Steric, Polar, and Resonance Effects in Reactivity and Regioselectivity of Aryl Radical Addition to α,β-Unsaturated Carbonyl Compounds

Attilio Citterio,* Francesco Minisci, and Elena Vismara

Istituto di Chimica del Politecnico, Piazza L. da Vinci 32, 20133 Milano, Italy

Received May 28, 1981

Free-radical decomposition of diazonium salts by titanous salts in the presence of olefins conjugated with carbonyl groups leads to reductive arylation or arylation and diazo coupling of the radical adduct, depending on the orientation of the aryl radical addition (β or α). The absolute rate constants of the addition (10^7–10^8 M^{-1} s^{-1} at 5 °C) were determined by comparison with the rate of the iodine abstraction by aryl radicals from isopropyl iodide. The obtained data of the addition rates to the β position correlate well with the E_s steric parameters. The influence of the resonance stabilization of the radical adduct on the reactivity can be significant, but the regioselectivity of the addition is mainly determined by steric effects. The different fate of the α- and β-radical adducts are discussed on the basis of their different polar character.

The addition of carbon-centered free-radicals to olefins has been a matter of many investigations both in gas phase[1] and in solution.[2] The reactivity and regioselectivity are due to a complex interplay of several factors: strength of the new bonds formed and stabilization of the radical adducts; steric and polar interactions between the attacking radical and the alkene. However, until recent years, the anti-Markovnikov orientation in the addition to unsymmetrical olefins has been mainly ascribed to the stabilization of the radical adducts. The most popular student testbooks of general organic chemistry[3] and also specific monographs of free-radical chemistry[4] emphasize this assumption. Three main reasons have led to this generally accepted statement.

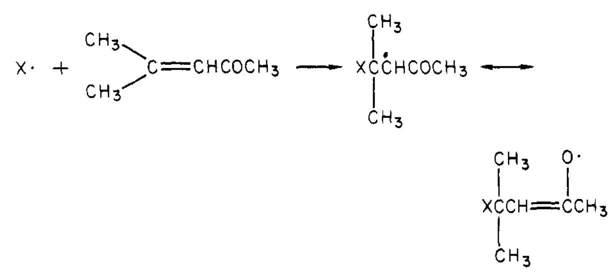
(a) The prevalent formation of the more stable radical adduct in free-radical addition to olefins has the corresponding rationalization in the Markovnikov orientation in the addition of electrophilic species to olefins with prevalent formation of the more stabilized adduct with carbocationic character. Frequently, general concepts in free-radical chemistry are derived from ionic reactions; however, this analogy is an oversimplification because the extent of the energetics and its influence on the kinetic parameters are quite different in the two cases.

(b) Steric and stabilizing effects often operate in the same direction: the addition to the less substituted olefinic carbon atom often leads to the more stabilized radical adduct because the substitution of hydrogen atoms always results in a stabilization of a radical-centered carbon atom. Thus it is generally quite a hard problem to quantitatively separate steric from stabilizing effects in these cases. When steric and resonance effects operate in opposite direction in polysubstituted olefins it is easier to evaluate their relative importance in determining the regioselectivity of the addition.

(c) The behavior of some polysubstituted olefins toward free-radical addition would appear to substantiate the dominant role of the stability of the radical adducts in determining the regioselectivity. Particularly, all the known free-radical additions to 3-penten-2-one or methyl crotonate and 4-methyl-3-penten-2-one occurred either exclusively or primarily at the β position in agreement with a stabilizing resonance effect of the carbonyl group (eq 1).

Table I. Regioselectivity in Addition of 4-Chlorophenyl Radical to the Double Bond of α,β-Unsaturated Carbonyl Compounds

compd	R_1	R_2	β addition, %	α addition, %	β/α
1a	H	H	>96	<4	24
1b	H	CH_3	78	22	3.5
1c	H	$CH(CH_3)_2$	53	47	1.1
1d	H	$C(CH_3)_3$	20	80	0.25
1e	CH_3	CH_3	16	84	0.19
1f	H	C_6H_5	24	76	0.32
methyl crotonate			75	25	3.0


(1)

However, these results are in marked contrast to a recent report of ours[5] concerning the addition of aryl radicals to 4-methyl-3-penten-2-one, in which the attack takes place mostly at the α position.

Thus we undertook an investigation concerning the structure–reactivity–selectivity relationships in the addition of aryl radicals to olefins conjugated with carbonyl groups in order to better understand the factors which govern this particular behavior and also to draw further indications about the more general problem of the free-radical addition reaction to olefins.

The aryl radicals are particularly interesting for this purpose because they add irreversibly to the double bonds and the observed regioselectivity is certainly kinetic in nature. Moreover, they are less sensitive to steric effects than other carbon-centered radicals, being sp^2–σ-type

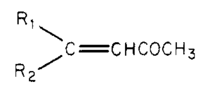
(1) J. M. Tedder and J. C. Walton, *Tetrahedron*, 36, 701 (1980), and references therein.
(2) (a) C. Walling and E. S. Huyser, *Org. React.* 13, 91 (1963); (b) F. W. Stacey and J. F. Marris, Jr., *ibid.*, 13, 150 (1963); (c) G. Sosnowsky, "Free Radical Reactions in Preparative Organic Chemistry", McMillan, New York, 1964; (d) B. Giese, G. Kretzchmar, and J. Meixner, *Chem. Ber.*, 113, 2787 (1980); (e) D. C. Nonhebel and J. C. Walton, "Free Radical Chemistry", Cambridge University Press, Cambridge, 1974; (f) P. I. Abell in "Free-Radicals", J. K. Kochi, Ed., Wiley-Interscience, New York, 1973, Vol. 2, p 63.
(3) R. T. Morrison and R. N. Boyd, "Organic Chemistry", Allyn and Bacon, Boston. J. D. Roberts and M. C. Caserio, "Basic Prenciples of Organic Chemistry", W. A. Benjamin, New York, 1960.
(4) R. L. Huang, "The Chemistry of Free-Radicals", E. Arnold, Ed., London, 1974, p 102.
(5) A. Citterio, F. Minisci, A. Albinati, and S. Bruckner, *Tetrahedron Lett.*, 2909 (1980).

0022-3263/82/1947-0081$01.25/0 © 1982 American Chemical Society

radicals, and can therefore add also to polysubstituted double bonds such as 4-methyl-3-penten-2-one, whereas the alkyl radicals do not react with this olefin for steric reasons, although they are very reactive with 3-buten-2-one. The aryl radicals are also very reactive and unselective species with poor sensitivity to polar effects.[6,7] It is a striking that quantitative data on reactivity and regioselectivity are not available for the addition of aryl radicals to this class of olefins in spite of the significant synthetic involvements (i.e., Meerwein reaction of diazonium salts[8]).

Results

The methyl alkenyl ketones **1a–f** of Table I were investigated. Methyl crotonate was also investigated in order to compare the behavior with that of 3-penten-2-one.

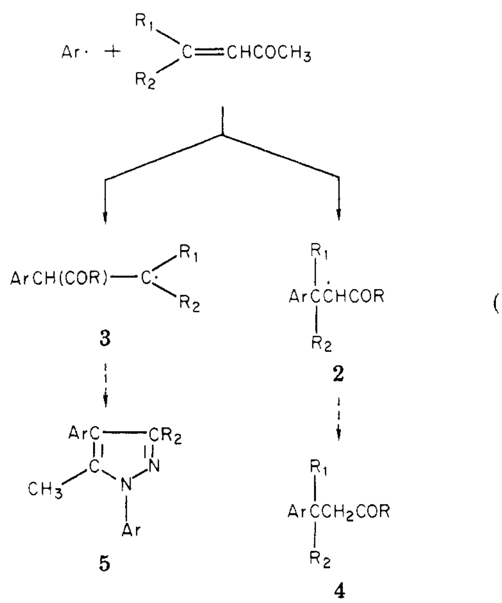


1

As an aryl radical model was chosen the 4-chlorophenyl radical which was generated from decomposition of 4-chlorobenzenediazonium tetrafluoroborate by titanous salt in water–acetic acid medium at 5 °C.

The research was carried out along three lines: (a) synthetic aspects, (b) regioselectivity, and (c) absolute rate constants.

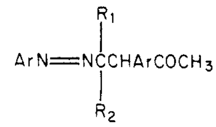
(a) In the presence of the olefins **1a–f** the aryl radicals add to both the β and α positions, giving **2** and **3** alkyl radical adducts, respectively (eq 2). The adducts **2a–f** lead



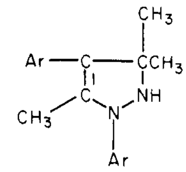
(2)

to the saturated ketones **4a–f**, which represents the products of the "reductive arylation" of the double bond [just as the haloarylation products are formed in the corresponding oxidative arylation (Meerwein reaction)[8]].

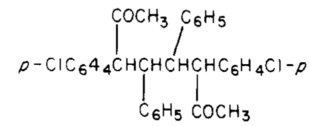
The α-adducts **3a–f** lead to the pyrazole derivative **5** by reaction with diazonium salts. With **1e** the azo compound **6** was obtained along with low amount of pyrazolidine **7**. With **1f** the compounds **4f** and **5f** were not the only products formed; the dimer **8** and the olefin **9** were also isolated. With methyl crotonate, the compounds **10** and



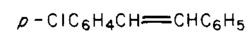
6e, $R_1 = CH_3$; $R_2 = CH_3$; $Ar = p\text{-}ClC_6H_4$



7, $Ar = p\text{-}ClC_6H_4$

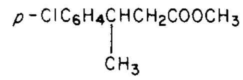


8

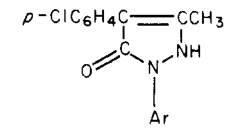


9

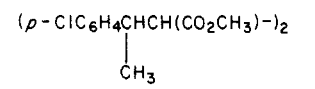
11, corresponding to **4** and **5**, were obtained along with some dimer **12**. Byproducts arising from diazonium salts,



10



11



12

which do not involve the olefin, are chlorobenzene, 4-4′-dichlorobiphenyl, and 4,4′-dichloroazobenzene (all in low yield, <10%). All the compounds were isolated and characterized by analytical procedures reported in the Experimental Section together with yields, physical constants, and analytical data.

(b) The regioselectivity data obtained in the addition of the 4-chlorophenyl radical to **1a–f** and methyl crotonate are summarized in Table I. The results were obtained by quantitative GLC analysis and in the case of **1f** and methyl crotonate by NMR quantitative analysis of the crude reaction product, after separation of the reaction products by chromatographic methods. With **1a** only the compound **4a** was easily detected; very small amounts of **5** (<4%) were detected by GLC/MS analysis; the quantitative analysis is therefore somewhat uncertain; moreover, the addition of primary alkyl radicals to diazonium salts is not effective as the addition of secondary and tertiary alkyl radicals;[9] this fact increases the uncertainty of the regioselectivity for this olefin.

With **1f**, the attack at the α position was evaluated by the sum of **5**, **8**, and **9**.

(c) The knowledge of the relative and absolute rates in the addition of aryl radicals to olefins conjugated with carbonyl groups is important for understanding the role played by the various factors.

Addition to the double bond is the main reaction of aryl radicals with **1a–f**; therefore, this process must be very fast because it successfully competes with other fast aryl radical reactions (i.e., hydrogen abstraction,[6,10] aromatic addition,[11] reduction by titanous salt, etc.). The iodine abstraction by aryl radical from isopropyl iodide (a very specific and fast radical reaction;[12] eq 3) therefore was chosen as the

(6) R. G. Kryger, I. P. Lorand, N. R. Stevens, and N. R. Merron, *J. Am. Chem. Soc.*, **99**, 7589 (1977), and references therein.
(7) F. Minisci, *Top. Curr. Chem.*, **62**, 1 (1976).
(8) C. S. Rondestveldt, Jr., *Org. React.*, **24**, 225 (1976); 11, 189 (1960).
(9) Unpublished results of this laboratory.
(10) The hydrogen abstraction rate from methanol was evaluated as 1.4×10^5 M^{-1} s^{-1} (J. E. Pacher, D. B. House, and E. S. Rasburn, *J. Chem. Soc. B*, 1574 (1971); hydrogen abstraction from toluene was estimated as 3.3 10^5 M^{-1} s^{-1} (K. U. Ingold, ref 2f).
(11) The addition rate constant to chlorobenzene was estimated to be 1.3×10^6 M^{-1} s^{-1} at 45 °C (ref 6) or 4.8×10^4 M^{-1} s^{-1} at 25 °C (A. Mac Lachlan and R. L. McCarthy, *J. Am. Chem. Soc.*, 84, 2519 (1962).

Table II. Decomposition of 4-Chlorobenzenediazonium Tetrafluoroborate (2×10^{-4} mol) by Ti(III) in the Presence of Isopropyl Iodide and Methyl Vinyl Ketone[a]

$(i\text{-PrJ})_{in}$, 10^3 mol	$(\mathbf{1a})_{in}$, 10^3 mol	R = **1a**/ *i*-PrJ	products, 10^4 mol			R′ = [**4a**]/ [4-ClC$_6$H$_5$J]
			4-ClC$_6$H$_5$J	**4a**	$(CH_3)_2CHCH_2CH_2COCH_3$	
2.50	20.1	8.04	2.8	5.3	2.6	1.85
1.91	12.2	6.39	3.2	4.8	3.0	1.50
2.51	15.0	5.98	3.55	5.25	3.4	1.48
2.50	10.1	4.04	4.1	3.9	3.9	0.95
2.49	5.0	2.01	5.7	2.7	5.4	0.47

[a] Acetic acid–water, 3:2; t = 5 °C.

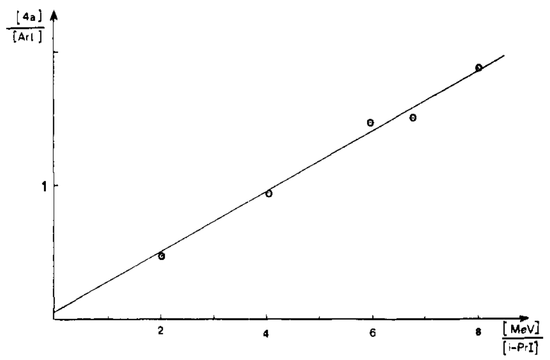
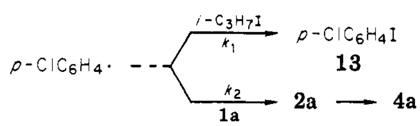


Figure 1. Plot of the ratio of the β-addition product to methyl vinyl ketone (MeV) and iodine transfer from isopropyl iodide by 4-chlorophenyl radicals against $[CH_2{=}CHCOCH_3]/[(CH_3)_2CHI]$.

reference reaction for evaluation of the absolute rate constant. Since the value of k_1 is very high (10^9 M^{-1} s^{-1}



(3)

at 45 °C, practically diffusion controlled), the most reactive olefin (**1a**) was used in competitive experiments. The results are reported in Table II. A plot of [**4a**]/[**13**] vs. [i-C_3H_7I]/[**1a**] gave a k_1/k_2 ratio of 4.35 (Figure 1), from which a value of 2.3 10^8 M^{-1} s^{-1} at 5 °C was deduced for k_2, using a k_1 value of 1.0 10^9 M^{-1} s^{-1}. The rates of the other less reactive olefins **1b–f** were determined by competition with **1a**. The results are summarized in Table III and the rate constants relative to the β and α position are given in Table IV. In all competitive experiments the reaction medium was homogeneous, and the conversions were kept less than 10%.

Discussion

The reduction of diazonium salts by titanous chloride (eq 4) is quite a useful source of aryl radicals in acetic medium for our purposes, because both the reduction[13] (eq 4) and decomposition of diazenyl radical[14] (eq 5) are fast processes. Moreover, titanous salt is important for selective evolution of the two radical adducts **2** and **3**. The alkyl radical adduct **2**, owing to the proximity of the carbonyl group, has a clear-cut electrophilic character[15] and it is reduced selectively by the titanous salt (eq 6). The

$$ArN^+{\equiv}N + Ti^{3+} \rightarrow Ti^{4+} + ArN{=}N\cdot \quad (4)$$

$$ArN{=}N\cdot \rightarrow Ar\cdot + N_2 \quad (5)$$

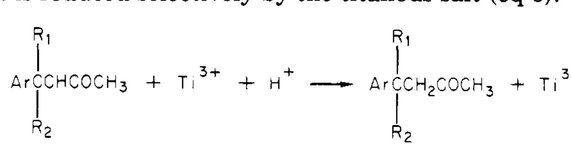
Table III. Relative Rates of 4-Chlorophenyl Radical Addition to the β Position of β-Substituted α,β-Unsaturated Carbonyl Compound[a]

reactants and concn, M		products and concn, 10^3 M		relative rate	
				obsd	av
1a	**1b**	**4a**	**4b**		
0.057	0.238	9.2	6.8	0.177	0.181
0.057	0.283	9.6	7.4	0.185	
1a	**1c**	**4a**	**4c**		
0.033	0.233	3.8	1.7	0.063	
0.075	0.561	7.4	4.2	0.076	0.068
0.033	0.167	3.25	1.08	0.066	
1a	**1d**	**4a**	**4d**		
0.033	0.235	7.49	0.96	0.018	0.0185
0.022	0.240	1.80	0.36	0.019	
1a	**1e**	**4a**	**4e**		
0.033	0.198	3.22	0.28	0.0145	
0.033	0.264	2.78	0.32	0.0144	0.0145
0.033	0.331	2.53	0.37	0.0146	
1a	**1f**	**4a**	**4f**		
0.041	0.042	4.1	0.73	0.173	0.175
0.068	0.042	6.85	0.75	0.177	
1b	**1e**	**4b**	**4e**		
0.051	0.152	4.8	1.61	0.100	0.100
1b	**1d**	**4b**	**4d**		
0.039	0.158	0.42	0.20	0.120	0.120
1b	**1c**	**4b**	**4c**		
0.051	0.050	0.1	2.55	0.41	0.41

[a] Acetic acid–water, 3:2; t = 5 °C; 0.003 M 4-chlorobenzenediazonium tetrafluoroborate.

Table IV. Absolute Rate Constant for Addition of 4-Chlorophenyl Radical to the β and α Position of Some α,β-Unsaturated Ketones at 5 °C

compd	k(β addition), M^{-1} s^{-1}	k(α addition), M^{-1} s^{-1}	rel rate (β)	rel rate (α)
1a	2.3×10^8	10^7	1	
1b	5.06×10^7	1.77×10^7	0.25	1
1c	2.53×10^7	2.3×10^7	0.11	1.3
1d	6.94×10^6	2.77×10^7	0.03	1.56
1e	5.63×10^6	2.76×10^7	0.024	1.50
1f	4.0×10^7	1.33×10^8	0.174	9.04



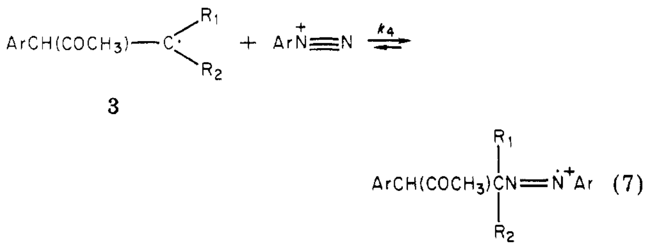
(6)

2a–f **4a–f**

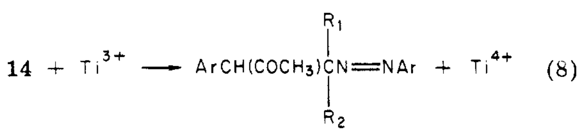
rate constant of the reaction 6 has been recently evaluated[16] by us in the same reaction medium ($k_3 = 10^4$ M^{-1} s^{-1} at 0 °C) and it explains the selectivity of the reduction and the fact that telomerization is avoided also with **1a**.

(12) W. C. Danen, "Methods in Free-Radical Chemistry", E. S. Huyser, Ed., Marcel Dekker, New York, 1974, Vol. 5.
(13) A. L. J. Beckwith and R. O. C. Norman, *J. Chem. Soc. B*, 403 (1969).
(14) E. M. Kosower, *Acc. Chem. Res.*, **4**, 193 (1971); N. A. Porter, G. R. Dubay, and J. G. Green, *J. Am. Chem. Soc.*, **100**, 920 (1978); O. Brede, R. Mehuert, and W. Naumann, *Ber. Bunsenges. Phys. Chem.*, **84**, 666 (1980); **84**, 672 (1980).
(15) A. Citterio and F. Minisci, *Adv. Free-Radical Chem.*, **6**, 65 (1980).
(16) A. Citterio, F. Minisci, and M. Serravalle, *J. Chem. Res., Synop.*, 198 (1981); *J. Chem. Res., Miniprint*, 2174 (1981).

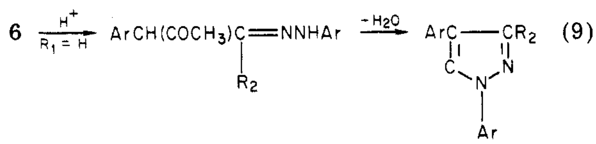
The alkyl radical adducts **3**, owing to their nucleophilic character,[15] are not easily reduced by titanous salts and add very fast to the diazonium salts[17,18] (eq 7).



14



6



5

Polar effects play a relevant role in reaction 7, as it results from the higher reactivity of tertiary alkyl radicals ($k_4 \simeq 10^8$ M^{-1} s^{-1} at 5 °C) compared with primary alkyl radicals ($k_4 \simeq 10^6$ M^{-1} s^{-1});[9] thus the radical adducts **3b–f** obtained from the olefins **1b–f** react with diazonium salts faster than the radical adduct **3a** and therefore with very high selectivity. A pronounced charge-transfer character of the transition state (eq 10), due to a strong interaction of SOMO–LUMO orbitals,[19] must be responsible for this strong polar effect. This behavior provides a further example of violation of the reactivity–selectivity principle, due to polar effects, in agreement with previous reports[20,21]

$$[\mathrm{R}\cdot\ \mathrm{N{=}N^+Ar}] \leftrightarrow [\mathrm{R^+}\ \cdot\mathrm{N{=}NAr}] \qquad (10)$$

An excess of titanous salt was used to reduce the intermediate azo radical cation **14a–f**, minimizing the reversibility effect.

Compounds of type **6** are intermediates in the reaction. When the radical adduct **3** is a tertiary alkyl radical (i.e., from the olefin **1e**), azo compound **6** is quite stable;[5] when R_1 or R_2 is hydrogen, they rearrange to the corresponding hydrazones, which cyclize to the pyrazole **5**[17] (eq 9). The azo compound **6** can be reduced by the excess of Ti(III) and this process is slower than tautomerization and cyclization; only for **6a** were low yield of products of azo group reduction observed.[17]

The more complex behavior of the olefin **1f** can be related to an accentuated reversibility of reaction 7, due to the benzylic nature of the alkyl radical adduct, so that a partial dimerization of the radical adduct **3** takes place (eq 11). Both diastereoisomers (meso and *d,l*) of **8** were obtained in equimolecular amount, indicating a free-radical dimerization. *trans*-4-Chlorostilbene (**9**) arises from β scission of the radical adduct **3**, favored by the formation of the conjugated olefin (eq 12). Evidences for the re-

$$\mathrm{2ArCH(COCH_3)\dot{C}HC_6H_5} \rightarrow \mathbf{8} \qquad (11)$$

$$\mathrm{ArCH(COCH_3)\dot{C}HC_6H_5} \rightleftarrows \mathrm{CH_3CO\cdot} + \mathrm{ArCH{=}CHC_6H_5} \qquad (12)$$

versibility of the acyl radical addition to olefins has been reported.[22]

A mechanism analogous to those leading to **4** and **5** gives rise to **10** and **11** with methyl crotonate. The dimerization product **12** is observed in this case owing to the lower reduction rate of the radical **2** by Ti(III) salt.

It is noteworthy that isopropyl radicals, arising from the iodine abstraction from isopropyl iodide, add very efficiently to **1a**, giving the ketone **15** in almost equimolecular amount to the aryl iodide (Table II; eq 13 and 14). The

$$\mathrm{(CH_3)_2CHI} + \mathrm{Ar\cdot} \rightarrow \mathrm{ArI} + \mathrm{(CH_3)_2CH\cdot} \qquad (13)$$

$$\mathrm{(CH_3)_2CH\cdot} + \mathbf{1a} \rightarrow \mathrm{(CH_3)_2CHCH_2\dot{C}HCOCH_3} \xrightarrow[\mathrm{H^+}]{\mathrm{Ti^{3+}}} \mathrm{(CH_3)_2CHCH_2CH_2COCH_3} \qquad (14)$$

selectivity of eq 14 is plainly justified by our previous studies,[23,24] concerning the absolute rate constants in the addition of alkyl radicals to conjugated olefin: secondary alkyl radicals are more reactive than primary toward electron-deficient olefins owing to their higher nucleophilic character. This side reaction does not, however, significantly affect the kinetic results because the conversions are kept low (<10%) during the competitive experiments.

Chlorobenzene appears to be formed more from reduction of the aryl radical by titanous salt (eq 15) than by hydrogen abstraction (the amount of chlorobenzene increases with the titanous salt concentration). The 4,4′-

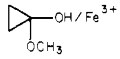
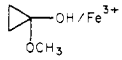
$$\mathrm{Ar\cdot} + \mathrm{Ti^{3+}} + \mathrm{H^+} \rightarrow \mathrm{ArH} + \mathrm{Ti^{4+}} \qquad (15)$$

dichloroazobenzene, obtained always in small amounts (1–4%), can be formed by a mechanism analogous to that leading to **6**; the low amount can be related to the lower nucleophilic character of the aryl radicals compared with the alkyl radicals. Only symmetric 4,4′-dichlorobiphenyl was observed, although in small amounts (1–2%), indicating that some kind of dimerization is involved and not the homolytic arylation of chlorobenzene.[25]

The results of Table I and IV clearly show that the steric effect is the dominant factor governing the regioselectivity. With the exception of **1f**, the reactivity of the α position to the carbonyl group toward aryl radicals is only marginally affected by the substituent at the β position, whereas the reactivity of the β position is significantly affected although the same resonance stabilized α-keto alkyl radical is formed in this case with all the olefins. The only effect of the substituents is therefore the steric deactivation of the vinylic carbon bonded to it. A phenyl group at the β position has, however, a significant effect on the reactivity of the α position because the intermediate radical adduct is a resonance-stabilized benzylic radical (it cannot be excluded that this activation is polar[24]). However, also with the olefin **1f** the regioselectivity is

(17) A. Citterio, E. Vismara, and M. Ramperti, *J. Heterocycl. Chem.*, 18, 763 (1981); A. Citterio and F. Minisci, *J. Org. Chem.*, in press (1981).
(18) J. E. Packer, C. J. Heighway, H. M. Muller, and B. C. Dobson, *Aust. J. Chem.*, 13, 965 (1980), and references therein.
(19) I. Fleming, "Frontier Orbitals and Organic Chemical Recation", Wiley, London, 1980.
(20) A. Citterio, F. Minisci, and V. Franchi, *J. Org. Chem.*, 45, 4252 (1980).
(21) J. A. Baban and R. P. Roberts, *J. Chem. Soc., Perkin Trans. 2*, 161 (1981).
(22) F. Bertini, T. Caronna, L. Grossi, and F. Minisci, *Gazz. Chim. Ital.*, 104, 471 (1974).
(23) T. Caronna, A. Citterio, M. Ghirardini, and F. Minisci, *Tetrahedron*, 33, 793 (1977).
(24) A. Citterio, A. Arnoldi, and F. Minisci, *J. Org. Chem.*, *44*, 2674 (1979).
(25) R. Ito, T. Migita, N. Morikawa, and O. Simamura, *Tetrahedron*, 21, 955 (1965).

Table V. Regioselectivity in the Addition of Some Free Radicals to Compounds 1a-f and Methyl 2-Butenoate

radical	method of generation	substrate	β addition	α addition	ref
$C_3H_7CO\cdot$	C_3H_7CHO/perox	$CH_3CH{=}CHCOCH_3$	100		32
$CH_3OCOCH_2CH_2\cdot$		$CH_3CH{=}CHCOCH_3$	100		33
$CH_3CO\cdot$	CH_3CHO/perox	$(CH_3)_2C{=}CHCOCH_3$	100		32
$C_3H_7CO\cdot$	C_3H_7CHO/perox	same as above	90	10	32
$CH_3OCOCH_2CH_2\cdot$		same as above	100		33
$CH_3COS\cdot$	CH_3COSH/perox	same as above	100		31
$NCCH_2CH_2PH\cdot$	$NCCH_2CH_2PH_2$/perox	same as above	100		34
$HOOCCH_2S\cdot$	$HOOCCH_2SH$/perox	$CH_3CH{=}CHCOOEt$	100		35
$CCl_3\cdot$	CCl_3Br/perox	same as above	100		36
$CH_3CO\cdot$	CH_3CHO/perox	same as above	100		37
$(n\text{-}C_4H_9O)_2OP\cdot$	$(n\text{-}C_4H_9O)_2OPH$/perox	same as above	90	10	38
$C_6H_5CH_2\cdot$	$C_6H_5CH_3$/DTBO	same as above	100		39
primary, secondary, and tertiary alkyl radicals	$RHgX/NaBH_4$	same as above	100		2d
$R\dot{C}HOH$	RCH_2OH/ray	same as above	100		40
$XC_6H_5\cdot$	$XC_6H_4N_2^+/CuCl_2$	same as above	100		41

mainly determined by the steric effect because the reactivity of the α position in **1f** ($k = 1.6\ 10^8\ M^{-1}\ s^{-1}$ at 5 °C) is lower than that of the β position in **1a** ($k = 2.3\ 10^8\ M^{-1}\ s^{-1}$ at 5 °C). So, the phenyl group in the β position to the carbonyl group has a double effect: it decreases the addition reactivity of the β position for steric reasons and increases the reactivity of the α position owing to the formation of a resonance-stabilized radical adduct. The extent of the steric effect, however, is higher than that of the resonance effect.

The prominent role of the steric effect in determining the regioselectivity is emphasized by the linear relationship (Figure 2) between the addition rate constants to the β position and the steric parameters E_s.[26]

Methyl crotonate behaves quite similarly to 3-penten-2-one; the only difference is related to the less selective reduction of the α-carboxyalkyl radical by Ti(III) than that of the α-carbonyl alkyl radical.

These conclusions are in complete agreement with the extensive studies[1] of Tedder and co-workers concerning the free-radical addition to olefin in gas phase, particularly fluorinated alkyl radicals and fluoro olefins, where, however, the polar effects are important, due to the presence of fluorine atoms, and the steric effects are not particularly marked for the size of the fluorine so that exceptionally polar effects can prevail over steric effects in determining the regioselectivity.

The results of this work once again emphasize the importance of steric effects in free-radical reactions, rationalized by Rüchardt in a series of fundamental review articles.[27]

From the combined results reported by Russell[28] and Lorand[29] it is possible to evaluate the rates of addition of phenyl radical to simple unconjugated olefins (10^5–$10^6\ M^{-1}\ s^{-1}$). This evaluation is in accord with the results of Table IV because the same radical clock[28] (iodine abstraction from isopropyl iodide) is common to both determinations. It indicates that olefins conjugated with carbonyl groups are significantly more reactive than the corresponding unsubstituted olefins. Since the activation involves both

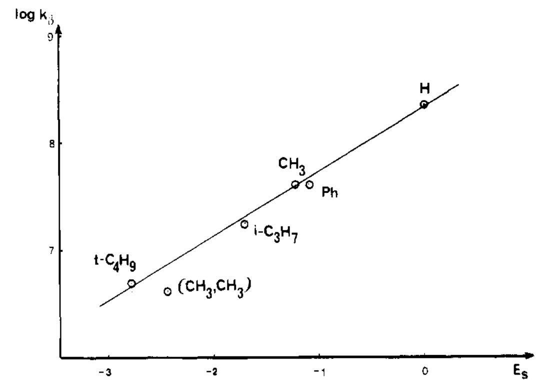


Figure 2. Plot of log k_β vs. E_s steric parameters for substituted 3-buten-2-ones (E_s value for the 4,4-dimethyl derivative was taken as twice the E_s value of the methyl group).

α and β positions, it appears to be due more to a polar than a resonance effect.

The most intriguing aspect of the results reported in Tables I and IV concerns the comparison with the regioselectivity in the olefin addition reported for a variety of other free radicals. With **1f** the regioselectivity of some of the known radical additions agrees with our results,[30] even if a complete selectivity of attack at the β position has been reported in some cases with thiyl radicals[31] (however, competitive ionic addition cannot be excluded in these cases). In Table V the regioselectivity of various free radicals with **1b**, **1e**, and methyl crotonate are reported. To the best of our knowledge no free-radical addition prevailing in the α position has been reported previously with these olefins. On the other hand, the dominant attack at the β position in **1e** cannot be ascribed to polar effects because it occurs with both electrophilic (RS·) and nucleophilic radicals ($R\dot{C}{=}O$). Two possible explanations can be envisaged for the opposite regioselectivity observed with aryl radicals and the other radicals reported in Table V for **1e**.

(a) The addition of aryl radicals to olefins is certainly irreversible and a kinetic regioselectivity is observed,

(26) S. H. Huger and C. Hansch, *Prog. Phys. Org. Chem.*, **12**, 91 (1976).
(27) Ch. Ruchardt, *Angew. Chem., Int. Ed. Engl.*, 830 (1970); *Zh. Vses. Khim.*, **24**, 21 (1979); *Top. Curr. Chem.*, **88**, 1 (1980).
(28) R. F. Bridger and G. A. Russell, *J. Am. Chem. Soc.*, **85**, 3754 (1963).
(29) D. Griller and K. U. Ingold, *Acc. Chem. Res.*, **13**, 317 (1980).
(30) R. L. Huang, *J. Chem. Soc.*, 1342 (1957); M. S. Karasch and M. Soge, *J. Org. Chem.*, **14**, 537 (1949); L'Ecuyer and L. Olivier, *Can. J. Res. Sect. B*, **27**, 689 (1949).
(31) B. H. Nicolet, *J. Am. Chem. Soc.*, **57**, 1098 (1935); R. Brown, W. E. Jones, and A. R. Pinder, *J. Chem. Soc.*, 2123 (1951).

whereas the addition of the other radicals reported in Table V can be reversible and the observed regioselectivity can result from a balance between kinetic and equilibrium factors. If this explanation is correct, the results with aryl radicals are particularly significant as regards the kinetic regioselectivity of the addition and they support the Tedder statement[1] that "when there is more than one substituent on the vinylic site, the orientation becomes harder to predict, although steric repulsion remains the dominant factor controlling the orientation of the addition".

(b) The addition of aryl radical, being very fast (highly exothermic), has a early transition state and the contribution of the resonance stabilization of the radical adduct to the transition state is small, although the approach of the radical to the double bond is close enough for mutual repulsion of the nuclei, bonding electrons, and adjacent atoms to control the orientation of addition at the position. With less reactive radicals (less exotermic), bonding in the transition state has proceeded so far that an appreciable contribution of the resonance stabilization of the radical adduct to the transition state is attained and the attack takes place at the β position even in the presence of bulky groups.

Whatever the explanation, the results of this work suggest that great care must be used in postulating general rules concerning the regiolectivity in free-radical additions to olefins and what in student textbooks is often given as a consolidated concept must be yet considered for many aspects as open problem. What is sure is the increasing importance assigned to steric effects, following the important suggestions of Rüchardt.

Experimental Section

General Methods. Melting and boiling points (determined on Köffler apparatus) are uncorrected. NMR spectra were run in $CDCl_3$ (Me_4Si as internal standard), using a Varian A 90 spectrometer. Mass spectra were obtained on a Hitachi Perkin-Elmer RMU-6D mass spectrometer at 70 eV; GLC/MS data were obtained on a Perkin-Elmer E-270 instrument, using a glass column (2 m) packed with 10% OV-17 on Chromosorb W-DMCS with a programm (10 °C/min) from 80 to 240 °C. GLC analyses were performed on a DANI 3600 gas chromatograph, using glass columns (2 m) packed with (A) 3% OV-17 on Chromosorb W-DMCS or (B) 3% FFAP on Chromosorb W-AW-DMCS (80–100 mesh). The identity of all isolated products was confirmed by coinjection with an authentic sample (when known) or by elemental analysis and comparison of spectral data. Quantitative GLC were obtained by the internal standard method after calibration.

Materials. Acetic acid was reagent grade and was used after distillation. Titanous chloride was obtained as 15% water solution from Carlo Erba and was standardized against cerium(IV) sulfate (0.1 N).

Isopropyl iodide was distilled twice, the fraction with a boiling point of 82–83 °C being used; methyl vinyl ketone (Merck) was distilled at 300 torr prior to use; *trans*-3-penten-2-one (bp 123–124 °C, 99% purity), 4-phenyl-3-penten-2-one (mp 38–39 °C), and methyl 2-butenoate (bp 121 °C) were obtained from Aldrich and distilled or recrystallized; 4-methyl-3-penten-2-one (bp 130.5 °C) was obtained from Carlo Erba. 5-Methyl-3-hexen-2-one (bp 156–157 °C, $n^{20}{}_D$ 1.4450) was obtained by following the known procedure[42] and was used contaminated with 2% of the 4-ene isomer. 5,5-Dimethyl-3-hexen-2-one [bp 85 °C (50 mmHg), $n^{20}{}_D$ 1.4446; lit.[42] bp 78–80 °C (40 mmHg)] was obtained by two different procedures[42,43] and purified by fractional distillation (it was contaminated by less than 2% of 4-methyl-3-penten-2-one). 4-Chlorobenzenediazonium tetrafluoroborate (mp 134–135 °C) was synthesized by the method of Starkey[44] and stored at 0 °C. Compounds **4a**,[45] **4e**,[46] and **4f**[47] were synthesized by known methods and purified by distillation and preparative liquid–liquid chromatography (*n*-hexane–ethyl acetate, 95:5). 4,4′-Dichlorobiphenyl (mp 147 °C, lit.[48] mp 148 °C) was prepared according to Shaw et al.[48] 4,4′-Dichloroazobenzene (mp 185–186 °C, lit.[49] mp 187 °C) and *p*-chlorostilbene (mp 128 °C, lit.[50] mp 129 °C) were obtained by using known procedures.[49,50]

Synthesis and Isolation of the Arylation Products of α,β-Unsaturated Carbonyl Compounds. 4-Chlorobenzenediazonium tetrafluoroborate (4.5 g, 20 mmol) was dissolved in acetic acid–water (9:1, 20 mL) at 5 °C and added in 10 min to a solution, thermostated at 5 °C, made by dissolving the α,β-unsaturated carbonyl compound (20 mmol for **1a** and 40 mmol for all the other products) in acetic acid (80 mL) and adding the titanous solution (40 mL, 43 mmol). The reactions were run for 3 h and then diethyl ether (150 mL) was added, the organic phase was separated, and the water was extracted with diethyl ether (40 mL) and ethyl acetate (2 × 40 mL). (The pyrazole derivatives precipitated during the reaction dissolved in the organic phase.) The organic extracts were washed at 0 °C with 20% NaOH until the value was 8 and then with saturated NaCl solution, dried, and distilled at atmospheric pressure to remove the solvent. The residue was chromatographed on silica gel (0.032–0.063 mesh), using pentane–diethyl ether (10:0, 7:3) as an eluant.

Yields, physical constants, and analytical data for compounds **4a–f**, **5a–f**, and **11** are reported in Tables VI and VII, respectively. Small amounts of 4,4′-dichlorobiphenyl (0.5–2% in diazonium salt) and 4,4′-dichloroazobenzene (1–4%) were detected in the reaction mainly with the less reactive substrates (analyses by column B).

The regioselectivity data were obtained from the quantitative data obtained by GLC/MS analysis of the reaction products (column B, programmed 10 °C/min from 180 to 250 °C, or column (2 m) packed with 5% OV-1 on Chromosorb W-DMCS, programmed 10 °C/min from 200 to 280 °C).

With 4-phenyl-3-buten-2-one the regioselectivity was determined on the basis of the yield of isolated products from column chromatography (*n*-hexane-ether, 9:1): *trans*-4-chlorostilbene (4%), 4-phenyl-3-(4-chlorophenyl)-butan-2-one (1.5%) [mass spectrum, *m/e* 258 ($M^{+}\cdot$, 28), 215 (100), 180 (30), 179 (48), 148 (46), 165 (12), 137 (14), 103 (18), 91 (38)], **4f** (21%), **5f** (29%), and 8 (mixture of two diastereoisomers). First diastereoisomer to be eluted from GLC/MS (column OV-1): mass spectrum, *m/e* 514 ($M^{+}\cdot$, 0.1), 492 (3), 471 (1), 267 (6), 214 (25), 180 (10), 178 (10), 177 (50), 112 (21), 77 (100), 43 (40). Second diastereoisomer to be eluted: mass spectrum *m/e* 514 ($M^{+}\cdot$, 0.1), 429 (5), 471 (2), 330 (2), 267 (5), 214 (10), 180 (18), 178 (11), 177 (63), 111 (25), 77 (100), 43 (80); 32% yield. The data of regioselectivity were confirmed by NMR of the reaction crude, integrating the hydrogens of methyl groups. With methyl crotonate the dimers 12 (1:1 mixtures of distereoisomers) were detected by the GLC/MS

(32) J. M. Patrick, Jr., *J. Org. Chem.*, 17, 1269 (1952).
(33) S. E. Schaafsma, R. Jorritzma, H. Steinberg, and Th. deBoer, *Tetrahedron Lett.*, 827 (1973).
(34) H. M. Rauhut, H. A. Currier, A. M. Semsel, and V. P. Wystrach, *J. Org. Chem.*, **26**, 5138 (1961).
(35) I. G. Cadogan and I. H. Sadler, *J. Chem. Soc.*, 1191 (1966).
(36) R. L. Huang, *J. Chem. Soc.*, 1749 (1956).
(37) K. Okawara, *Nippon Kagaku Kaishi*, **57**, 760 (1954).
(38) *Chem. Abstr.*, **50**, 10124 (1956); **46**, 8145 (1952).
(39) R. L. Huang, H. H. Lee, and L.-Y. Wong, *J. Chem. Soc.*, 6730 (1965).
(40) M. Tokuda, Y. Yokoyama, T. Taguchi, A. Suzuki, and M. Itoh, *J. Org. Chem.*, **37**, 1859 (1972).
(41) C. F. Koelsch and V. Boekelheide, *J. Am. Chem. Soc.*, **66**, 412 (1944).
(42) R. Heilmann, G. Gaudemaris, P. Arnuad, and G. Scheuerbrandt, *Bull. Soc. Chim. Fr.*, 112 (1957).
(43) Z. N. Kolyaskina, *Zh. Org. Chim.*, **5**, 1908 (1969).
(44) E. B. Starkey, "Organic Syntheses", Collect. Vol. 2, Wiley, New York, 1966, p 225.
(45) S. Boatman, T. M. Harris, and C. R. Hauser, *J. Org. Chem.*, **30**, 3321 (1965).
(46) J. Corse and E. Rohrman, *J. Am. Chem. Soc.*, **70**, 370 (1948).
(47) C. F. Woodward, G. T. Borcherdt, and R. C. Fuson, *J. Am. Chem. Soc.*, **56**, 2103 (1934).
(48) F. R. Show and E. E. Turner, *J. Chem. Soc.*, 294 (1932).
(49) C. P. Johua and V. N. R. Pillai, *Indian J. Chem.*, **12**, 60 (1974).
(50) F. Bergman, J. Weisman, and D. Shapiro, *J. Org. Chem.*, **9**, 408 (1940).

Table VI. Analytical Data for Substituted 2-Butanones (4a–f, β-Addition Products)

compd	% yield	bp or mp, °C	NMR ($CDCl_3$) δ: Ar	R	R′	CH_2CO	$COCH_3$	mass spectrum, m/e
4a	82	90–91/0.5 (106/05)[9]	7.0–7.3 (m, 4 H)	2.6–3.0 (m, 2 H)		2.60–3.0 (m, 2 H)	2.08 (s, 3 H)	182 ($M^{+\cdot}$, 92), 167 (24), 147 (33), 139 (44), 125 (100), 103 (47), 89 (17), 77 (27), 43 (58)
4b	53	114–115/0.5 (105/0.1)	7.0–7.5 (m, 4 H)	3.29 (m, 1 H)	1.20 (d, 3 H)	2.64 and 2.63 (two d, J = 6.6, 8.0 Hz)	2.03 (s, 3 H)	196 ($M^{+\cdot}$, 20), 195 (21), 180 (10), 139 (100), 103 (36), 43 (70)
4c	42	120–122/0.5	7.0–7.4 (m, 4 H)	2.8 (m, 1 H)	0.9 and 0.7 (d, J = 6.5 Hz) 1.8 (m, 1 H)	2.7–3.0 (m, 2 H)	1.98 (s, 3 H)	224 ($M^{+\cdot}$, 10), 182 (18), 181 (23), *166* (100), 147 (20), 140 (21),
4d	15	128–130/0.5	7.0–7.4 (m, 4 H)	2.8 (m, 1 H)	1.2 (s, 9 H)	2.7–2.9 (m, 2 H)	2.02 (s, 3 H)	238 ($M^{+\cdot}$, 5), 223 (5), 206 (3), *182* (100), 167 (21), 165 (13), 147 (38), 125 (20), 77 (12), 57 (79), 43 (58)
4e	12	125–6/0.5 (169–171/16)	7.30–2.4 (m, 4 H)	1.4 (s, 3 H)	1.4 (s, 3 H)	2.72 (s, 2 H)	1.86 (s, 3 H)	210 ($M^{+\cdot}$, 16), *153* (100), 125 (42), 115 (13), 77 (8), 43 (94)
4f	21	161–3/0.5 (180–182/4)	7.0–7.3 (m, 4 H)	4.55 (t, 1 H)	7.3 (s, 5 H)	3.10 (s, 2 H)	2.02 (s, 3 H)	258 ($M^{+\cdot}$, 37), 243 (7), 241 (5), 215 (22), *201* (100), 178 (13), 166 (42), 165 (73), 137 (15), 103 (14), 43 (12)
10	60	92/0.5	7.0–7.5 (m, 4 H)	3.25 (m, 2 H)	1.3 (d, 2 H)	2.5 and 2.8 (d, 2 H)	3.6 (s, 3 H)	212 ($M^{+\cdot}$, 21), 197 (8), 181 (9), 180 (12), 139 (100), 111 (62), 76 (20)

Table VII. Analytical Data for Pyrazole and Azo Derivatives (α-Addition Products)

compd	% yield	mp, °C	NMR ($CDCl_3$) δ	mass spectrum, m/e	formula[a]
5b	15	196–197	7.2–7.5 (m, 4 H), 7.5 (s, 4 H, A_2), 2.28 (s, 3 H, CH_3), 3.00 (s, 3 H, CH_3)	*316* ($M^{+\cdot}$, 100), 315 (24), 280 (10), 266 (8), 240 (8), 204 (12), 111 (15), 75 (14)	$C_{17}H_{14}Cl_2N_2$
5c	38	117	7.1–7.5 (m, 4 H), 7.48 (s, 4 H, A_2), 3.04 (septet, 1 H), 2.20 (s, 3 H, $COOH_3$), 1.21 (d, 6 H)	344 ($M^{+\cdot}$, 81), *329* (100), 317 (11), 295 (10), 280 (10), 153 (15), 111 (28), 75 (35)	$C_{19}H_{18}Cl_2N_2$
5d	60	169–170	7.1–7.5 (m, 4 H), 7.4 (s, 4 H), 2.05 (s, 3 H, $COCH_3$), 1.24 (s, 9 H, CH_3)	358 ($M^{+\cdot}$, 14), *343* (100), 316 (15), 241 (8), 152 (20), 111 (25), 75 (10)	$C_{20}H_{20}Cl_2N_2$
6e[b]	63	97–98	7.3–7.7 (m, 4 H), 7.2–3 (s, 4 H), 4.32 (s, 1 H), 2.1 (s, 3 H, $COCH_3$), 1.47 (s, 3 H), 1.18 (s, 3 H)	348 ($M^{+\cdot}$, small 1%), *209* (100), 166 (30), 139 (31), 122 (17), 89 (8), 75 (32), 43 (30)	$C_{18}H_{18}Cl_2N_2O$
5f	29	179–180	7.1–7.4 (m, 8 H), 7.52 (m, 5 H), 2.26 (s, 3 H)	*378* ($M^{+\cdot}$, 100), 377 (32), 341 (9), 189 (M^{2+}, 5), 171 (10), 152 (11), 11 (18), 75 (10)	$C_{22}H_{16}Cl_2N_2$
11[c]	20	229–230	7.3–8.0 (m, 8 H), 2.32 (s, 3 H), 11.5 (br, 1 H, NH)	318 ($M^{+\cdot}$, 100), 289 (12), 283 (15), 255 (17), 248 (10), 192 (10), 179 (25), 151 (42), 125 (23), 115 (31), 111 (50)	$C_{16}H_{12}Cl_2N_2O$

[a] Elemental analyses for all compounds agree (C, ±0.2; H, ±0.2; N, ±0.2; Cl, ±0.2) with the molecular formula reported. [b] UV (EtOH) ν_{max}(log ε) 223 nm (4.36), 271 (4.18), 4.10 (2.3). The structure of the compound was also confirmed by X-ray analysis. [c] IR ν_{max} 1600–1630 cm^{-1} (CO); NMR was run in Me_2SO-d_6.

system. First diastereoisomer eluted: mass spectrum, m/e 354 ($M^{+}\cdot$, 2), 392 (2), 363 (1), 320 (8), 217 (65), 203 (48), 139 (100), 77 (80). Second diastereoisomer: mass spectrum, m/e 354 ($M^{+}\cdot$, 1), 392 (6), 321 (10), 320 (14), 217 (78), 203 (62), 139 (82), 77 (100).

Competitive Rate Determination. The amount of isopropyl iodide and methyl vinyl ketone reported in Table II was added to acetic acid (30 mL) at 5 °C under stirring, the solution of $TiCl_3$ (20 mL, 1.02 M) was added, and the mixture was cooled to 5 °C. 4-Chlorobenzenediazonium tetrafluoroborate was dissolved in CH_3COOH-H_2O (8:2, 3 mL) at 5 °C and this was added in one portion to the solution. The reaction was run for 2 h. Diethyl ether was added (100 mL), and the aqueous solution was separated and extracted twice with ether (10 mL); the combined extracts were basified at 0 °C with NaOH until the value pH was 8, washed with saturated NaCl solution, dried, and analyzed by GLC on columns A and B after addition of 1-phenyl-2-propanone as internal standard. The results are reported in Table II and plotted in Figure 1.

Competitive Experiments. The amounts of α,β-unsaturated carbonyl compound reported in Table III were dissolved in acetic acid (40 mL), and $TiCl_3$ solution (20 mL, 21 mmol) was added. The diazonium salt (0.043 g, 0.19 mmol) dissolved in CH_3COOH-H_2O (2:1, 3 mL) was added to the resulting solution cooled to 5 °C. Te reaction was run for 2 h. Following the separation procedure used above, the extracts were distilled to 20 mL and analyzed for the β attack by GLC on the same columns at 200–240 °C. The results of these competitive experiments are reported in Table III.

Registry No. 1a, 78-94-4; *trans*-**1b**, 3102-33-8; **1c**, 5166-53-0; **1d**, 26465-92-9; **1e**, 141-79-7; **1f**, 122-57-6; **4a**, 3506-75-0; **4b**, 74395-07-6; **4c**, 79083-88-8; **4d**, 79083-89-9; **4e**, 6269-30-3; **4f**, 29869-86-1; **5b**, 79083-90-2; **5c**, 79083-91-3; **5d**, 79083-92-4; **5f**, 79083-93-5; **6e**, 75478-75-0; **8**, 79083-94-6; **10**, 24254-65-7; **11**, 79083-95-7; **12**, 79083-96-8; 4-chlorobenzenediazonium tetrafluoroborate, 673-41-6; methyl crotonate, 18707-60-3.

Metabolites of Four Nudibranchs of the Genus *Hypselodoris*

Jill E. Hochlowski, Roger P. Walker, Chris Ireland, and D. John Faulkner*

Scripps Institution of Oceanography, La Jolla, California 92093

Received September 17, 1981

The nudibranchs *Hypselodoris agassizi*, *H. ghiselini*, *H. californiensis*, and *H. porterae* contain selected metabolites of dietary origin. A new sesquiterpene furan, agassizin (**1**), was isolated from *H. agassizi* collected in Mexico. *H. ghiselini* from the Gulf of California contained a diterpene epoxide, ghiselinin (**4**), dendrolasin (**6**), nakafuran 9 (**3**), and a related methoxy butenolide (**5**). *H. californiensis* from the Gulf of California contained dendrolasin (**6**) and nakafuran 8 (**7**), while specimens from San Diego, CA, contained furodysinin (**8**), euryfuran (**9**), and pallescensin A (**10**). Furodysinin (**8**) and euryfuran (**9**) were also isolated from *H. porterae*. The sponge *Euryspongia* sp. was found to be the source of euryfuran (**9**). The structures of the new natural products **1**, **4**, **5**, and **9** were determined by interpretation of spectral data.

As part of a study of the chemical defense mechanisms of opisthobranch molluscs,[1] we have recently investigated the metabolites of a number of dorid nudibranchs. Although adult dorid nudibranchs are among the most brightly colored of marine animals and have no obvious physical defense mechanisms, they have few predators. In order to deter predators, many dorid nudibranchs concentrate selected metabolites from their sponge diet in nonmucous skin glands located in the dorsum and employ these metabolites in a defensive secretion.[2] We have shown that the biologically active metabolites of *Cadlina luteomarginata* were easily extracted by soaking the nudibranchs in an appropriate solvent.[3] We therefore proposed that the major metabolites obtained in this fashion from nudibranchs constitute the major components of a defensive secretion. In this paper, we report the structural elucidation of the major metabolites of the dorid nudibranchs *Hypselodoris agassizii*, *H. ghiselini*, *H. californiensis*, and *H. porterae*.

Specimens of the nudibranch *Hypselodoris agassizi* (Bergh, 1894)[4] were collected intertidally at Cruz de Juanacaxtle, Nayarit, Mexico. Seventy animals were soaked in methanol for 8 days, after which the methanol was decanted. Evaporation of the solvent under vacuum gave an aqueous suspension that was extracted with dichloromethane. Examination of the crude extract by TLC and ^1H NMR revealed three components, steroids, fats, and a furanoid sesquiterpene, agassizin (**1**, 0.76 mg/animal; see Chart I).

Agassizin (**1**), $[\alpha]_D$ −94° (c 1.2 MeOH), had the molecular formula $C_{15}H_{18}O$. The UV spectrum [266 nm (ϵ 3500), 220 (9250)] was consistent with the furan and homocyclic diene moieties although the intensities of the peaks were low compared with those of pallescensin G (**2**) [lit.[5] 266 nm (ϵ 18 000), 220 (16 000)]. The ^{13}C NMR spectrum contained four furan carbon signals at δ 112.2 (d), 117.6 (s), 139.4 (d), and 142.5 (s) and four olefinic signals at δ 120.4 (d), 123.1 (d), 132.1 (d), and 149.3 (s); the disubstituted furan agassizin (**1**) must therefore be tricyclic. The ^1H NMR spectrum (C_6D_6) contained two furan proton signals at δ 7.06 (d, 1 H, J = 1.5 Hz) and 5.99 (d, 1 H, J = 1.5 Hz), and AB quartet at δ 3.47 (d, 1 H, J = 15 Hz) and 3.27 (d, 1 H, J = 15 Hz) due to the bis allylic methylene protons, an isolated CH_2CH_2 system at δ 2.45 (m, 1 H), 2.26 (m, 1 H), and 1.63 (m, 2 H), and a methyl signal at δ 0.77 (s, 3 H). Irradiation at δ 1.63 reduced the signals at δ 2.26 and 2.45 to an AB quartet (J = 16 Hz). The protons on the six-membered ring gave signals at δ 5.51 (d, 1 H, J = 5 Hz, C-1), 5.74 (br dd, 1 H, J = 9, 5 Hz, C-2), 5.40 (dd, 1 H, J = 9, 2.5 Hz, C-3), and 2.59 (m, 1 H, J = 7, 7, 7, 2.5 Hz, C-4), the latter signal being coupled to a methyl signal at δ 0.82 (d, 3 H, J = 7 Hz). Irradiation of the signal at δ 2.59 caused

(1) Walker, R. P.; Faulkner, D. J. *J. Org. Chem.* **1981**, *46*, 1475. Hochlowski, J. E.; Faulkner, D. J. *Tetrahedron Lett.* **1981**, *22*, 271. Ireland, C.; Faulkner, D. J. *Tetrahedron, Suppl.* **1981**, 233. Ireland, C.; Faulkner, D. J. *Bioorg. Chem.* **1978**, *7*, 125. Faulkner, D. J.; Ireland, C. In "Marine Natural Products Chemistry"; Faulkner, D. J., Fenical, W. H., Eds.; Plenum Press: New York, 1977; pp 23–34 and references cited therein.
(2) Thompson, T. E. *J. Mar. Biol. Assoc. U.K.* **1960**, *39*, 123.
(3) Thompson, J. E.; Walker, R. P.; Wratten, S. J.; Faulkner, D. J. submitted for publication in *Tetrahedron*.
(4) Bergh, L. S. R. *Bull. Mus. Comp. Zool.* **1894**, *25*, 125.
(5) Cimino, G.; De Stefano, S.; Guerriero, A.; Minale, L. *Tetrahedron Lett.* **1975**, 1421.

0022-3263/82/1947-0088$01.25/0 © 1982 American Chemical Society