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Acyl nitroxides: reactions and reactivity

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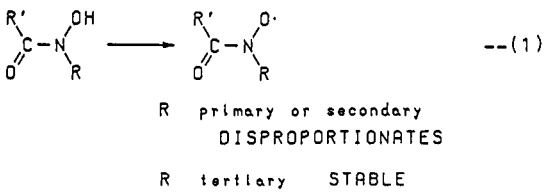
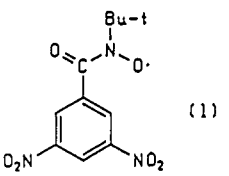
Abstract - The structure and reactions of acyl t-alkyl nitroxides are summarised. Intramolecular reactions of nitroxides in this class are reported, and their intramolecular reactivities are expressed as EM-values by comparison with suitable intermolecular models. The results, which may be representative of free radical reactions in general, suggest that intramolecular additions are likely to have EM-values several orders of magnitude greater than intramolecular hydrogen atom transfer. This parallels observations in ionic chemistry.

The one-electron oxidation of hydroxamic acids gives acyl nitroxides. N-Alkylhydroxamic acids give the corresponding alkyl acyl nitroxides, and when the alkyl group is tertiary these may often be isolated (equation 1. ref 1). Indeed, the crystal structure for the green t-butyl 3,5-dinitrobenzoyl nitroxide (1) has been reported and shows an essentially coplanar geometry for the carbonyl nitroxide unit, with the oxygen atoms anti (ref. 2). Although

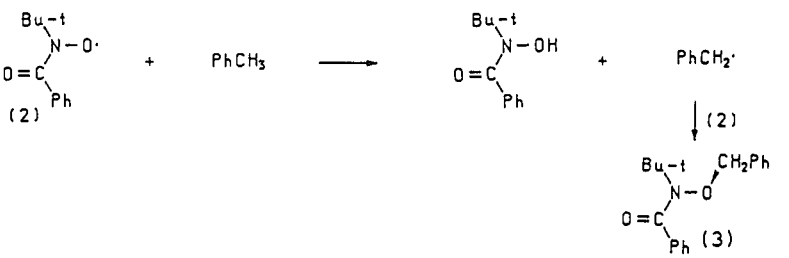


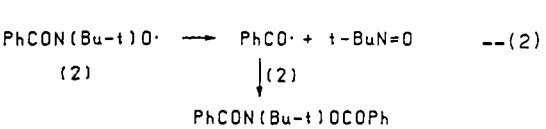
--(1)



(1)

these nitroxides may be isolated, they have proved to be much more reactive than the more familiar di-t-alkyl nitroxides (refs. 3,4). For example, in oxygen-free toluene heated to 75° C, benzoyl t-butyl nitroxide (2) disappears with a half-life of ca. 1 hr (ref. 3b) in a reaction with the solvent involving hydrogen abstraction followed by interception of the resulting benzyl radical by a second molecule of nitroxide. In benzene, at the same temperature, there is a very much slower first order decay (half-life > 50 hr) in which homolysis of the benzoyl nitrogen bond apparently occurs (equation 2). With other aralkanes or with cyclohexane, relative reactivity is similar to that of the bromine atom.

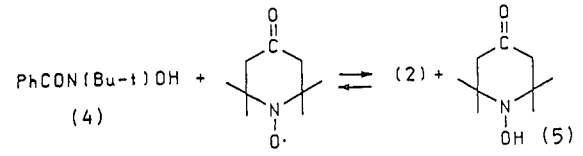




--(2)

$t_{1/2}$(Toluene; 75C) ca 1hr

The greater reactivity of these nitroxides compared with their dialkyl analogues can be associated with a greater OH bond dissociation energy in the parent hydroxylamine derivative.



--(3)

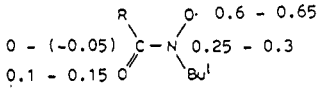
This has been investigated by equilibration studies where ΔG for Reaction 3 has been equated with the difference in OH bond strengths of (4) and (5). The OH bond dissociation energy for (5) is well established and the experimental results yield an OH bond strength for (4) of ca. 78 kcal mol^{-1} (ref 4). This value has been corroborated by a photoacoustic technique (ref 5), and the equilibrium method has been extended to give a number of further values listed in Table 1 (refs.4,6,7). Not surprisingly, there is a steric component in these values, with the N-isopropylbenzohydroxamic acid giving a value ca. 1½ kcal mol^{-1} greater than its t-butyl analogue (ref. 6).

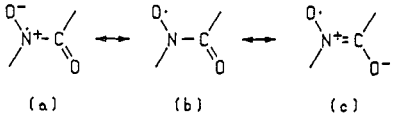
TABLE 1. Estimated OH bond dissociation energies of N-substituted hydroxamic acids

Acid [RCON(R′)O·] R	R′	BDE (OH) (kcal mol^{-1})
Ph	t-Bu	78
p-$O_2NC_6H_4$	t-Bu	80.2
p-$MeOC_6H_4$	t-Bu	75.9
n-$C_{10}H_{21}$	t-Bu	75.8
Ph	i-Pr	79.3
$(CH_2)_5N$-	t-Bu	74.4
Ph	3,5-$(Bu\text{-}t)_2C_6H_3$	80.5

Both e.s.r. studies and semi-empirical molecular orbital calculations support the view that the dominant effect of the carbonyl substituent in the radical is to delocalise the nitrogen lone pair and consequently to concentrate spin on nitroxide oxygen, as represented by structure (6c). An estimate of p-orbital spin density distribution based on isotropic hyperfine splittings in benzoyl and acetyl t-butyl nitroxide is shown in Figure 1.

Fig. 1. Approximate p-orbital spin density distribution in carbonyl nitroxides





(6)

One concern regarding the data of Table 1 is the possibility that intramolecular hydrogen bonding may make a significant contribution to the stability of the hydroxamic acid. This has been investigated using the recently developed PM3 semi-empirical molecular orbital procedure which is reported to give good results for hydrogen bonded structures (ref. 8). In fact, the (anti) structure is found to be more stable than the intramolecularly hydrogen bonded (syn) alternative, no doubt in part because the OH bond adopts an out-of-plane geometry. This has been demonstrated for hydroxamate derivative (3) in which the benzylic protons show n.m.r. non-equivalence at room temperature (200 MHz), and a rotational barrier of ca. 12 kcal mol^{-1} has been estimated (ref. 6). PM3 calculations on heats of formation of the simple models shown in Figure 2 lead to a ca. 3 kcal mol^{-1} difference between the OH bond strength in hydroxylamine and that in its formyl derivative. This is rather less than the difference suggested by the experimental data, although the particularly strong steric crowding of two t-alkyl substituents probably depresses the OH strength of (5).

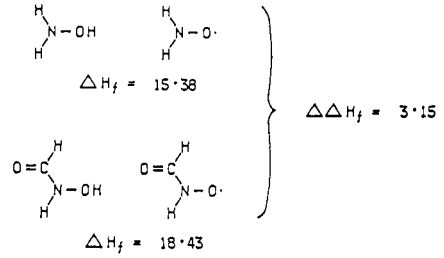
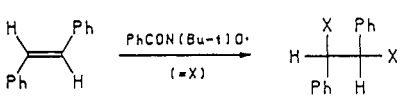
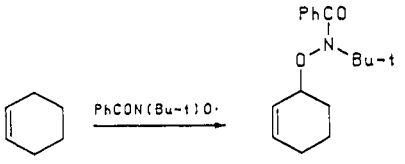


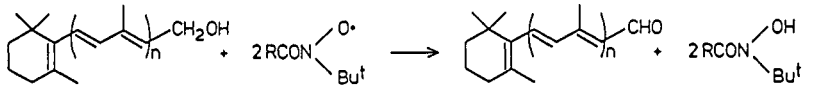
Figure 2

Benzoyl t-butyl nitroxide gives 2:1 adducts with alkenes having no abstractable allylic hydrogen (ref. 3b), but in many other cases, e.g. cyclohexene, the only isolated products are those of allylic substitution (ref. 3b). This type of reaction will be referred to again later in the context of intramolecular reactivity.



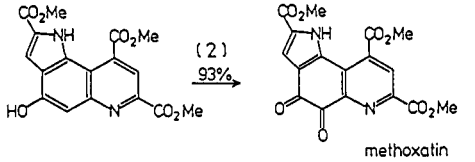


Oxidation of more reactive substrates is clearly of synthetic utility, and the two examples illustrated below show how valuable these nitroxide reagents can be (refs. 9,10). They have the advantage over Fremy's radical (ref. 11) that they can be used in non-polar organic solvents, although it must be pointed out that this drawback of the nitrosodisulphonate has been partially overcome with the aid of phase-transfer catalysis (ref. 12).



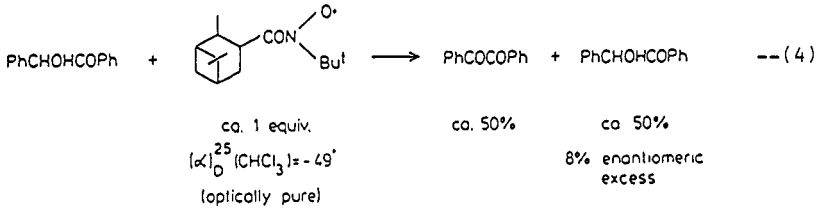
n=1 R=Ph >70% yield

n=2(Vit. A) R=$C_{10}H_{21}$ ca. 90% (retinal)



methoxatin trimethyl ester

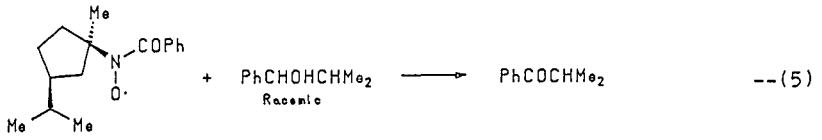
Partial oxidation of racemic benzoin by optically active t-butyl pinanecarbonyl nitroxide has shown modest enantioselectivity (equation 4) (ref. 9) although a similar experiment with the benzoyl fenchelyl nitroxide (equation 5) showed only tiny discrimination (ref. 13). The most interesting feature of the latter experiment was the use of HPLC equipped with a polarimetric detector (ref 14) which allowed an enantiomeric excess of less than 1% in the recovered alcohol to be assayed with reasonable precision. The choice of fenchelyl for these experiments, which are designed to test an underlying principle pertinent to chiral discrimination (ref. 15), was dictated by the general difficulties associated with synthesis of optically active hydroxamic acids with alternative chiral t-alkyl groups.



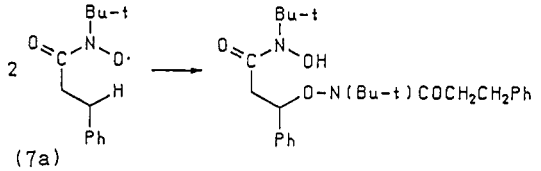
ca. 1 equiv. ca. 50% ca 50%

$[\alpha]_D^{25}(CHCl_3) = -49°$ 8% enantiomeric excess

(optically pure)



Most recently, our interests have focussed on intramolecular reactions of acyl nitroxides. This has been prompted by the now widespread utility of intramolecular free radical reactions in synthesis, and by general interest in comparing intra- with inter-molecular reactivity (ref. 16). The reactions of the acyl nitroxides lend themselves to kinetic study both by e.s.r. methods and by optical spectroscopy.



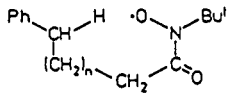
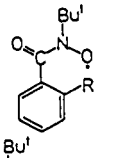
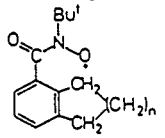
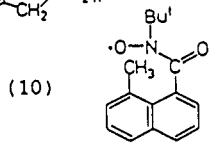
(7a)

In early work, we had examined intramolecular benzylic hydrogen abstraction in the hydrocinnamoyl nitroxide (7a). The rate of this reaction and rates of similar reactions of the longer chain analogues (7b-d) (see Table) were compared with the rate of the intermolecular reaction between an alkanoyl t-butyl nitroxide and ethylbenzene. This allowed the rates of the intramolecular reactions to be expressed as effective-molarity (EM) values which are shown in Table 2 (ref. 17). The higher rates of the reactions involving 7- and 8-membered ring transition states (7b,c) were interpreted in terms of roughly perpendicular

delivery of benzylic hydrogen on to nitroxide oxygen which is incorporated in a relatively rigid carbonyl nitroxide "template". The reaction geometry has since been supported by semi-empirical MO calculations of hydrogen transfer to an acyl nitroxide.

Higher EM values were found for a variety of other intramolecular hydrogen transfers included in Table 2. In each case, EM is calculated as the ratio of k_{intra}, the first order rate constant for the intramolecular reaction, to k_{inter}, the second order rate constant for a suitable intermolecular model. For example, the model reaction for (9a) was that between benzoyl t-butyl nitroxide and indane (assuming only two hydrogens are available in the intramolecular process).

TABLE 2. Effective molarities for intramolecular benzylic hydrogen abstraction

		EM
 (7)	a:n=0	0.5
	b:n=1	1.4
	c:n=2	1.3
	d:n=3	0.03
 (8)	a:R=Me	13
	b:r=Et	22
	c:R=i-Pr	12
 (9)	a:n=1	1.8
	b:n=2	45
	c:n=3	4.9
 (10)		44

The EM values for nitroxides (8) - (10) are generally about one order of magnitude larger than those for compounds (7), consistent with the freezing out of rotational freedom of one of the bonds linking together the reaction sites (ref 18). The results are comparable in magnitude to EM values found for analogous intramolecular proton transfers (ref. 19).

In contrast, ionic reactions in which a single bond is formed in the transition state, such as the two examples of nucleophilic processes shown in Figure 3 (ref. 20) and Figure 4 (ref. 21) reveal much higher EM values, approaching the theoretical entropy-controlled limit of ca. 10^8 (ref. 22).

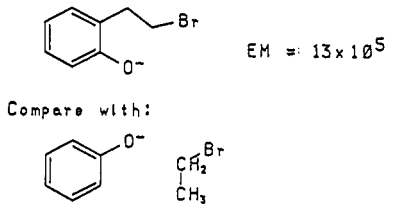


Figure 3

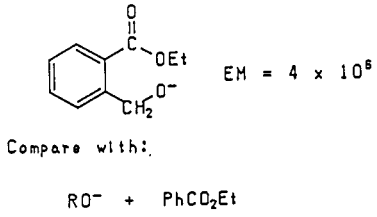
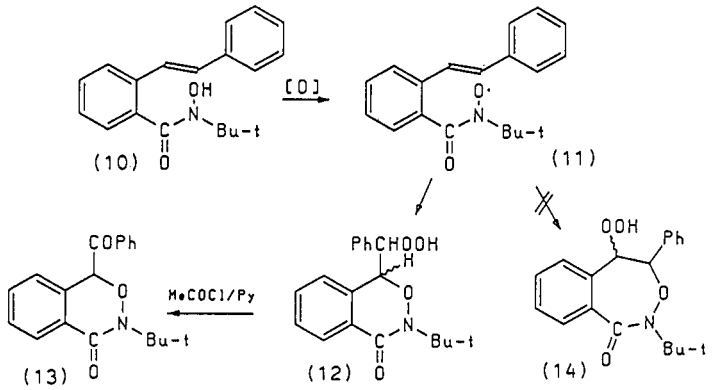
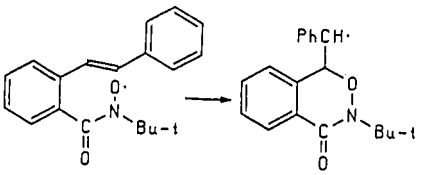


Figure 4

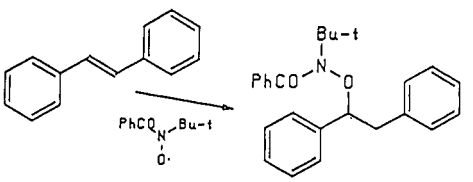
To investigate the possibility that intramolecular radical addition would similarly give much higher EM values we have synthesised some suitable unsaturated acyl nitroxide precursors. The first of these,(10), unlike any other hydroxamic acids which we have examined, undergoes a facile autoxidation to the stereoisomeric hydroperoxides (12). (ref 23) These compounds were differentiated from the alternative 7-endo cyclisation products (14) by dehydration to (13) which gave am n.m.r. spectrum with features characteristic of an unsubstituted benzoyl group. This autoxidation reaction suggested an extremely facile cyclisation of the intermediate nitroxide (11).



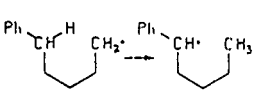
In the absence of oxygen, the decay rate of nitroxide (11) was measured over the temperature range -10 to -40° C. Extrapolation of the results to 125° C, at which temperature the rate of addition of benzoyl t-butyl nitroxide to stilbene was determined, gave an EM for the cyclisation of ca. 5 x 10^5 (ref. 23).



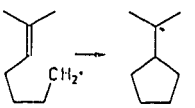
Compare with:



Examination of literature rate data for radical reactions reveals few examples for which satisfactory comparison of inter- with intra-molecular rates are possible. Two which we have located are shown below (ref. 24) and support the tentative conclusion that for radical reactions, just as for ionic reactions, the intramolecular transfer of hydrogen shows dramatically lower EM-values than does intramolecular single-bond formation.

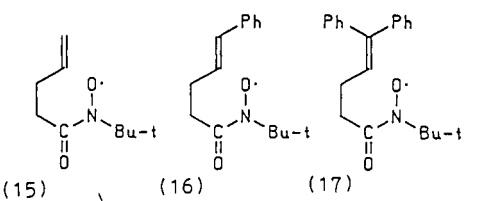


EM ca. 3

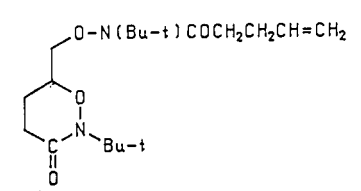


EM ca. 10^5

Three further examples of unsaturated acyl nitroxide precursors (15) - (17) are currently under investigation. The first gives a moderately persisent radical which decays slowly on warming, apparently to give the dimer (18). Interestingly, intramolecular addition, rather than the allylic abstraction which is preferred for the intermolecular process, is taking place. Presumably this is because of the much more favourable EM for the addition process. In the other two cases, the hydroxamic acids have been difficult to purify; our observations suggest that, like (10), they are giving cyclic autoxidation products.



(15) (16) (17)



(18)

We thank the Science and Engineering Research Council for support.

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