Thermolysis of 3-Methyl-3-alkyl-1,2-dioxetanes: Steric Effects on the Activation Parameters

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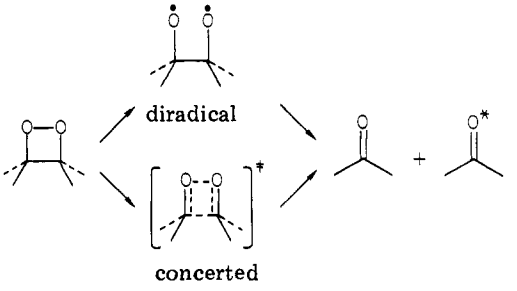
A series of 3-methyl-3-alkyl-1,2-dioxetanes (1–5) was synthesized by the bromo hydroperoxide method. The activation parameters for the thermal decomposition of 1–5 were determined by the chemiluminescence method [for 3-methyl-3-ethyl-1,2-dioxetane (1), E_a = 24.5 kcal/mol, log A = 13.1, $k_{60°C}$ = 1.0 × 10^{-3} s^{-1}; for 3-methyl-3-(1-propyl)-1,2-dioxetane (2), E_a = 24.6 kcal/mol, log A = 13.1, $k_{60°C}$ = 1.0 × 10^{-3} s^{-1}; for 3-methyl-3-(1-butyl)-1,2-dioxetane (3), E_a = 24.4 kcal/mol, log A = 13.0, $k_{60°C}$ = 9.6 × 10^{-4} s^{-1}; for 3-methyl-3-(2-propyl)-1,2-dioxetane (4), E_a = 25.0 kcal/mol, log A = 13.2, $k_{60°C}$ = 5.8 × 10^{-4} s^{-1}; and for 3-methyl-3-*tert*-butyl-1,2-dioxetane (5), E_a = 25.8 kcal/mol, log A = 13.3, $k_{60°C}$ = 2.6 × 10^{-4} s^{-1}]. Thermal decomposition of 1–5 produced the expected cleavage products in all cases. As expected for alkyl dioxetanes, thermolysis of 1–5 resulted in high yields (~10%) of triplet excited products and low yields (<0.01%) of singlet excited products as determined by the 9,10-dibromoanthracene/9,10-diphenylanthracene method. The data showed that increased steric interactions due to branched substituents produced increased activation energies with little or no effect observable in the ΔS^* terms. The results are in agreement with a diradical mechanism of dioxetane thermolysis.

The thermolysis of alkyl-1,2-dioxetanes has been shown to produce two carbonyl fragments, one of which may be produced in an excited state (high yields of excited triplets).[2] The electron-transfer-type mechanisms of chemiluminescent decomposition (high yields of excited singlets)[2e] do not occur readily with alkyl-substituted dioxetanes. Most of the experimental evidence on the thermal decomposition of simply substituted dioxetanes has been interpreted[2] in favor of a diradical (two-step) mechanism rather than a concerted mechanism (Scheme I).

The activation parameters of dioxetane thermolysis show insensitivity[2,3] to some substituent effects. Recent results have shown that substituent effects can influence the activation parameters of the thermal decomposition of alkyldioxetanes in unexpected ways.[4] 3,4-Cyclic substituents have been shown[4b-d,5] to have large effects on alkyldioxetane activation parameters. A recent study showed[4a] that the activation energy for the thermal decomposition of 3,3-diethyl-1,2-dioxetane was higher than expected. Richardson had shown[2,6] that the formal replacement of methyl groups by phenyl groups in 3,3-disubstituted dioxetanes had essentially no effect on the activation energy. Thus the E_a for 3,3-diphenyl-1,2-dioxetane and that for 3,3-dimethyl-1,2-dioxetane were found to be approximately 23 kcal/mol.[6] The E_a for 3,3-diethyl-1,2-dioxetane was found[4a] to be 1.5 kcal/mol higher than that for 3,3-dimethyl-1,2-dioxetane (little or no effect was noted on ΔS^*). The magnitude of the steric effect for the formal replacement of 3,3-dimethyl groups with 3,3-diethyl groups was sufficient to account for the observed ΔE_a in the comparison of the E_a for tetraethyl-1,2-dioxetane[4c] with that for tetramethyl-1,2-dioxetane. An interpretation suggested[4a] that 3,3 steric interactions were of major importance when compared to 3,4 steric interactions in dioxetane thermolysis. We report here the characterization of a series of 3-methyl-3-alkyl-1,2-dioxetanes (with increasing steric bulk) to examine the effect of steric interactions on the activation parameters for dioxetane thermolysis.

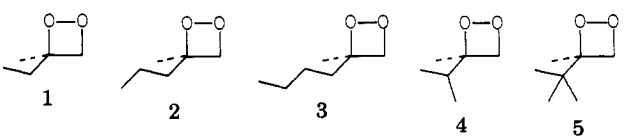
Scheme I[a]



[a] Asterisk denotes excited state.

Results

3-Methyl-3-ethyl-1,2-dioxetane (1), 3-methyl-3-(1-propyl)-1,2-dioxetane (2), 3-methyl-3-(1-butyl)-1,2-dioxetane (3), 3-methyl-3-(2-propyl)-1,2-dioxetane (4), and 3-methyl-3-*tert*-butyl-1,2-dioxetane (5) were synthesized in 5–10% yield by closure of the bromo hydroperoxides in CCl_4 with base at 0 °C. The dioxetanes, isolated by low-



temperature column chromatography, were determined to be of better than 95% purity. The compounds were characterized by NMR spectroscopy and by analysis of the thermolysis products. As expected, the signals for the ring protons were observed as AB-type patterns for compounds 2–5. The signal for the ring protons was observed as a singlet for compound 1.

Thermal decomposition of 1–5 produced the expected cleavage products. The rates of thermal decomposition

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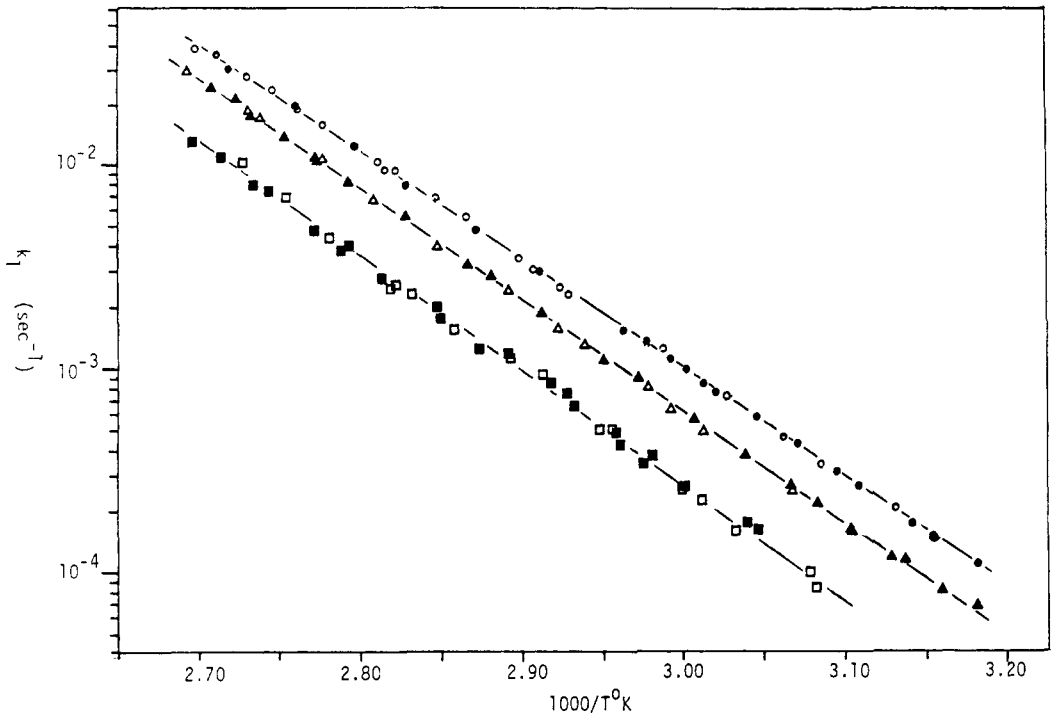

Figure 1. Arrhenius plots for the thermal decomposition of 3-methyl-3-ethyl-1,2-dioxetane [(●) DBA, (○) DPA)]; 3-methyl-3-(2-propyl)-1,2-dioxetane [(▲) DBA, (△) DPA)]; 3-methyl-3-*tert*-butyl-1,2-dioxetane [(■) DBA, (□) DPA)] in xylenes.

of **1-5** were determined by the chemiluminescence method. Semilog plots of relative light intensity (dioxetane concentration) vs. time were linear for at least 3 half-lives. The rates of dioxetane decomposition (initial dioxetane concentration, $\sim 10^{-4}$ M) were not effected by low concentrations of 9,10-dibromoanthracene (DBA) or 9,10-diphenylanthracene (DPA). The first-order rate constants (k_1) for compounds **1-3** were essentially identical over the temperature range employed (>50 °C). The k_1's for compounds **4** and **5** were readily distinguishable from one another and from those of **1-3**. The Arrhenius plots for the thermal decomposition of **1**, **4**, and **5** are shown in Figure 1. The activation parameter data for **1-5** are summarized in Table I. The activation parameters for compounds **1-3** are essentially identical. The activation energy for **4** is slightly larger than those of **1-3**, while that for **5** is clearly greater than those of the other compounds. Little or no differences are observed in log A terms for all five compounds. The observed differences in the activation energies are roughly equal in magnitude to the 95% confidence limits and must be viewed with caution. However, the results are reproducible and the relative stabilities of this series of dioxetanes are in accord with the activation energy differences.

Without added fluorescers, the thermal decompositions of **1-5** exhibited very weak chemiluminescence. Addition of fluorescers [9,10-dibromoanthracene (DBA) or 9,10-diphenylanthracene (DPA)] resulted in large increases in chemiluminescence intensity without increasing the rate of dioxetane decomposition. The yields of excited products directly produced during the thermolysis of **1-5** were determined by the DBA/DPA method. The thermal decomposition of **1-5** produced high yields of excited triplets (~10%) and extremely low yields of excited singlets (<0.01%).

Discussion

The present series of 3,3-dialkyl-1,2-dioxetanes has increased steric interactions compared to those of 3,3-dimethyl-1,2-dioxetane (**6**). An interpretation of the data

Table I. Activation Parameters for the Thermal Decomposition of 3-Methyl-3-alkyl-1,2-dioxetanes in Xylenes

dioxetane	3-alkyl group	E_a, kcal/mol	log A	$k_{60°C}$, s^{-1}
1	ethyl	24.5 ± 0.2[a]	13.1	1.0×10^{-3}
2	1-propyl	24.6 ± 0.4	13.1	1.0×10^{-3}
3	1-butyl	24.4 ± 0.3	13.0	9.6×10^{-4}
4	2-propyl	25.0 ± 0.3	13.2	5.8×10^{-4}
5	*tert*-butyl	25.8 ± 0.3	13.3	2.6×10^{-4}

[a] 95% confidence limits, correlation coefficient > 0.998 (for all cases).

is that an increased number of formal substitutions (of a methyl group) results in an increase in the values of the activation energies. An estimation of the magnitude of this effect can be obtained by determining the relationship of the ΔE_a of dioxetanes **1-6** with the number of formal substitutions. An empirical relationship for the steric interactions of 3,3-disubstituted dioxetanes of approximately +0.8 kcal/mol per formal substitution on **6** is obtained. The 95% confidence limit for this empirical relationship is ±0.6 kcal/mol. This observation may be used to predict the activation energies of new dioxetanes. For example, E_a's of 28 and 26.5 kcal/mol are predicted for 3,3-di-*tert*-butyl- and 3,3-bis(2-propyl)-1,2-dioxetane, respectively. Confirmation as to the predictive value of this empirical relationship awaits further experimentation.

The results for these compounds fit into the general framework[2] of a diradical mechanism of dioxetane thermolysis. The types and yields of electronically excited cleavage products are consistent with those reported for other disubstituted dioxetanes.[2] An interpretation of the observed increase in E_a with increased formal substitution (based on a diradical process) suggests that steric interactions are more important in the transition state (and in the diradical) than in the ground state. This explanation is consistent with 3,4 steric or 3,3 steric interactions as the origin of the steric effect. Previously, Richardson accounted[6b] for the increased stability of 3,3-dibenzyl-1,2-

dioxetane by estimation of the increased steric interactions of the diradical intermediate due to gauche-phenyl–CH_2O· interactions (a type of 3,4 steric interaction). The study on 3,3-diethyl-1,2-dioxetane suggested[4a] 3,3 steric interactions as the origin of the steric effect. The results from a study of the thermolysis of a series of *cis/trans*-3,4-dialkyl-1,2-dioxetanes were interpreted[7] to show that 3,4 steric interactions were of minor importance. Adam has concluded,[8] based on a study of monospiroadamantane-substituted dioxetanes, that the introduction of one adamantyl moiety was sufficient to promote stabilization of the dioxetane. It was further concluded[8] that compressional effects did not apply in that case. These studies show that 3,3-substitutions are sufficient to produce steric interactions in alkyldioxetanes that result in stabilization of the compounds. The agreement or disagreement of calculated dioxetane activation parameters by a group additivity-type method[6b,9] with the experimental values could be used, in theory, to discover the nature of the steric effect. However, at present, the thermochemical values of oxygen-containing groups required for the calculations must be estimated. Thus, unfortunately, the origin of the steric effect on dioxetane decomposition as a 3,3 steric effect or a 3,4 steric effect can not be resolved at this time.[10]

The results for dioxetanes with 3,4 cyclic substituents have been used[4b-d] to suggest a twisting mechanism[4c] of diradical formation during thermolysis. This notion has received further support in a study[5] of dicyclodioxetanes. These studies suggest that conformation can affect dioxethane activation parameters. The dioxetane, prepared by the reaction of singlet oxygen with 7-methyl-1,3,5-cycloheptatriene, was found[11] to be unusually unstable. This may represent an additional example of conformational effects on dioxetane stability. The present results could also fit into this pattern. Progress has been made in the understanding of steric interactions in the dioxetane system. However, several sets of reported activation parameters of dioxetane thermolysis do not fit the general patterns of steric effects discussed above. For example the activation energy of 3,4-di-*n*-butyl-3,4-dimethyl-1,2-dioxetane[12] and those of several tetrasubstituted dioxetanes reported by Lechtken[4d] are less than that of tetramethyl-1,2-dioxetane.[2,3b] On the basis of steric effects, these dioxetanes would have been expected to be more stable.

Experimental Section

All solvents were of reagent grade. ^1H NMR spectra were recorded on a Varian EM 360 L NMR spectrometer. Gas chromatographic studies were performed on a Varian Model 920 GC with a 6 ft × 0.25 in. SE-30 on chromosorb W column (helium flow rate of 60 mL/min). The alkenes were available commericially. 9,10-Diphenylanthracene (Aldrich) was used without further purification. 9,10-Dibromoanthracene (Aldrich) was recrystallized from xylenes (Aldrich) before use. The chemiluminescence monitoring system is essentially identical with that described previously.[13]

Dioxetane Synthesis and Purification. The following procedure[2] for the synthesis of 3-methyl-3-ethyl-1,2-dioxetane (1) was employed for the preparation of the dioxetanes. 2-Methyl-1-butene (5.16 g, 74 mmol) was converted to 1-bromo-2-hydroperoxy-2-methylbutane in 60% yield by the standard procedure developed by Kopecky.[14] The bromo hydroperoxide (an oil, **caution!**) was placed in 10 mL of carbon tetrachloride and cooled to 0 °C (ice bath). The solution was stirred rapidly (magnetically). Five grams of KOH in 20 mL of cold distilled (deionized) H_2O was added dropwise during a 15-min period to the reaction mixture in the dark. The bright yellow CCl_4 layer was separated from the reaction mixture after complete reaction of the bromo hydroperoxide (approximately 15 min) via a (cooled) separatory funnel. The CCl_4 layer was dried over anhydrous $MgSO_4$ and filtered. The dioxetane was partially purified and concentrated by low-temperature distillation. Purification and isolation were accomplished by low-temperature column chromatography. A jacketed column (15 mm i.d.) was packed with 20–25 g of silica gel/Na_2 EDTA (100/1) with pentane as the solvent. The sample of impure dioxetane in 1 mL of CCl_4 was placed on the column with the temperature at −30 °C. The sample was eluted with 50-mL portions of a step-gradient [10% (v/v)] of pentane/methylene chloride. Fractions (10 mL) were collected in vials and set on dry ice. The temperature of the column was maintained at −30 °C and the entire procedure was carried out in less than 10 min. [Pressure from a nitrogen tank was used to speed up the procedure.] The fractions were analyzed for dioxetane content in a chemiluminescence apparatus. A small aliquot from each fraction was added to a heated solution of 9,10-dibromoanthracene ($\sim 5 \times 10^{-3}$ M) in xylenes and the relative light intensity recorded. The solvent for the fractions that produced the most light intensity was removed under reduced pressure to yield the dioxetane (6%) as a light yellow oil. NMR spectroscopy and iodometric titration showed the dioxetane to be of better than 95% purity. NMR (CCl_4) for **1**: δ 0.95 (br t, J = 7 Hz, 3 H), 1.53 (s, 3 H), 1.8 (br q, J = 7 Hz, 2 H), 4.83 (s, 2 H). NMR for **2**: δ 0.95 (br t, $J \sim 6$ Hz, 3 H), 1.4 (m, 2 H), 1.53 (s, 3 H), 1.7 (m, 2 H), 4.80 (AB pattern, 2 H). NMR for **3**: δ 0.95 (br t, 3 H), 1.4 (m, 4 H), 1.53 (s, 3 H), 1.7 (m, 2 H), 4.82 (AB pattern, 2 H). NMR for **4**: δ 0.90 (d, J = 7 Hz, 3 H), 0.94 (d, J = 7 Hz, 3 H), 1.50 (s, 3 H), 2.3 (m, J = 7 Hz, 1 H), 4.81 (AB pattern, 2 H); for **5**: δ 1.01 (s, 9 H), 1.59 (s, 3 H), 4.8 (wide AB, 2 H). The dioxetanes were stored as ~ 0.2 M solutions in CCl_4 at −30 °C. The dioxetane concentrations of the solutions were determined by iodometric titration by the method of Wilson and Schaap[13] and checked by NMR analysis vs. added external standard.

Product Studies. The following procedure was employed for **1–5**. A 0.2 M solution of dioxetane in CCl_4 was heated at 60 °C in a sealed NMR tube until the yellow color disappeared. The corresponding ketone and formaldehyde (trace noted) were the only products detected by NMR spectroscopy. The ketone was detected by GC analysis of the solution.

Kinetic Studies and Yields of Excited States. The temperature (±0.2 °C) of the reaction mixture in the chemiluminescence apparatus was monitored by use of a YSI Model 425C telethermometer with no. 423 probe before and after each run.

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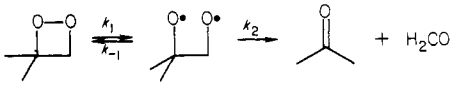
(10) A reviewer suggested the following interpretation: "For example, if thermolysis is stepwise why isn't reclosure to starting material condisered? In that case the reported rate constant would really be $k_{obsd} = (k_1/k_{-1})k_2$ or $K_{eq}\,k_2$. One might expect the substituent effects on K_{eq} and



k_2 to be in opposite directions. That is, large substitutents would depress K_{eq} (the well-known Thorpe–Ingold effect) and enhance k_2, since the product-forming step must relieve nonbinding interactions. The surprisingly small change on going from ethyl to *tert*-butyl might thus be understood as the result of partial cancellation of larger, but opposite, substituent effects". Group additivity-type calculations of dioxetane activation parameters have been based[9] (in part) on the assumptions that $k_2 \gg k_{-1}$ and that E_{-1} is constant. The activation energy is assumed to be equal to $[\Delta H_f°(\text{diradical}) - \Delta H_f°(\text{dioxetane})] + E_{-1}$.[9] Bechara and Wilson have pointed out[4c] that E_{-1} may not be invarient in all cases. However, the assumption that O-O bond cleavage ($k_2 \gg k_{-1}$) is rate determining in alkyl dioxetane thermolysis seems valid.

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The jacketed cell was pretreated with an aqueous Na_2EDTA solution. All runs were carried out in xylenes (Aldrich) as the solvent. The initial dioxetane concentration of a run was kept at $\sim 10^{-4}$ M to avoid induced decomposition of the dioxetane. Runs carried out without added fluorescer, with DPA, and with DBA were of the first order for at least 3 half-livers and showed no dependence on type or amount of added fluorescer. The yields of excited states produced upon dioxetane thermolysis was determined at 50.0 °C by variation of the concentration of fluorescer at constant dioxetane concentration (DBA/DPA method). The method of calculation has been discussed in detail.[2a] The value of ϕ_{ET} for energy transfer of triplet carbonyls to DBA was assumed to be 0.2 for all five cases. The apparatus was calibrated by taking the yield of triplet excited products from thermolysis of trimethyl-1,2-dioxetane determined by the DBA method, as 0.15.[15]

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Registry No. 1, 86954-68-9; 2, 86954-69-0; 3, 86954-70-3; 4, 86954-71-4; 5, 86954-72-5; 1-bromo-2-hydroperoxy-2-methylbutane, 86954-73-6.

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Inert Carbon Free Radicals. 4. Spin Labeling of Amino Acids and Peptides

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The first examples of spin labeling with inert free-radical reagents are presented. Those here described involve tagging of amino acids and peptides, the labeling reagents being tetradecachloro-4-(chlorocarbonyl)triphenylmethyl (**2**), 4-aminotetradecachlorotriphenylmethyl (**18**), and tetradecachloro-4-hydroxytriphenylmethyl (**25**) radicals, which give rise to derivatives of the so-called C-, N-, and O-link series, respectively. The labeled amino acids and peptides are as follows: from glycine, **4** and **9** (C link), **19** and **20** (N link); from alanine, **5**, **8**, and **10** (C link), **30** and **36** (O link); from phenylalanine, **6** and **11** (C link), **31** and **37** (O link); from leucine, **7** and **12** (C link); from valine, **32** and **38** (O link); from proline, **33** and **39** (O link); from alanylglycine, **23** and **24** (N link); from glycylglycylphenylalanine, **15** and **16** (C link). In this connection, inert free radicals **3** and **22** have also been obtained. The IR, UV–vis, and ESR spectra of the above-mentioned derivatives have been recorded. The hyperfine (ESR) spectra of the compounds of the N-link series show, in addition to the ^{13}C couplings, those with ^{1}H and ^{14}N. Some of the radicals here described display abnormal variations of the magnetic susceptibility with temperature.

The EPR spectrum of an organic free radical may afford information on its structure and on that of its immediate environment. The relevant parameters are the *g* values (Lande factor), the line width, and the hyperfine structure: the number of lines and their relative intensities and the coupling constants with the spin-active nuclei in the molecule.

When a free radical is attached somehow to a nonradical molecule, the EPR spectrum of the resulting species also affords structural information on the added molecule. This technique, called "spin labeling", has been employed extensively in the domains of chemistry, biochemistry, molecular biology (proteins,[1-3] nucleotides,[2] enzymes,[1,3] nucleic acids,[1] lipids and membranes,[1-3] immunology,[1,2] drug detection,[1,2] etc.), and industrial research (polymers,[2,4] detergents,[2] liquid crystals,[2] etc.). Practically, all the work done so far has been performed with conveniently stable aminyl oxide (nitroxide) radicals.

With the discovery of the "inert free radicals" (IFR),[5-7] some extremely stable trivalent carbon species, new prospects within the spin-labeling technique have emerged. In fact, such radicals withstand extremely aggressive chemicals, as well as temperatures up to 300 °C,[5] and in those containing functional substituents, their substituents usually react without impairment of the radical character,[6,7] some features that might be of significance in certain spin-labeling applications. (Recall the well-known lability of aminyl oxide radicals in aqueous acidic media.)

The size of the triphenylmethyl system might pose nearly unsurmontable problems in some applications, although it might as well be a desirable feature in others. The possibility of an anchoring of the inert spin label by a long "umbilical cord" might afford additional prospects.

In this connection it was decided to attempt the spin labeling of some amino acids and peptides[8] with functionalized inert free radicals, mainly to seek information on the relevant synthetic aspects. This aim has been achieved, and the results obtained are presented here.[10]

According to the spin-label reagent employed, the products reported next are grouped in three classes: C-link, N-link, and O-link series.

Results and Discussion

The inert spin labels used here are the radicals tetradecachloro-4-(chlorocarbonyl)triphenylmethyl (**2**), 4-

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