Manganese(III) Acetate Induced Cyclization of α-Arylalkyl and α-(Aryloxy)alkyl β-Dicarbonyl Derivatives

Attilio Citterio,* Daniele Fancelli, Claudia Finzi, and Luca Pesce

Dipartimento di Chimica del Politecnico, P.za L. da Vinci 32, 20133 Milano, Italy

Roberto Santi

Istituto G. Donegani, via Fauser 4, 28100 Novara, Italy

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The oxidation of the title compounds by manganese(III) acetate in acetic acid at 50–80 °C affords products of intramolecular aromatic alkylation. High yield and selectivity are observed in six-membered ring closures, whereas five- and seven-membered ring closures are associated with side products of dimerization and/or hydrogen abstraction. The aromatic substitution is favored in all cases by a high electron density of the aromatic carbon atom α to the carbonylalkyl substituent. The activation parameters for the oxidative cyclization of diethyl α-(2-naphthoxyethyl)malonate were determined ($\Delta H^{\ddagger}$ = 25.2 ± 0.3 kcal/mol, $\Delta S^{\ddagger}$ = 2.1 ± 0.5 cal/K mol). The reaction is interpreted to proceed through electrophilic Mn(III)-complexed β-dicarbonylalkyl radicals, formed by reversible inner-sphere electron transfer of Mn(III) carbonyl complexes, which add reversibly to the aromatic ring.

Introduction

C–C bond-forming reactions by free-radical addition to π-unsaturated systems have proved powerful tools for the synthesis of useful and complex molecules.[1] Much attention has been devoted to free-radical cyclizations of alkenes,[2] and, in this field, interesting examples of oxidative cyclizations of unsaturated α-acyl- or α-cyanoalcanoic acids or esters induced by manganese(III) acetate, showing remarkable yield and selectivity, have been recently reported.[3,4] Similar processes that use more classical free-radical sources (i.e., thermal decomposition of peroxides) have also been previously reported,[5] and in both cases the relative yield of adduct arising from exo and endo ring closure was found to depend upon the experimental conditions, endocyclic products being generally preferred under thermodynamic control.[6]

Cyclization processes by homolytic aromatic substitution have been less widely investigated[7] and few examples are known which use manganese(III) acetate, and involve alkyl radicals formed by inter-[8] or intramolecular[3] oxidative addition of carbonyl compounds to an alkene. Therefore, our recent results[9] of intermolecular aromatic substitution by malonyl groups induced by manganese(III) acetate prompted us to investigate the intramolecular version of this useful reaction. As observed in the intermolecular process,[9] we found that the cyclization cannot be obtained by using peroxidic sources. Here, we report the results obtained in the manganese(III) acetate oxidation of substituted α-arylalkyl or α-(aryloxy)alkyl β-dicarbonyl compounds **1a–s** to give the cyclized derivatives **2a–s** (eq 1), the study being mainly centered on substituted diethyl malonates.

Table I. Yields of the Cyclization Compounds 2a–s in the Mn(III) Oxidation of Substrates 1a–s

2	t, h	1 (conv, %)	2 (yield, %)[a]	bp/mmHg or mp (°C)
2a	3	90	85	125/0.05
2b	3.5	86	80	77–8
2c	4	96	88	nd[d]
2d	10	90	85	65–6
2e	3	96	93	182–4/0.1
2f	3	95	90	110/0.05
2g	3	96	91	170/0.2
2h	3	92	90	85–6
2i	3	95	92	nd
2j	4 (12)	93 (10)	8	nd
2k	0.3 (4)[b]	100 (92)	13 (40)[b]	71–3
2l	8	75	39	120/0.2
2m	3	93	47	135/0.05
2m′	3	93	44	140/0.05
2n	24	60	30	138/0.05
2p	4	95	90	96–7
2p′	4	95	3.5[c]	51–2
2q	2	85		
2r	7	75	15	140/0.05
2s	5	83	70	86–7

[a] Isolated product. [b] Reaction performed at 20 °C. [c] Determined by GLC-MS. [d] nd = not determined.

Results

Preliminary experiments indicated that ethyl esters of carboxylic acids were stable toward transesterification in acetic acid solutions in the presence of sodium acetate (12 h at 80 °C) and that manganese(III) acetate was completely consumed in the presence of **1h** in 3 h at the same temperature. Moreover, the presence of sodium acetate increased the yield of substitution product. Therefore, a general procedure was chosen in which solutions of compounds **1a–s** (0.2 M) and sodium acetate (0.4 M) in acetic acid were treated with 2 equiv of manganese(III) acetate at room temperature under nitrogen, and the resulting solution was kept at 70–80 °C for 2–24 h. The results obtained by using the dihydrated form of manganese(III) acetate are reported in Table I.

No significant difference in yield of cyclization products is observed between dihydrate and anhydrous[10] form of

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(2) (a) Ramaiah, M. *Tetrahedron* **1987**, *43*, 3541. (b) Beckwith, L. J.; Ingold, K. U. In *Rearrangements in ground and excited states*; de Mayo, P., Ed.; Academic Press: 1980; Vol. 1, p 161.
(3) (a) Snider, B. B.; Mohan, R. M.; Kates, S. A. *J. Org. Chem.* **1985**, *50*, 3659. (b) Snider, B. B.; Mohan, R. M.; Kates, S. A. *Tetrahedron Lett.* **1987**, *28*, 841, 845. (c) Snider, B. B.; Patricia, J. J.; Kates, S. A. *J. Org. Chem.* **1988**, *53*, 2137.
(4) Corey, E. J.; Kang Myung-chol *J. Am. Chem. Soc.* **1984**, *106*, 5384.
(5) Julia, M. *Acc. Chem. Res.* **1971**, *4*, 386.
(6) Julia, M.; Mamny, M. *Org. Synth.* **1976**, *55*, 57.
(7) Kurz, M. E.; Barn, V.; P-Nhi Nguyen *J. Org. Chem.* **1984**, *49*, 1603.
(8) Heiba, E. I.; Dessau, R. M. *J. Am. Chem. Soc.* **1972**, *94*, 2888.
(9) (a) Citterio, A.; Fancelli, D.; Santi, R. *Gazz. Chim. Ital.* **1988**, *118*, 415. (b) Citterio, A.; Santi, R.; Tiziana, F.; Strologo, S. *J. Org. Chem.*, preceding paper in this issue.

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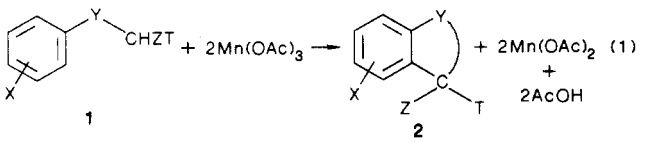
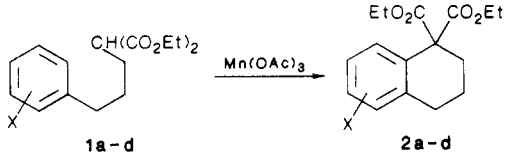


1 2

	X	Y	Z	T
1a	H	$-(CH_2)_3-$	COOEt	COOEt
1b	4-OMe	$-(CH_2)_3-$	COOEt	COOEt
1c	4-$NHCOCH_3$	$-(CH_2)_3-$	COOEt	COOEt
1d	4-NO_2	$-(CH_2)_3-$	COOEt	COOEt
1e	2-C_6H_5	$-CH_2-$	COOEt	COOEt
1f	H	$-O(CH_2)_2-$	COOEt	COOEt
1g	2,3-(CH=CHCH=CH)-	$-O(CH_2)_2-$	COOEt	COOEt
1h	3,4-(CH=CHCH=CH)-	$-O(CH_2)_2-$	COOEt	COOEt
1i	2,3-(CH=CHCH=CH)-	$-O(CH_2)_2-$	COOEt	COMe
1j	H	$-O(CH_2)_2-$	COOEt	CN
1k	H	$-O(CH_2)_2-$	COMe	COMe
1l	H	$-(CH_2)_2-$	COOEt	COOEt
1m	3-OMe	$-(CH_2)_2-$	COOEt	COOEt
1n	4-OMe	$-(CH_2)_2-$	COOEt	COOEt
1p	3,4-(CH=CHCH=CH)-	$-(CH_2)_2-$	COOEt	COOEt
1q	H	$-(CH_2)_4-$	COOEt	COOEt
1r	H	$-O(CH_2)_3-$	COOEt	COOEt
1s	3,4-(CH=CHCH=CH)-	$-O(CH_2)_3-$	COOEt	COOEt

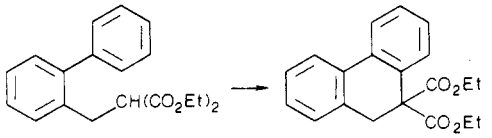
the Mn(III) salt, whereas the rate of disappearance of Mn(III) is widely different depending on the structure of the carbonyl substrate and side reactions. The time reported in Table I is indicative of 95% decomposition of Mn(III) complexes, except for the derivative **1n** for which the Mn(III) conversion was 80% after 24 h.

Among compounds **1a–k**, which can afford Ar_26 cyclization, the malonic acid derivatives **1a–h** and the acetoacetate derivative **1i** gave six-membered cyclic products in nearly quantitative isolated yield (>85%). Compounds



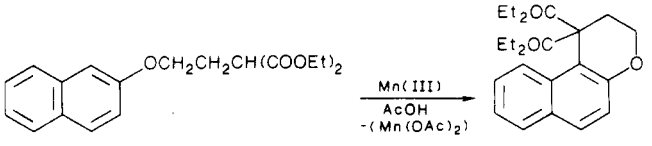
1a–d **2a–d**

a, X = H; **b**, X = 4-OCH_3; **c**, X = 4-$NHCOCH_3$; **d**, X = 4-NO_2



1e **2e**

1a–d gave tetrahydronaphthalene derivatives **2a–d**, compound **1e** gave the dihydrofenantryl derivative **2e**, and compounds **1f–i** gave the chroman derivatives **2f–i** (eq 2).



1h **2h** (2)

The cyano ester **1j** and the acetylacetone derivative **1k** give only traces of cyclization products at 70 °C. However, whereas **1i** is unreactive toward manganese(III) acetate at 30 °C for 12 h, **1k** is converted to **2k** in 40% yield in 5 h.

The main side product observed was the corresponding α-hydroxymalonate, which was found to increase in the presence of oxygen.

With compounds **1a–k** no regioselectivity problem arises from the cyclization, except with **1h**, for which two different products can be expected from the cyclization to position 1 or 3 of the naphthalene ring. Only the product of substitution to position 1 (**2h**) is selectively obtained, the regioisomer from the cyclization to position 3 was undetected by capillary GLC, HPLC, and NMR analyses.

In reaction 2 no side product arising from nuclear acetoxylation is observed in contrast with the results obtained in the intermolecular malonylation process.[9] The kinetics of reaction 2 can be easily followed by HPLC analysis of **1h** and **2h** and by iodometric titration of Mn(III). At all conversions, the data follow a second-order equation, rate = k[Mn(III)][**1h**], which allows the rate constants of the reaction 2 at three different temperatures, 60, 70, and 80 °C (Table II), to be obtained.

Table II. Second-Order Rate Constant and Activation Parameters for the Oxidation of Compound 1h with $Mn(OAc)_3$

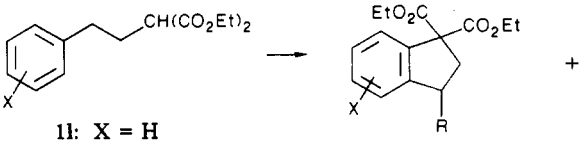
T, °C	k (M^{-1} s^{-1}) × 10^4	E_a, kcal/mol	$\Delta H^{\ddagger}$, kcal/mol	$\Delta S^{\ddagger}$, cal/°C·mol
80.0	45.7 ± 0.6			
70.0	15.9 ± 0.5	35.9 ± 0.3	25.2 ± 0.3	2.1 ● 0.5
60.0	4.94 ± 0.5			
80.0[a]	22.6 ± 0.8			
80.0[b]	23.6 ± 0.9			

[a,b] In the presence of manganese(II) acetate (1.1 and 4.5 mmol, respectively).

A ln (K_{obsd}/T) vs $1/T$ plot and least-squares analysis of the k_{obsd} data yielded $\Delta H^{\ddagger}_{obsd}$ = 25.2 ± 0.3 kcal/mol and $\Delta S^{\ddagger}$ = 2.1 ± 0.5 cal/K mol.

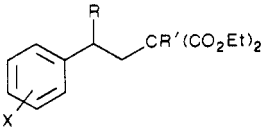
No retarding effect of Mn(II) concentration was found in the kinetics of reaction 2 (Table II, entries 4 and 5).

Ar_25 cyclization products **2l–p** were analogously obtained in the oxidation of compounds **1l–p** by manganese(III) acetate. However, differently from the Ar_26 processes, side products of benzylic acetoxylation and dimerization at the malonic position were commonly observed with less reactive substrates. Diethyl α-(phenylethyl)malonate (**1l**) affords the indan **2l** in 39% yield at 75% conversion by using 2 equiv of manganese(III) acetate. The yield can be increased to 51% by using 3 equiv of the oxidant. Several side products are detected by HPLC; the more relevant were identified as the products of benzylic acetoxylation of starting and cyclic product (**4l** and **3l**, 5% and 4% yield, respectively) and the dimer **5l** (15%).



1l: X = H
1n: X = 4-OMe

2l: X = H, R = H
2n: X = 4-OMe, R = H
3l: X = H, R = OAc
3n: X = 4-OMe, R = OAc



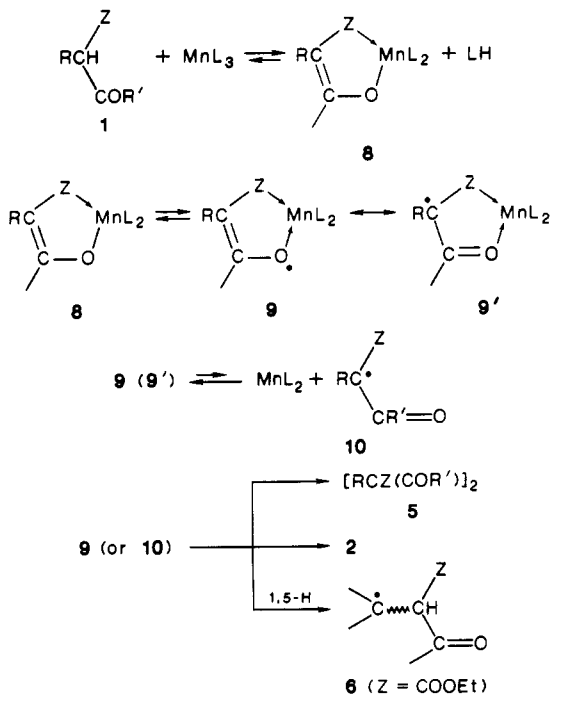
(3)

4l: X = H, R′ = H
4n: X = 4-OMe, R = OAc, R′ = H
5l: X = H, R = H, R′ = $-C(COOEt)_2(CH_2CH_2Ph)$
5n: X = 4-OMe, R = H, R′ = $-C(COOEt)_2(CH_2CH_2$-*p*-OMePh)

The oxidation of the 4-methoxy derivative **1n** is slower but affords similar product distribution. A 30% yield of indan **2n** was obtained after 24 h with a 60% conversion of **1n** and a 80% conversion of Mn(III). Compounds **3n**, **4n**, and **5n** were formed in 3, 6, and 10% yield, respectively.

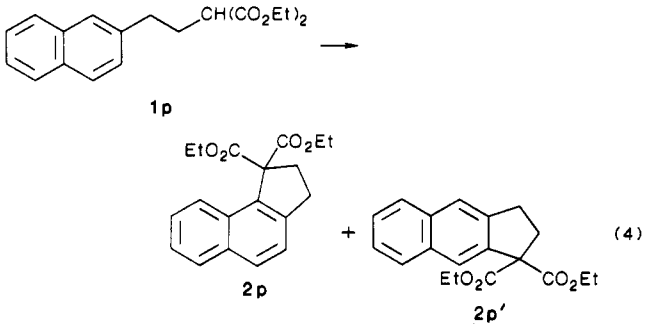
(10) Lux, H. *Handbook of Preparative Inorganic Chemistry*; Braner, G., Ed., Academic Press: New York, 1965; p 1470.

Scheme I



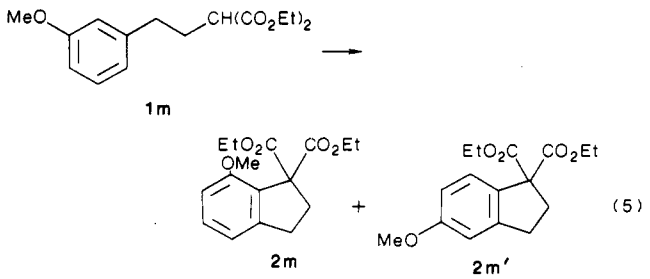
With both substrates **1l** and **1n** the side-chain acetoxylation products **3** and **4** were found to decrease with the decrease of the concentration of **1** (compound **3n**, for instance, was obtained in 5 and 0.8% yield starting from 0.2 and 0.02 M solution, respectively). This result can also be used to increase the yield of substitution product.

On the contrary, nearly quantitative yields of Ar_25 cyclization are observed with the naphthalene (**1p**) and the 3-methoxyphenyl derivatives (**1m**) and the 3,4-dimethoxy derivative. In the first case, the substitution occurs mainly at position 1 to give the compound **2p** (90% yield), whereas the isomer **2p'** was formed in 3.5% yield (eq 4).



(4)

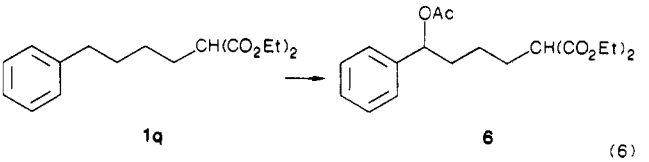
In the second case, the two possible substitution isomers (**2m** and **2m'**) are obtained in comparable amounts (47 and 44%, respectively) (eq 5).



(5)

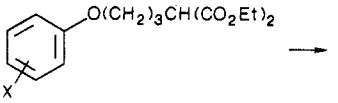
The presence, or the absence, of acetate ions as well as lower temperatures does not affect significantly the ratio of the isomers **2m** and **2m'**.

The study was extended to compounds **1q–s** which can, in principle, give the less favorable Ar_27 cyclization process. However, although the reaction between compound **1p** and manganese(III) acetate is fast (2 h), no aromatic substitution product was observed, and the product of benzylic acetoxylation **6** is obtained in high yield (eq 6).

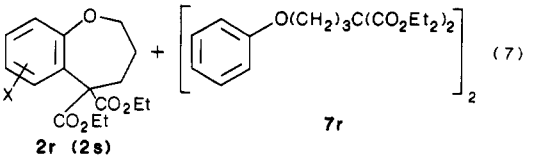


(6)

With the more electron-rich aromatic substrates **1r** and **1s**, for which the 1,6-intramolecular H-abstraction can be ruled out, the seven-membered cyclization products **2r** and **2s** were obtained in 15 and 60% yield, respectively. However, the conversion of the aromatic substrates was high and a 40% yield of dimer **7r** was obtained with the less electron-rich compound **1r** (eq 7).



1r: X = H
1s: X = 3,4-CH=CHCH=CH



(7)

Discussion

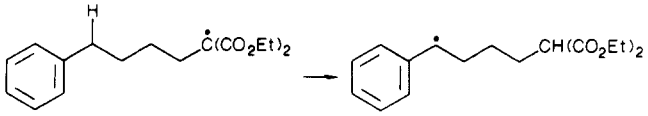
The results obtained in this study suggest the involvement of α-carbonyl alkyl radical intermediates and therefore the monoelectronic oxidation of substrates at the β-dicarbonyl moiety. No evidence for the involvement of aromatic radical cations can be deduced although these intermediates were reported[11] to be responsible for the oxidation of similar substrates under similar conditions and we have described in the preceding paper[9] that aromatic acetoxylation competes with intermolecular aromatic malonylation. This process must be strongly reversible or different Mn(III) species, which are not able to oxidize the aromatic nucleus, must be present in the medium. It is known that Mn(III) β-dicarbonyl complexes[12] are relatively stable in acetic acid, and our results suggest that these are involved in the oxidation of substrates **1a–s**. The rate constants observed in the oxidation of **1h** are in a range expected for electron-transfer processes of Mn(III)-complexed β-dicarbonyl compounds (i.e., E_{att} = 25.2 kcal/mol for $Mn(acac)_3$[13]).

The widely different rates of oxidation observed for compounds **1a–s**, particularly with the isomeric esters **1m** and **1n**, indicate that radical generation cannot be rate limiting in all cases. A strong dependence of rates of Mn(III) oxidation on the structure of unsaturated β-dicarbonyl substrates has been previously observed.[4] However, in a fast process, i.e., reaction 2, the addition of manganese(II) acetate does not affect the overall rate,

(11) Andrulis, P. J., Jr.; Dewar, M. J. S.; Dietz, R.; Hunt, R. L. *J. Am. Chem. Soc.* **1966**, *88*, 5473.
(12) Nikolaev, A. F.; Belogorodskaya, K. V.; Schibalovich, V. G.; Andreva, E. D.; Bogdanova, L.V.; Vinogradov, M. V. *J. Appl. Chem. USSR* **1973**, *46*, 2875.
(13) Nikolaev, A. F.; Belogorodskaya, K. V.; Shibalovich, V. G.; Andreva, E. D.; Ivanova, G. I. *J. Appl. Chem. USSR* **1975**, *48*, 2096.

indicating that no direct interaction between α-carbonylalkyl free radicals and Mn(II) occurs. In our opinion, a possible explanation of these results can be accommodated by the reaction scheme proposed in Scheme I.

α-Carbonylalkyl radicals (**10**) are formed via reversible electron transfers from Mn(III)-complexed substrates (**8**) and they probably remain linked to Mn(II) (**9**), favoring the back-transfer process. Malonyl radicals are clearly oxidant species for which the redox potential in the range $E° = 0.7–0.9$ V vs NHE[14] have been reported. The similar values[15] of redox potential for the couple Mn(II)/Mn(III) in acetic acid suggest that an equilibrium between the malonyl radicals and Mn(III) can be established and further evolution of radicals can become rate determining if $k_{-1} > k_a$ or k_H. In fact, hydrogen abstraction from saturated C–H bond is usually a slow process for α-dicarbonylalkyl radicals owing to the significant thermodynamic stabilization conferred by the two electron-withdrawing substituents to the radical center (H_r = 3.15, 6.5, and 5.5 kcal/mol for COOalkyl, COalkyl, and CN, respectively[16]). Secondary benzylic or allylic C–H bonds can be more easily involved owing to the stabilization of the benzyl or allyl substituent (H_r = 8.4 and 8.5 kcal/mol, respectively[16]). Intramolecular 1,6-H transfer from the benzylic position can therefore be expected to be a fast process ($k > 10^4$ M^{-1} s^{-1})[17] and compete effectively with intramolecular aromatic substitution or radical dimerization, as observed for substrate **1g** (eq 8).



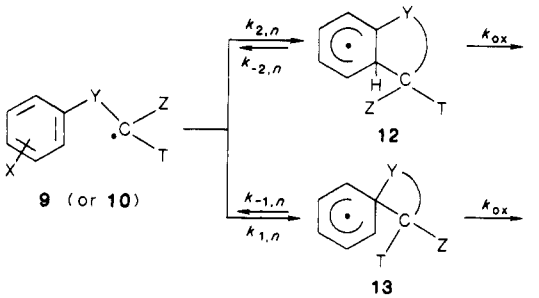
9 (or **10**) **11** (8)

The fact that benzylic acetoxylation of starting and cyclic products was observed as side products in the oxidation of less reactive substrates **1i** and **1k** and that their yield decreases with dilution indicates that they arise from intermolecular hydrogen abstration and not through the benzylic deprotonation of an aromatic radical cation.

Regarding the intramolecular aromatic alkylation process, the following general considerations can be made.

(i) Ar_25, Ar_26, and Ar_27 cyclizations are favored by the presence of an electron-rich aromatic ring or, more correctly, by the higher electron density of the aromatic carbon atom near the α-carbonylalkyl substituent, i.e., by a high coefficient of HOMO orbital of carbon atom involved. The influence of substituents H, OMe, $NHCOCH_3$, and NO_2 in the para position of diethyl phenylpropylmalonates (and meta to the aromatic carbon involved in the cyclization) is apparent from the time of Mn(III) disappearance (compounds **1a–d**, Table I), but Ar_26 cyclization products were obtained in all cases in good yield. A more pronounced effect is observed with the corresponding phenylethyl derivatives for which the cyclization reaction was undetected with the 4-nitro derivative and competitive with dimerization with less electron-withdrawing substituents. These results arise from the strong electrophilic behavior of β-dicarbonylalkyl radicals,[18] which are related to their oxidant properties.

Scheme II



(ii) Ar_26 cyclizations are easier than Ar_25 cyclization and these, in turn, are easier than Ar_27 processes. Relative rate constants for these processes can be roughly estimated from the ratio of products of cyclization and dimerization. The values found are 12:1:<0.01 for the phenylalkyl derivatives and >100:1:0.02 for the phenoxyalkyl derivatives. A precise determination of rate constants at present is difficult, is under further study, and is complicated by the reversibility of the addition reaction and side reactions.

(iii) No evidence for the involvement of the Ar_1n mode of ring closure could be deduced from this work. Previous results[19] indicate that both Ar_15 and Ar_26 modes of ring closures are available to 4-arylbutyl (**10**, Y = $(CH_2)_3$; X, Z, T = H) and related radicals (Scheme II). These studies provide evidences for reversible formation of the spiro intermediate,[20] whereas the Ar_16 cyclization was irreversible at high temperatures. Calculations of the relative stability of the Ar_15 and Ar_16 radicals indicate the first to be about 2.5 kcal less stable and the second 6.2 kcal more stable than the open-chain radicals.[20] The rate constants for the last process has been estimated to be in the range $1–5 \times 10^4$ s^{-1} at 50–80 °C,[20] but subsequent ESR work[21] indicated that the value is probably an order of magnitude lower.

Radicals containing substituents capable of delocalizing the free spin (where either or both Z and T are Ar, CN, COOR, CO, etc.) are known to have a significant effect on the rate and regioselectivity of ring-closure reactions of olefins.[22] Our results indicate that the carbon free radicals substituted by two electron-withdrawing carbonyl groups add to electron-rich aromatics in the Ar_2n mode faster than unsubstituted alkyl radicals. The results depend not only on the ratio of rate constants $k_{1,n}/k_{2,n}$ but also on further reaction of cyclized radicals with the oxidant present in the medium (k_{ox}) and on the reversibility of the $Ar_{1,n}$ addition ($k_{1,n}/k_{-1,n}$) and $Ar_{2,n}$ addition ($k_{2,n}/k_{-2,n}$). The reversibility is particularly important when two electron-withdrawing delocalizing substituents are present and when steric hindrance in the adduct radical significantly decreases the strength of the bond formed.[22] This situation is more pronounced for the spiro adducts than for the Ar_2n adduct. Several cases of reversibility in the addition of α-dicarbonylalkyl radicals to olefins have been reported.[23]

(iv) The regioselectivity observed in the cyclization appears to be related to the electronic effect more than to the steric hindrance of the bulky tertiary radical inter-

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mediates. High regioselectivity is obtained for the 1 position in the 2-naphthylalkyl and 2-naphthoxyalkyl derivatives, whereas with substrate **1** a very similar ratio of ortho and para cyclic malonates were obtained. This isomer distribution compares well with the results[9] of intermolecular addition of diethyl methylmalonate and diethyl malonate to naphthalene, 2-methoxynaphthalene, and anisole, respectively, indicating that no peculiar steric effect operates in the intramolecular reaction.

The aromatic substitution by malonyl radicals shows positional selectivity resembling the aromatic substitution by charged electrophiles. This is certainly the result of strongly electrophic behavior of α-carbonylalkyl radicals in the addition to π-systems.

(v) The increase of resonance stabilization on the open carbon radical seems to hinder the substitution. This result is probably related to the reversibility of the addition step and to a reduced addition rate.

The absence of concurrent oxidation of the aromatic nucleus and of benzylic position makes the use of the metal salts in high oxidation state extremely attractive for intramolecular aromatic substitution of compounds **1**. Attempts to generate α-carbonylalkyl radicals from compounds **1d** and **1h** by thermal decomposition of dibenzoyl peroxide and di-*tert*-butyl peroxalate in the range of 50–110 °C in acetic acid or benzene and chlorobenzene result in products of oxidation of the benzylic position. This behavior is quite different from the analogous processes of addition to olefins, where metals and peroxide sources are reported to work equally well[5,19] and suggests a higher extent of reversibility in the addition to aromatic than olefins. Therefore, the role of the metal is probably 2-fold in these reactions: (i) it controls the chemoselectivity of the oxidation at the β-dicarbonyl moiety of the substrate and (ii) it assists the homolytic aromatic substitution via complexation of the radical, a process that increases the electrophilic character of the radical center and reduces the reversiblity of the addition by increasing the oxidation rate (k_{ox}) of cyclohexadienyl radical intermediates.

Experimental Section

General Methods. Melting points were obtained on Hoover a capillary melting point apparatus and are uncorrected. Boiling points were determined in a short path distillation apparatus (Büchi). ^1H and ^{13}C NMR spectra were obtained in $CDCl_3$ on a Bruker WH 90 or an AM 300 spectrometer; the data are in ppm relative to tetramethylsilane. Mass spectra (MS) were obtained at 70 eV on a Varian Mat 112 F GC-MS spectrometer equipped with a SP 2100 coated fused silica capillary column (25 m × 0.22 mm i.d.) with helium as a carrier gas. Quantitative gas chromatographic analyses for determination of conversions and isomers distributions were performed by the internal standard method on a DANI 6500 HR capillary gas chromatograph equipped with a PTV injection, a WSCOT capillary column (25 m × 0.22 mm i.d.) coated with polydimethylsiloxane (CP-Sil 5, film thickness 1 μm), FID detector, hydrogen as carrier gas, and temperature programmed from 50 °C to 190–250 °C at 10°/min. Integration of chromatographic traces was carried out on a Spectra Physics SP 4200 computing integrator. HPLC analyses were performed on a Bruker LC 21-51 instrument equipped with an autosample injection device under isocratic conditions using a Si 60 column (5 m, 20 × 0.25 cm i.d.) (Merck) and a mixture of hexane/ethyl acetate (95:5 or 70:30) as eluent at a flow rate of 1.5 mL/min and UV detection at 254 nm. Preparative separations were carried out on silica gel 60 (230–400 mesh, Merck) using the flash chromatography technique. In the case of high yield reactions the residue was directly crystallized from pentane/diethyl ether or distilled.

Materials. Manganese(III) acetate dihydrate was obtained from Fluka; anhydrous manganese(III) acetate was prepared as described.[11] Both salts were tested by iodometric titration for purity, and only samples having more than 98% manganese(III) acetate were used. Starting materials **1a–s** were synthesized by a standard procedure, which involves the nucleophilic substitution of the corresponding alkyl bromide with the anion of the β-diketo derivative (prepared from NaH and β-dicarbonyl compounds in THF, adding eventually anhydrous DMF when the salt became insoluble), followed by refluxing the mixture under N_2 for 12 h. The resulting mixture was concentrated, dissolved in the minimum amount of diethyl ether, and chromatographed on a silica gel column; the fractions containing the malonate were distilled at 0.1 mmHg or recrystallized from pentane–diethyl ether mixtures. The substituted alkyl bromides were synthesized starting from the corresponding alcohol by using PBr_3[21] or PPh_3/CBr_4[22] or from sodium phenates and α,ω-dibromoalkanes under PTC conditions. The overall yield of these preparations starting from the alcohol or phenol were in the range 70–80%. 3-(4-Nitrophenyl)propyl bromide was obtained by nitration of 3-phenylpropyl bromide with 90% HNO_3 at −20 °C for 90 min, followed by separation of the nitration isomers by column chromatography (SiO_2 230–400 mesh (Merck) eluting with a 8:2 hexane–benzene mixture). The compound **1c** was obtained by H_2 reduction of the nitro derivative **1d** with 5% Pd/C in acetic anhydride. All starting products were checked for purity by capillary GLC and used when >98% pure.

General Procedure for the Cyclization Reaction. Compound **1** (10 mmol) and anhydrous sodium acetate (20 mmol) were dissolved in acetic acid (30 mL) and dihydrated manganese(III) acetate (20 mmol) was added to the resulting solution at room temperature under N_2. The mixture was placed into a thermostatic bath at 70 °C for the time reported in Table I. The solution becomes dark brown and homogeneous, then the color fades, and manganese(II) acetate separates. Quantitative analyses of the resulting mixture were carried out by GLC or HPLC after addition of diethyl phenylmalonate as internal standard, dilution with diethyl ether (150 mL), and filtration. For isolation purposes, the resulting solution (without the internal standard) was washed with water (2 × 25 mL), 10% NaOH solution (2 × 30 mL), and water (2 × 25 mL), dried over Na_2SO_4 and flash chromatographed using a mixture of hexane/ethyl acetate (90:10 or 80:20) as the eluent. The yield and the analytical data of the isolated cyclic product are reported in Table I and Table III (supplementary material), respectively.

Determination of Rate Constant for Reaction 2. A solution of **1h** (2 g, 6.08 mmol), sodium acetate (1.01 g, 12.1 mmol), and diphenyl ether (0.511 g as internal standard) in acetic acid (20 mL) was kept in a thermostatic bath under nitrogen at the desired temperature, for 20 min, then the solid manganese(III) acetate dihydrate (4.22 g, 12.1 mmol), preheated to the same temperature, was added at once under magnetic stirring. At different times, 0.2 mL of the solution was withdrawn and added to a mixture of 0.5 M $TiCl_3$ (0.3 mL) and ethyl acetate (1 mL). Back titration of the excess Ti(III) with 0.1 N cerium(IV) sulfate gives the amount of Mn(III) reacted, whereas HPLC analysis of the ethyl acetate solution, dried and filtered, gives the conversion of **1h** and the yield of **2h**. Two similar experiments were carried out in the presence of anhydrous manganese (II) acetate. The concentrations of Mn(III) and **1h** were plotted against time, and a second-order kinetic equation was fitted at all conversions. Least-squares analysis of data allows the determination of the rate constant at three different temperatures. A mean of two independent values was measured at each temperature. The rate constants obtained are reported in Table II, along with the activation parameters of the process.

From the reaction mixture of oxidation of **1** the following compounds were identified by column chromatography (SiO_2, 100 g, 9:1 hexane/ethyl acetate as eluent).

1,1-Dicarbethoxy-3-acetoxyindan (3l). ^1H NMR ($CDCl_3$, δ): 7.58 (1 H, dd), 7.4–7.1 (3 H, m), 5.95 (1 H, dd), 4.23 (4 H, q), 3.1–2.7 (2 H, m), 1.32 (6 H, t). MS: *m/e* (relative intensity) 320 (M^+, 2), 277 (5), 260 (23), 204 (18), 188 (33), 187 (42), 160 (39), 131 (67), 116 (52), 115 (100), 103 (27), 43 (78).

Tetraethyl 1,2-Bis(phenylethyl)-1,1,2,2-ethanetetracarboxylate (5l). ^1H NMR ($CDCl_3$, δ): 7.2–7.3 (5 H, m, Ar), 4.2 (4 H, q), 2.7–2.5 (2 H, m), 2.4–2.2 (2 H, m), 1.3 (6 H, t). IR ν_{max} (cm^{-1}): 1735.

Diethyl α-(2-Phenylethyl)-α-hydroxymalonate (isolated by **4l** hydrolysis). ^1H NMR ($CDCl_3$, δ): 7.3–7.1 (5 H, m, Ar), 4.3 (4 H, q), 3.5 (1 H, br, OH), 3.0–2.7 (2 H, m), 2.5–2.3 (2 H, m), 1.3

(6 H, t). MS: *m/e* (relative intensity) 280 (M^+, 0.5), 279 (4), 265 (65), 252 (25), 250 (13), 235 (16), 176 (100), 160 (21), 148 (25), 133 (30), 120 (39), 105 (76), 91 (99).

From the oxidation of **1n** the following compounds were isolated (SiO_2, hexane/ethyl acetate, 8:2).

Diethyl α-[3-(4′-Methoxyphenyl)-3-acetoxypropyl]-malonate (4n). ^1H NMR ($CDCl_3$, δ): 6.92 (d, 2 H, H_2, H_6), 7.32 (d, 2 H, H_3, H_5), 5.73 (dd, 1 H, CHOAc), 4.22 (q, 4 H, CH_2CH_3), 3.80 (s, 3 H, OCH_3), 3.38 (dd, 1 H, $CH(COOEt)_2$), 2.25–2.5 (m, 4 H, CH_2CH_2), 2.04 (s, 3 H, $OCOCH_3$), 1.28 (t, 6 H, CH_2CH_3). MS: *m/e* (relative intensity) 352 (M^+, 11), 309 (8), 265 (22), 217 (12), 192 (70), 150 (100), 137 (32), 43 (8).

1,1-Dicarbethoxy-3-acetoxy-6-methoxyindan (3n). ^1H NMR ($CDCl_3$, δ): 6.9 (dd, 1 H, H_6), 7.12 (d, 1 H, H_2), 7.25 (dd, 2 H, H_5), 6.17 (dd, 1 H, CHOAc), 3.21 and 2.71 (dd, 2 H, CH_2), 2.06 (s, 3 H, $OCOCH_3$), 1.26 (t, 6 H, CH_2CH_3). MS: *m/e* (relative intensity) 350 (M^+, 1), 308 (20), 307 (27), 291 (23), 234 (98), 217 (100), 205 (18), 189 (20), 161 (40), 145 (41), 133 (12), 43 (13).

Tetraethyl 1,6-Bis(4′-methoxyphenyl)-1,1,2,2-hexanetetracarboxylate (5n). ^1H NMR ($CDCl_3$, δ): 6.81 (d, 4 H, H_2, H_6), 7.12 (d, 4 H, H_3, H_5), 4.28 (m, 8 H, CH_2CH_3), 3.76 (s, 6 H, OCH_3), 2.64 (m, 4 H, $ArCH_2$), 2.29 (m, 4 H, $ArCH_2CH_2$), 1.31 (t, 12 H, CH_2CH_3).

Diethyl α-(4-Phenyl-4-acetoxybutyl)malonate (6) (isolated in 80% yield from **1q**). ^1H NMR ($CDCl_3$, δ): 7.46–7.25 (m, 5 H), 5.75 (t, 1 H), 4.18 (q, 4 H), 3.30 (t, 1 H), 2.18–1.5 (m, 8 H), 1.25 (t, 6 H). MS: *m/e* (relative intensity) 290 (M^+, 3), 245 (5), 216 (11), 199 (12), 173 (11), 130 (100), 129 (17), 107 (15), 91 (11), 42 (36).

From the oxidation mixture of compound **1r** the dimer **7r** was isolated in 40% yield (SiO_2, hexane/ethyl acetate 1% gradient starting from 9:1).

Tetraethyl 1,2-Bis(3-phenoxypropyl)-1,1,2,2-ethanetetracarboxylate (7r). ^1H NMR ($CDCl_3$, δ): 7.8–7.43 (m, 4 H), 7.4–7.1 (m, 6 H), 4.22 (q, 8 H), 3.98 (t, 4 H), 2.63–1.80 (m, 8 H), 1.30 (t, 12 H). ^{13}C NMR ($CDCl_3$): 169.62 (C_q, COOEt), 158.95 (CH, C_1), 129.31 (C_q, C_2, C_6), 120.54 (CH, C_4), 114.53 (CH, C_3, C_5), 62.75 (C_q, $C(COOEt)_2$), 67.84 (CH_2O), 61.56 ($COOCH_2CH_3$), 28.03 (OCH_2CH_3), 25.69 ($OCH_2CH_2CH_2$), 13.86 ($COOCH_2CH_3$).

Registry No. **1a**, 26395-09-5; **1b**, 34795-65-8; **1c**, 118598-36-0; **1d**, 118598-37-1; **1e**, 78383-16-1; **1f**, 1787-17-3; **1g**, 118598-38-2; **1h**, 118598-39-3; **1i**, 118598-40-6; **1j**, 118598-41-7; **1k**, 118598-42-8; **1l**, 6628-68-8; **1m**, 111171-90-5; **1n**, 118598-43-9; **1p**, 118598-44-0; **1q**, 78573-23-6; **1r**, 6345-89-7; **1s**, 118598-45-1; **2a**, 115860-33-8; **2b**, 118598-46-2; **2c**, 118598-47-3; **2d**, 118598-48-4; **2e**, 118598-49-5; **2f**, 118598-50-8; **2g**, 118598-51-9; **2h**, 118598-52-0; **2i**, 118598-53-1; **2j**, 118598-54-2; **2k**, 118598-55-3; **2l**, 115860-31-6; **2m**, 118598-56-4; **2m′**, 118598-57-5; **2n**, 118598-58-6; **2p**, 118598-59-7; **2p′**, 118598-60-0; **2q**, 118598-61-1; **2r**, 118598-62-2; **2s**, 118598-63-3; **3l**, 118629-54-2; **3n**, 118598-65-5; **4l**, 118598-71-3; **4n**, 118598-66-6; **5l**, 118598-64-4; **5n**, 118598-67-7; **6**, 118598-68-8; **7r**, 118598-69-9; diethyl α-(2-phenylethyl)-α-hydroxymalonate, 118598-70-2; manganese(III) acetate, 993-02-2.

Supplementary Material Available: Characterization data for **2a–s** (4 pages). Ordering information is given on any current masthead page.

Electrochemical Oxidation of 5-Hydroxytryptamine in Acidic Aqueous Solution

Monika Z. Wrona and Glenn Dryhurst*

Department of Chemistry and Biochemistry, University of Oklahoma, Norman, Oklahoma 73019

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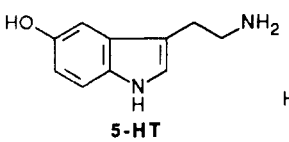
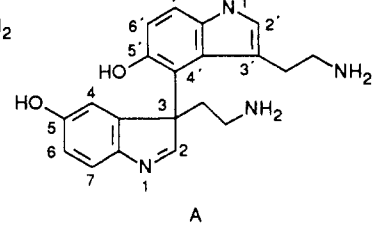
The electrochemical oxidation of 5-hydroxytryptamine (5-HT) has been studied in aqueous solution at pH 2.0 using a pyrolytic graphite electrode. Eight major products formed in the early stages of oxidation of millimolar solutions of 5-HT have been isolated and their structures elucidated by spectroscopic techniques.

The electrochemical oxidation of 5-hydroxytryptamine (5-HT) in acidic (1.05 M $HClO_4$) acetonitrile at a platinum electrode yields a single dimeric product in 80% yield. ^1H and ^{13}C NMR evidence indicates that this dimer is the asymmetric 3,4′-linked indolenine–indole A. Under the

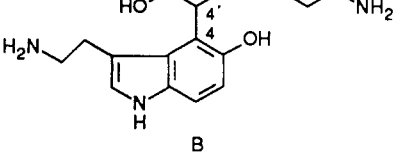


5-HT



A

latter conditions cyclic voltammetric evidence suggests that the initial electrode reaction involves a one-electron abstraction to produce a radical cation with the unpaired electron located at the C(3) position of 5-HT. Coupling of this radical with 5-HT then apparently yields a 3,4′-dimer radical cation. A disproportionation-like second electron transfer then occurs in solution between the 5-HT radical cation and the 3,4′-dimer radical cation to generate 5-HT and, following deprotonation, A. In an earlier report we showed that electrochemical oxidation of very low concentrations (≥30 μM) of 5-HT in acidic (0.01 M HCl) aqueous solution at a pyrolytic graphite electrode also proceeds through the initial formation of a radical intermediate.[2] At low applied potentials (i.e., corresponding to the rising segment of the first voltammetric oxidation peak of 5-HT), the major product is the symmetrical 4,4′-dimer (B) along with a much smaller amount of an



B

asymmetric dimer which, based primarily on ^1H NMR data, was proposed to be 5,5′-dihydroxy-1,4′-bitryptamine. At higher applied potentials the initial radical intermediate is further oxidized (1 e, 1 H^+) to a very reactive quinone imine. Nucleophilic attack by water on the latter intermediate forms 4,5-dihydroxytryptamine, which is rapidly

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