron*, **25**, 2615 (1969); *J. Am. Chem. Soc.*, **91**, 238 (1969); *J. Chem. Soc A*, 463 (1971).

(9) (a) See for example: E. Clar, "Polycyclic Hydrocarbons", Vol. I, Academic Press, Springer-Verlag, London, 1964, Chapter 22. (b) Reference 9a, Chapter 6. (c) E. Clar, "The Aromatic Sextet", Wiley, London, 1972.

(10) A. W. Hanson, *Acta Crystallogr.*, **18**, 599 (1965).

Formation of the radical form **3a** from **3** could occur if the balance between the delocalization energy of the benzene ring gained in **3a** and the loss of the DE of the [18]annulene ring of **3** is favorable. Simple MO calculations support this approach.

Calculations

Standard Hückel molecular orbital (HMO) and Pariser–Parr–Pople (PPP) π–SCF methods were used[12] to obtain the results reported in Table I. All calculations reported used idealized geometries: i.e., C–C bond length = 139.7 pm.; C–C–C bond angle = 120° for sp^2 hybrids and 180° for sp hybrids. The internal σ bonded bridge should not affect the calculations, since it merely serves to hold the periphary reasonably planar.[10] Some calculations were done by using a more realistic bond length for C≡C of 120.8 pm. which gave very similar results. The resonance integral, $\beta^0_{\mu,\nu}$, was assigned a value of −2.378 eV for nearest neighbors. All two-electron integrals, $\gamma_{\mu,\nu}$, were calculated by using the Mataga-Nishimoto relationship:

$$\gamma_{\mu,\nu} = \frac{1.4397}{R_{\mu\nu} + \dfrac{2.8794}{\gamma_{\mu\mu} + \gamma_{\nu\nu}}}\ \text{eV}$$

with a value of 10.67 eV for $\gamma_{\mu\mu}$ of the carbon atom. These are the same values used by Cremer and Günther,[13] and therefore the results given here are directly comparable to theirs. The HOMO–LUMO gap was taken directly from the output of the calculations.

The single configuration singlet–triplet energy gap $E_{\text{TRIP-SING}}$ ($E_{\text{TRIPLET}} - E_{\text{SINGLET}}$) was calculated as the difference between the π–SCF ground-state configuration and a single configuration triplet formed by moving one electron from the HOMO to the LUMO. The energy of the triplet configuration was calculated by using the same SCF orbitals as the ground state.

$E_{\text{TRIP-SING}}$ was also calculated by using a wave function for the triplet state which included all single excitations. There is some indication that this approach produces a value for $E_{\text{TRIP-SING}}$ which is reasonably good within the limits of the parameterization used. Schulten et al[14] found that a slightly different parameterization ($\beta^0_{\mu,\nu} = -2.600$ eV and $\gamma_{\mu\mu} = 11.16$ eV) and use of the Ohno formula for $\gamma_{\mu\mu}$ combined with all single excitations gave a good value for $E_{\text{TRIP-SING}}$ for benzene and some polyenes. Selected calculations were done by using this parameterization, and values of $E_{\text{TRIP-SING}}$ were obtained which were 0.2–0.5 eV higher than those reported here; however, the trends between molecules were the same. Given the uncertainty in all the calculations, we do not claim the parameterization reported here is the best one to use; however, all parameterizations examined predict small or negative values (the negative sign may not have much significance) for $E_{\text{TRIP-SING}}$ for those compounds with anomalous experimental results. CI calculations, where all singles and doubles are included, require much more computer time and, given the uncertainty in the paramerization, did not seem to be worth the trouble. Schulton et al.[14] found that inclusion of all doubles increased the singlet–triplet gap but did not change the trends. Attempts to make more accurate calculations will be made when more accurate data are available.

Some values of $E_{\text{TRIP-SING}}$ (Table I, values in parentheses) were obtained by plotting $E_{\text{LUMO}} - E_{\text{HOMO}}$ (π–SCF) vs. $E_{\text{TRIP-SING}}$ (π-SCF + singles CI) for those molecules for which $E_{\text{TRIP-SING}}$ was calculated and estimating the unknown values by interpolation from a rather smooth slightly nonlinear curve. The actual calculations were not done since, which molecules of this size, CI calculations require considerable computer time, particularly for the less symmetric molecules.

The π-SCF calculations indicated that only in the case of the parent [14]annulene, **5**, was the single-configuration triplet π–SCF calculation liable to be inconsistent. For **5** there is a near degeneracy of the two HOMO's and the two LUMO's. This would mean that a single configuration for the triplet is an unrealistic picture. The coefficients for the individual configurations in the π–SCF + all singles CI function bear this out in that the single configuration used above is the dominant one except for **5**.

An alternate approach to estimating $E_{\text{TRIP-SING}}$ is to calculate E_{TRIPLET} with a single configuration and E_{SINGLET} with a small CI calculation by using the ground-state configuration and the one single and one double configuration obtained by moving one and two electrons from the HOMO to the LUMO. The rationale for this approach is that it might estimate reasonably well the change in correlation energy caused by breaking open the filled HOMO to form the triplet (see ref 29a). Some calculations were done on selected molecules, and the calculated values were 0.2–0.3 eV higher than $E_{\text{TRIP-SING}}$ (single configuration) reported here. However, trends between molecules were again the same.

Results

Table I gives the energy difference between the HOMO and LUMO (in the HMO and π-SCF methods) and the energy differences between the triplet and singlet states calculated by using the single-configuration π-SCF and π-SCF with CI for **3**, **2**, and **1** as well as for 23 other related hydrocarbons. These are arranged in decreasing order of calculated stability of the triplet relative to the singlet state. Twelve of these hydrocarbons have been described, some of which provide experimental evidence which support our suggestions. Compounds **1** and **2** have been discussed above; therefore, consider first the dihydropyrenes: the parent **5**, the monobenzannelated compounds **6** and **7**, and the cisoid-dibenzannelated derivative **11** are all diatropic with no evidence for radicaloid behavior, consistent with the relatively large calculated $E_{\text{TRIP-SING}}$. The transoid dibenzannulene **3** (an anth-fused compound), however, is somewhat different, consistent with our suggestions above and its relatively small $E_{\text{TRIP-SING}}$.

We recently reported[17] the synthesis of **3**, and at room

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(11) While this obviously over simplifies the problem, it does provide a viewpoint easy to understand.

(12) See: J. N. Murrell and A. J. Harget, "Semi-empicial SCF-MO Theory of Molecules", Wiley, London 1972, Chapters 1 and 2; H. H. Greenwood, "Computing Methods in Quantum Organic Chemistry", Wiley, London, 1972, and references therein. Programs reported by Greenwood were modified to allow for changes in geometry and parameterization.

(13) D. Cremer and H. Günter, *Justus Liebigs Ann. Chem.*, **763**, 87 (1972).

(14) K. Schulten, I. Ohimine, and M. *Karplus*, *J. Chem. Phys.*, **64**, 4422 (1976).

(15) T. Otsubo, R. Gray, and V. Boekelheide, *J. Am. Chem. Soc.*, **100**, 2449 (1978).

(16) A. Yashuhara, M. Iyoda, T. Satake, and M. Nakagawa, *Tetrahedron Lett.*, 3931 (1975).

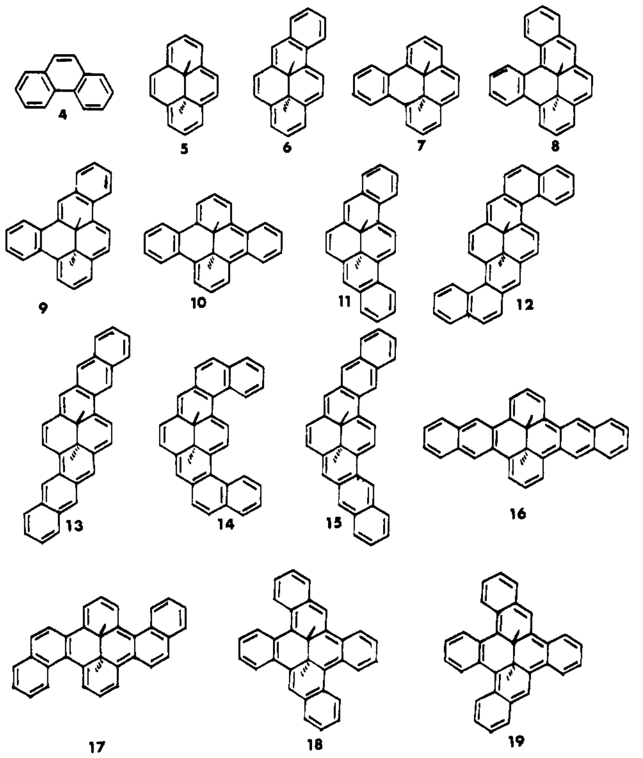
(17) R. H. Mitchell, R. J. Carruthers, and L. Mazuch, *J. Am. Chem. Soc.*, **100**, 1007 (1978); R. H. Mitchell, R. V. Williams, and T. W. Dingle, *ibid.*, **104**, 2560 (1982).

(18) M. Iyoda, M. Morigaki, and M. Nakagawa, *Tetrahedron Lett.*, 817 (1974).

(19) R. H. Mitchell and J. S. H. Yan, *Can. J. Chem.*, **55**, 3347 (1977).

(20) R. H. Mitchell, R. J. Carruthers, L. Mazuch, and T. W. Dingle, *J. Am. Chem. Soc.* **104**, 2544 (1982).

Chart I

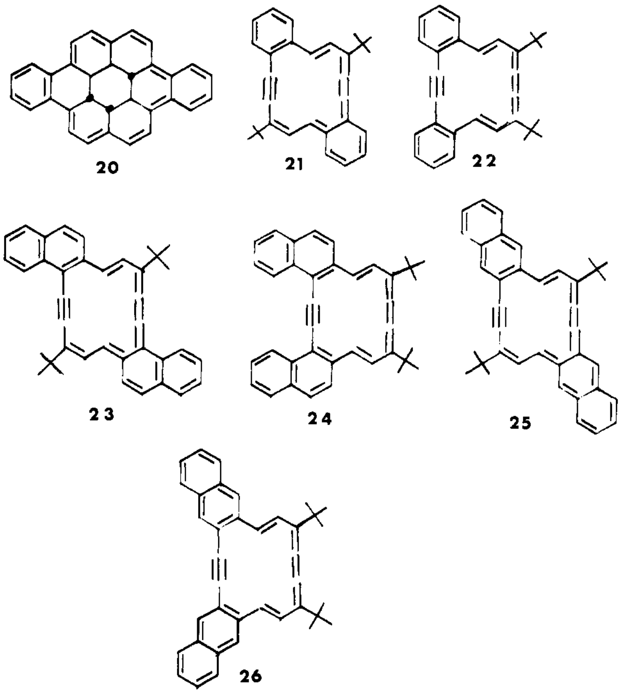


temperature its ^1H and ^{13}C NMR spectra clearly indicated it to be diatropic in solution. The internal protons and carbons were highly shielded, consistent with them being in the cavity of a π-electron cloud of a diamagnetic annulene.[23]

We were, however, somewhat surprised at the width of the lines in the spectrum of **3** (~7 Hz average line width) relative to those of the normal isomeric compound **11** (<2 Hz). Later we discovered that on cooling the ^1H NMR sample of **3**, the methyl signal, for example, broadened and almost collapsed at −70 °C in $(CD_3)_2CO$, but returned to normal on rewarming. In contrast, the signal for **11** was still intense at −95 °C. This behavior is consistent with an increase contribution of **3a** as the temperature is lowered and possibly indicates a triplet ground state.[24] The actual temperature of collapse dependes upon the solvent (e.g., ~−100 °C in THF), and this probably indicates that the stability of **3** relative to **3a** is enhanced by solvation. Moreover, in the solid state a paramagnetic sample of **3** has been obtained. At the time, we were attempting to measure the diamagnetic susceptiblity exhaltations[25] for **3**, **6**, **7**, and **11** which we anticipated would parallel the NMR results.[26]

While **6**, **7**, and **11** were diamagnetic and showed exhaltations[27] consistent with the magnetic resonance data, the particular sample of **3** tested was, on the other hand, paramagnetic with about two free electron spins per mole.[28]

Chart II



In solution (especially in chlorinated solvents) **3** is extremely sensitive to oxygen, much more so than **6**, **7**, or **11**.

Similarly, Nakagawa has reported[16] that the analogous compound in his series, **21**, also rapidly decomposes, and he was not able to record an NMR spectrum. This is consistent with our calculations and suggests that **21** might have significant radicaloid character. Nakagawa also reports[18] that **23**, the analogous dinaphtho compound, is likewise extremely sensitive to O_2 but reasonably stable in solution in its absence. This compound was diatropic in solution. Whereas **23** could not be obtained in the solid state, a compound analogous to **24** was.[29]

Finally, Boekelheide has prepared **20** and reports[15] that the ^1H NMR spectral lines of **20** are considerably broader than those of the analogous monobenzannelated compound.

Conclusions

Taken collectively the evidence suggests that anth-fused compounds such as **1**, **3**, **20**, and **21** are experimentally best represented by inclusion of significant contributions of radicaloid structures such as **3a**. To our kmowledge, despite extensive interest in diradicals[30] and in hydrocarbons with triplet ground states,[31] no such examples involving

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(21) V. Boekelheide and J. B. Phillips, *J. Am. Chem. Soc.*, **89**, 1695 (1967).

(22) Reference 9, Chapter 21.

(23) R. DuVernet and V. Boekelheide, *Proc. Nat. Acad. Sci. U.S.A.*, 71 2961 (1974).

(24) It is also possible that a dimer–diradical of **3a** is being formed and that this is a reversible process. See ref 9a, p 30, for an example in a purely benzoid system. **3** does not simply become less soluble at low temperature.

(25) H. J. Dauben, J. D. Wilson, and J. L. Laity, *J. Am. Chem. Soc.*, **91**, 1991 (1969).

(26) R. H. Mitchell, *Isr. J. Chem.*, **20**, 594 (1980).

(27) These were determined on a Faraday balance in the solid state. The crystals seem subject of mechanically derived organic radical formation. This can affect the susceptibility values determined, and thus these will be discussed in detail elsewhere.

(28) Not all samples are paramagnetic. This seems to depend upon the rate of crystallization. Both paramagnetic and diamagnetic samples have been obtained from cyclohexane which range in color from green to blue. Dissolution of the crystals, however, gives identical ^1H NMR spectra and TLC properties. For **3** the susceptibility measured depended upon the field strength, e.g., $10^6\ \lambda_m = 4987\ cm^3\ mol^{-1}$ at $2.5 \times 10^6\ G^2\ cm^{-1}$ and $3181\ cm^3\ mol^{-1}$ at $6.7 \times 10^6\ G^2\ cm^{-1}$. This is interesting in that such as effect is usually observed in ferromagnetics, where there is a degree of cooperativeness between molecules.

(29) M. Iyoda and M. Nakagawa, *Chem. Lett.*, 815 (1975).

(30) See for example: (a) L. Salem and C. Rowland, *Angew. Chem., Int. Ed. Engl.*, 11, 92 (1972); W. T. Borden and E. R. Davidson, *Annu. Rev. Phys. Chem.*, **30**, 125 (1979). (b) N. C. Yang and A. J. Castro, *J. Am. Chem. Soc.*, **82**, 6208 (1960); (c) E. A. Chandross, *ibid.*, **86**, 1263 (1964); (d) M. S. Plantz, *ibid.*, **101**, 3398 (1979), **102**, 1192 (1980); M. Ballester, J. Castaner, J. Riera, and M. Camps, *Tetrahedron Lett.*, **21**, 193 (1980).

a [4*n* + 2]annulene have been yet reported.

We hope that this report will now stimulate a search for further examples and more definitive evidence for a ground-state triplet. We ourselves are actively attempting the synthesis of **10**, **13**, **16**, and **18** in the hope of providing more data, and also we are further probing the nature of **3** by ESR.[32]

Acknowledgment. We thank the Natural Sciences and Engineering Research Council and the University of Victoria for financial assistance.

Registry No. **1**, 206-92-8; **2**, 120-12-7; **3**, 80664-93-3; **4**, 85-01-8; **5**, 27786-82-9; **6**, 58746-77-3; **7**, 83561-31-3; **8**, 83561-32-4; **9**, 83561-33-5; **10**, 83561-34-6; **11**, 83561-35-7; **12**, 83561-36-8; **13**, 83561-37-9; **14**, 83561-38-0; **15**, 83561-39-1; **16**, 83561-46-0; **17**, 83561-47-1; **18**, 83561-48-2; **19**, 83561-40-4; **20**, 66965-78-4; **21**, 83561-41-5; **22**, 83561-49-3; **23**, 83561-42-6; **24**, 83561-43-7; **25**, 83561-44-8; **26**, 83561-45-9.

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(31) See for example: D. Kearns and S. Ehrenson, *J. Am. Chem. Soc.*, 84, 739 (1962); E. Wasserman, R. S. Hutton, V. J. Kuck, and E. A. Chandross, *ibid.*, 96, 1965 (1974); W. D. Laidig and H. F. Schaefer, *ibid.*, 101, 7184 (1979).

(32) To date, attempts to record an ESR signal of **3a** both in solution and in the solid state have not been successful between 300 and 77 K. In contrast, Yang's biradical[30b] and bisgalvanoxy[30c] both gave ESR spectra[33] as have more recent examples.[34]

(33) R. Kreilick, *J. Chem. Phys.*, 43, 308 (1965).

(34) P. W. Kopf and R. W. Kreilick, *J. Am. Chem. Soc.*, 91, 6569 (1969); A. M. McPherson, et al., *ibid.*, 101, 3425 (1979).

A Simplified Synthesis of (±)-4-Hydroxy-*N*-methylmorphinan-6-one[1,2]

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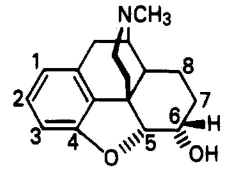
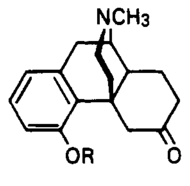
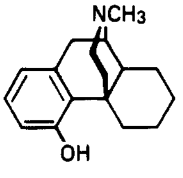
The finding of exceptional antinociceptive activity[3-7] of the morphine derived[4,8] 6-oxomorphinan (−)-**2** and its methyl ether (−)-**3**, and the observation[8] that the former could serve as a key intermediate to (−)-3-deoxy-7,8-dihydromorphine [(−)-**1**], made **2** and **3** particularly attractive candidates for total synthesis. This preparation[8] of **2** also provided access to (−)-4-hydroxy-*N*-methylmorphinan (**4**) that showed morphine-like antinociceptive activity and had previously[9] only been prepared by nonregiospecific Grewe-type cyclization. Total synthesis of racemic **2**[10,11] and **3**[11] was accomplished from 2,4-dihydroxy-*N*-formylmorphinan-6-one (**5**), but the route utilized was cumbersome since it afforded **2** only after the 4,5-oxide bridge has been closed and then reopened through a reductive fission. A regioselective O-alkylation of **5** with 5-chloro-1-phenyl-1*H*-tetrazole followed by hydrogenolysis[12] seemed a more attractive path to follow. Initial attempts in pursuing this approach, however, resulted in the formation of a rather complex mixture of O- and C-5 alkylated products.[13] It seemed likely that these complications, obviously originating from alkylation of the enolate ion, could be avoided if the 6-keto group was reduced to an alcohol prior to alkylation of the 2-hydroxy function and subsequent hydrogenolysis. We now report on a successful completion of this variant.[2]



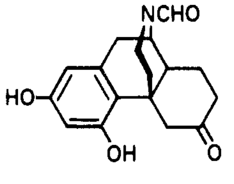
1



2 R=H
3 R=CH$_3$



4



5

Reduction of ketone **5** with L-Selectride in DMF and THF at −70 °C afforded the triol **6** in 93% yield (Scheme I). The α-configuration in **6** followed from its successful conversion into **14** of established stereochemistry.[1,3] O-Alkylation of **6** with 5-chloro-1-phenyl-1*H*-tetrazole in DMF in the presence of potassium carbonate at 70–75 °C afforded by crystallization and chromatography of the mother liquor 57% of the ether **7**, and 3% of the isomeric ether **8** as the slower moving eluate. The catalytic reduction of **7** over Pd/C in acetic acid at 60 °C and under 50-psi hydrogen pressure gave after chromatography over silica gel 28% of the faster moving acetate **10** and 32% of the slower moving diol **9**.

Hydrolysis of **9** and **10** with methanolic HCl afforded the amine **11** in 84% and 79% yield, respectively, which was converted by reductive N-methylation into the diol **12** (69%). Oppenauer oxidation of **12** with benzophenone in the presence of potassium *tert*-butoxide afforded the interesting diphenylmethylene ketone **13** as the major product and 27% of the desired ketone **2** after chromatography. The structure of **13** followed from spectral data and is apparently formed in an aldol type of reaction. A superior conversion of diol **12** into the desired compounds was accomplished by a reversal of the reaction sequence. O-Methylation of **12** with phenyltrimethylammonium chloride afforded the ether alcohol **14** in 65% yield. This alcohol was found identical by ^{1}H NMR, MS, and TLC with the α epimer obtained earlier in the (−) series.[1] Op-

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(1) The compounds described here are (±) entities except those that are marked with the prefix (−), originating from natural morphine.

(2) Presented by one of us (F.L.H.) at the 183rd National Meeting of the American Chemical Society, Las Vegas, NV, March 1982; ORGN 214.

(3) Jacobson, A. E.; Hsu, F.-L.; Rozwadowska, M. D.; Schmidhammer, H.; Atwell, L.; Brossi, A.; Medzihradsky, F. *Helv. Chim. Acta* **1981**, *64*, 1298.

(4) Manmade, A.; Dalzell, H. C.; Howes, J. F.; Razdan, R. K. *J. Med. Chem.* **1981**, *24*, 1437.

(5) Brossi, A. *Chimia* **1981**, *35*, 225.

(6) Jacobson, A. E.; Hsu, F. L.; Rozwadowska, M. D.; Schmidhammer, H.; Atwell, L.; Brossi, A.; Medzihradsky, F. *NIDA Res. Monogr.* **1981**, *41*, 86–92.

(7) Brossi, A. *Trends Pharmacol. Sci.* **1982**, *3*, 239.

(8) Hsu, F.-L.; Jacobson, A. E.; Rice, K. C.; Brossi, A. *Heterocycles* **1979**, *13*, 259.

(9) Mohacsi, E.; Leimgruber, W. U.S. Patent 3 914 234, Oct 21, 1975.

(10) Hsu, F.-L.; Rice, K. C.; Brossi, A. *Helv. Chim. Acta* **1980**, *63*, 2042.

(11) Hsu, F.-L.; Rice, K. C.; Brossi, A. *Helv. Chim. Acta* **1982**, *65*, 1576.

(12) Beyerman, H. C.; Berkelyan, J.; Lie, T. S.; Maat, L.; Wessels, J. C. M. *Red. Trav. Chim. Pays-Bas* **1978**, *97*, 127.

(13) Hsu, F.-L.; Rice, K. C.; Brossi, A. *Heterocycles*, **1982**, in press.

(14) Rice, K. C. *J. Med. Chem.* **1977**, *20*, 164.