BIOORGANIC CHEMISTRY, 3, 66–71 (1974)

Sterically Hindered Chlorinating Agents That Relate to Terminal Biological Oxidations

N. C. DENO, DOUGLAS G. POHL, AND HARRY J. SPINELLI

Department of Chemistry, Pennsylvania State University, University Park, Pennsylvania 16802

Received April 5, 1973

N-Chloro-2,2,6,6-tetramethylpiperidine chlorinates primary hydrogen more rapidly than secondary hydrogen in 2,2-dimethylbutane and secondary hydrogen more rapidly than tertiary hydrogen in simple alkanes. With pentane, it chlorinates the less hindered 2-position five times faster than the more hindered 3-position. These selectivities approach the selectivity for ω (terminal) and ω-1 (penultimate) carbons that are widely exhibited by enzymic systems.

Studies on the oxidation of alkanes by lower organisms uniformly report that oxidation takes place at a terminal (ω) methyl (*1–4*) and to a minor extent on the penultimate (ω-1) methylene (*1*). The most dramatic examples of this effect occur with alkenes where 1-heptene forms 6-heptenoic acid (*5*) and 1-hexadecene forms esters of 15-hexadecen-1-ol (*4*). Similar ω and ω-1 oxidations occur in carboxylic acid substrates (*1, 6, 7*) as well as a wide variety of terminally functionalized alkane chains (*1*). Many labeling experiments have shown similar effects in a less direct fashion.

It is attractive to consider that ω oxidations occur by an initial, free-radical, H atom abstraction because this type of reagent is the most effective for attacking unactivated primary hydrogens. It is also attractive to consider that terminal selectivity is a result of high steric hindrance in the radical site of the enzyme since terminal oxidation is insensitive to chain length and to varying functional groups on the opposite end of the chain.

There are only four types of radicals that efficiently abstract H from alkanes (Cl·, Br·, RO·, and $R_3N^+\cdot$). Of these, only $R_3N^+\cdot$ (and $R_2NH^+\cdot$) have the capacity for structure complexity that would allow high steric hindrance, and they would be strong candidates for any agent in biological systems. Their use in photochlorinations has been reviewed (*8–11*).

The purpose of this work was to see if small (MW 100–500) $R_2NH^+\cdot$ reagents could be constructed that would terminally oxidize (chlorination was actually used and is regarded as a form of oxidation) alkanes. While any success would cast some light on the possibilities for biological systems, the major objective was to develop synthetic reactions of a type that have been undiscovered but which have been proven feasible by biological systems. This approach is termed "enzyme mimetic chemistry."

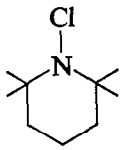
The objective has been achieved in part. Photochlorination of 2,2-dimethylbutane with the highly hindered *N*-chloro-2,2,6,6-tetramethylpiperidine gave 3.7 times as much attack at C-4 (primary) as on C-3 (secondary). The latter is more hindered. It also gave 8.3 times more attack at C-4 than C-1. Both are primary but C-1 is more hindered. Both

ratios have been corrected for the statistical effect of 9:2:3 for the number of hydrogens on C-1, C-3, and C-4. The data are summarized in Table 1.

These results are in sharp contrast to photochlorination with unhindered Cl· (from Cl_2) or moderately hindered $(2\text{-pr})_2NH^+\cdot$ (from *N*-chlorodiisopropylamine). With

TABLE 1

STERIC HINDRANCE EFFECTS IN THE PHOTOCHLORINATION OF 2,2-DIMETHYLBUTANE WITH *N*-CHLOROAMINES AT 15°C AND 20% CONVERSION

Chlorinating agent	Solvent[a]	Relative yields[b] of chlorination at			Relative rates[c] of attack at		
		C-1	C-3	C-4	C-1	C-3	C-4
Cl_2	CCl_4	44	41	15	1.0	4.1[d]	1
$(2\text{-pr})_2NCl$	TFA–10% H_2SO_4	58	20	22	0.9	1.36	1
	TFA–10% H_2SO_4	23	12	65	0.12	0.27	1
	TFA	16	17	67	0.08	0.37	1

[a] TFA is trifluoracetic acid and TFA–10% H_2SO_4 is a solution of 10% of concn (97%) H_2SO_4 in trifluoroacetic acid.

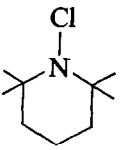
[b] Since no dichlorides were formed, these are the percentage yields based upon reactant consumed.

[c] After statistical correction for the varying number of hydrogens.

[d] A 2.3 ratio was reported on the basis of products isolated by distillation [Ref. (*18*)].

TABLE 2

STERIC HINDRANCE EFFECTS IN THE PHOTOCHLORINATION OF PENTANE AT 15°C AND 20% CONVERSION

Chlorinating agent	Solvent[a]	Relative yields[b] of			Relative rates[c] of attack at		
		1-Cl	2-Cl	3-Cl	C-1	C-2	C-3
Cl_2	CCl_4	26	49	25	1	2.8	2.9
$(2\text{-pr})_2NCl$	84% H_2SO_4	4	74	22	1	28.0	17.0
	TFA–10% H_2SO_4[d]	10	70	20	1	11.0	6.5
	TFA	6	85	9	1	19.4	4.1
	TFA–10% H_2SO_4	6	86	8	1	21.5	4.0

[abc] Same as in Table I.

[d] Similar results were obtained in TFA–30% H_2SO_4.

these two reagents, secondary hydrogen attack predominated and attack at both types of primary hydrogens were essentially equal (Table 1).

The total effect of steric hindrance in the 2,2,6,6-tetramethylpiperidyl cation radical is estimated to be at least 100-fold. This is calculated on the basis of the 3.7 factor of C-4:C-3 in 2,2-dimethylbutane multiplied by the factor of 28 for the selectivity of secondary over primary shown by the less hindered $(2\text{-pr})_2NH\cdot^+$ radical in the photochlorination of pentane (Table 2).

The photochlorination of pentane was also examined and the results appear in Table 2. Increasing steric hindrance in the attacking $R_2NH\cdot^+$ lowers the 2-Cl:1-Cl ratio from 28:1 to 22:1. More striking is the increase in the 2-Cl:3-Cl ratio from 28:17 to 22:4. This is attributed to the 3-position being more hindered. Bernardi, Galli and Minisci (*12*) had reported a similar effect, but in much smaller magnitude.

Equally important for synthesis is that *N*-chloro-2,2,6,6-tetramethylpiperidine chlorinates secondary hydrogens (of hexane) much more rapidly than tertiary hydrogens (of 2,3-dimethylbutane). This was shown by measuring the disappearance of hexane and dimethylbutane by gas chromatography (gc) using 1,2-dichloroethane as an inert internal standard. The results appear in Table 3. In the most complete reaction, 78% of the hexane reacted while $3 \pm 3\%$ of the dimethylbutane reacted.

TABLE 3

COMPETITIVE PHOTOCHLORINATION OF EQUIMOLAR HEXANE AND 2,3-DIMETHYLBUTANE AT 15°C IN TRIFLUOROACETIC ACID

Chlorinating agent and moles per mole hexane		% Concd H_2SO_4 added	% Reacted ± 3%	
			Hexane	me_2 butane
TMP–Cl[a]	0.1	0	31	0
	0.4	10	34	1
	1.0	10	78	6
$(2\text{-pr})_2NCl$	1.5	0	75	53
Cl_2	1.0	0	30	25
	1.0	10	30	25

[a] *N*-Chloro-2,2,6,6-tetramethylpiperidine.

Earlier, we had reported steric hindrance effects in the photochlorination of isopentane with *N*-chloroamines (*13*). The steric effects are greater than shown by these earlier data because of a previously unsuspected source of error. The reactions were conducted in 30–40% H_2SO_4 where there occurs sudden, nonreproducible, photodecompositions of R_2NHCl^+ and HCl to form $R_2NH_2^+$ and Cl_2, Table 4. The earlier set of data is a mix of photochlorination by R_2NHCl^+ and by Cl_2. There is also a slow dark reaction with the same stoichiometry, Table 4.

The data in Tables 1–3 do not suffer from these problems because in the higher acidities used the dark reaction becomes very slow and the sudden photodecompositions have never been observed. The acidity levels can be judged by the values of the H_0

TABLE 4

SLOW, DARK DECOMPOSITIONS AND SUDDEN PHOTODECOMPOSITION OF $(2\text{-pr})_2NHCl^+$ IN 30% H_2SO_4 AT 25°C

	%$(2\text{-pr})_2NHCl^+$ remaining[a]				
	Dark under air			Irradiated[b] under N_2	
Time (hr)	No HCl	0.50 *M* HCl	5.0 *M* HCl	0.50 *M* HCl	5.0 *M* HCl
0.25	97	91	—	87	—
2.00	—	—	76	—	70
4.00	84	89	—	80	—
5.00	—	—	49	—	40
7.00	80	83	—	6[b]	—

[a] Determined by NMR spectra. The initial concentration of $(2\text{-pr})_2NCl$ was 0.50 *M*.

[b] This number shows the sudden photodecomposition.

acidity function. Trifluoroacetic acid (TFA) and 10% H_2SO_4 in TFA are equal to 50 and 86% H_2SO_4, respectively (*14*).

The photochlorination of isopentane was reinvestigated in TFA where homogeneous conditions lead to shorter reaction times and the higher acidity eliminates formation of Cl_2 from R_2NHCl^+ decompositions. The data in Table 5 show that increasing steric hindrance in R_2NCl (a) drastically reduces the tertiary chloride, (b) lowers the ratio of attack on C_3 (secondary) to C_4 (primary), and (c) introduces a 2.5:1 difference between attack on the less hindered primary (C_4) relative to the more hindered primary (C_1).

TABLE 5

PHOTOCHLORINATION OF 2-METHYLBUTANE (ISOPENTANE) AT 15°C IN TFA AT 20% CONVERSION

Chlorinating agent	Time (min)	Relative attack after statistical correction			
		C_1	C_2[a]	C_3	C_4
Cl_2	30	0.9	3.2	2.9	1
$(2\text{-pr})_2NCl$	120	0.5	0.2	6.2	1
TMP–Cl[b]	120	0.4	0.0	2.8	1

[a] Solvolysis of this tertiary chloride is negligible in the 30–120 min reaction times since the half-life for solvolysis under the reaction conditions was found to be about 30 days.

[b] *N*-Chloro-2,2,6,6-tetramethylpiperidine.

EXPERIMENTAL METHODS

The reactions were conducted by irradiating a stirred solution of the alkane (1.0 *M*) in trifluoroacetic acid with a 300 W sunlamp. A test for positive Cl (formation of I_2 with aqueous KI) became negative in 1–4 hr. The products were isolated by pouring into water, washing the organic layer with water, and analyzing by gc. The *N*-chloroamines were prepared as described (*9*, *13*).

The analyses were conducted on a Barber Coleman 5000 gas chromatograph using 80–100 Gas Chrome RA as the solid support and 20% SE 30 as the stationary phase. Bands were identified by (a) direct comparison with authentic samples and demonstration of exact superposition, (b) the fact that ratios of products from chlorination by Cl_2 were as anticipated from studies on other alkanes (*15–17*), (c) demonstration of exact superposition from runs with different chlorinating agents, and (d) retention times increasing with increasing bp. The relative retention times for pentane and 1-, 2- and 3-chloropentane were 1:5.25:3.96:4.22. Relative retention times for 2,2-dimethylbutane and the products monochlorinated on the 1-, 3- and 4-position were 1:4.80:4.05:4.50.

Authentic samples of 1-, 2- and 3-chloropentane were obtained from Chemical Samples Co., Columbus, OH. 1-Chloro-3,3-dimethylbutane was obtained from Aldrich Chemical Co., Milwaukee, WI. 1-Chloro-2,2-dimethylbutane and 2-chloro-3,3-dimethylbutane were obtained from the alcohols (Chem. Samples Co.) and $SOCl_2$ containing a trace of pyridine. The samples agreed in bp with literature values (*18*) and showed no evidence of rearrangement by gc.

REFERENCES

1. D. F. Jones and R. Howe, *J. Chem. Soc.* C, 2801 (1968).
2. J. C. Senez and M. Konovaltschikoff-Mazoyer, *C. R. Acad. Sci.* **24**, 2873 (1956); J. E. Stewart, R. E. Kallio, D. P. Stevenson, A. C. Jones, and D. O. Schissler, *J. Bacteriol.* **78**, 441 (1959); M. H. Proctor, *Biochim. Biophys. Acta* **42**, 559 (1960); D. P. Stevenson, W. R. Finnerty, and R. E. Kallio, *Biochem. Biophys. Res. Commun.* **9**, 426 (1962); R. K. Gholson, J. N. Baptist, and M. J. Coon, *Biochemistry* **2**, 1155 (1963); J. N. Baptist, R. K. Gholson, and M. J. Coon, *Biochim. Biophys. Acta* **69** 40 (1963); W. R. Finnerty and R. F. Kallio, *J. Bacteriol* **87**, 1261 (1964); S. Ogino, K. Yano, G. Tamura, and K. Arima, *Agr. Biol. Chem.* **29**, 1009 (1965); J. A. Peterson, D. Basu, and M. J. Coon, *J. Biol. Chem.* **241**, 5162 (1966).
3. K. Yano, G. Tamura, and K. Arima, *Agr. Biol. Chem.* **29**, 1009 (1965).
4. E. J. McKenna and R. E. Kallio, *Annu. Rev. Microbial.* **19**, 183 (1965).
5. A. C. van der Linden and G. J. E. Thijsse, *Advan. Enyzmol.* **27**, 469 (1965).
6. M. Kusonose, E. Kusonose, and M. J. Coon, *J. Biol. Chem.* **239**, 1374, 2135 (1964).
7. B. Preiss and K. Block, *J. Biol. Chem.* **239**, 85 (1964).
8. F. Minisci, G. P. Gardini, and F. Bertini, *Can. J. Chem.* **48**, 544 (1970).
9. N. Deno, W. E. Billups, R. Fishbein, C. Pierson, R. Whalen, and J. C. Wyckoff, *J. Amer. Chem. Soc.* **93**, 438 (1971).
10. N. Deno, K. Eisenhardt, R. Fishbein, C. Pierson, D. Pohl, H. Spinelli, R. C. White, and J. C. Wyckoff, Int. Congr. Pure Appl. Chem., 23rd **4**, 157 (1971).
11. G. Sosnovsky and D. J. Rawlinson, "Advances in Free Radical Chemistry" (G. H. Williams, Ed.), Vol. 4, p. 203 Academic Press, New York, 1972; N. Deno, "Methods in Free Radical Chemistry" (E. S. Huyser, Ed.), Vol. 3, p. 135. Dekker, New York, 1972.
12. R. Bernardi, R. Galli, and F. Minisci, *J. Chem. Soc. B*, 324 (1968).

13. N. DENO, R. FISHBEIN, AND J. C. WYCKOFF, *J. Amer. Chem. Soc.* **93**, 2065 (1971).
14. H. H. HYMAN AND R. A. GARBER, *J. Amer. Chem. Soc.* **81**, 1847 (1959).
15. M. L. POUTSMA, "Methods in Free Radical Chemistry" (E. S. Huyser, Ed.), Vol. 1, p. 79. Dekker, New York, 1969.
16. J. M. TEDDER, *Quart. Rev.* **14**, 336 (1960).
17. G. CHILITZ, P. GOLDFINGER, G. HUYBRECHTS, G. MARTENS, AND VERBEKE, Chem. Rev. **63**, 355 (1963).
18. F. C. WHITMORE, H. I. BERNSTEIN, AND L. W. NIXON, *J. Amer. Chem. Soc.* **60**, 2539 (1938).