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Preferred Geometry of Unusual Nitrones. A Facile *E*–*Z* Isomerization of a *C*-Alkoxynitrone

David E. Gallis,[1] James A. Warshaw, Bruce J. Acken, and DeLanson R. Crist*

Department of Chemistry, Georgetown University, Washington, DC 20057

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A detailed structural study was carried out on *C*-methoxy-*C*-aryl-*N*-*tert*-butylnitrones (**1**), members of a relatively new class of compounds (acyclic imidate *N*-oxides). By ^{1}H NMR chemical shifts it was shown that **1** exist exclusively as the *E* isomers in $DCCl_3$ and the *Z* isomers in acetone-d_6. NOE difference spectra confirm these assignments and indicate a preferred conformation in which *O*-methyl and *C*-phenyl are more syn periplanar than anti in both cases. Configurations and conformations were similarly determined for *C*-phenyl-*N*-*tert*-butylnitrone (PBN), as well as several nitrone salts. Rates of *E* to *Z* isomerization of the phenyl, *p*-methoxyphenyl, and *p*-nitrophenyl derivatives of **1** were measured in acetone from 266 to 280 K giving $\Delta H^{\ddagger}$ values of 14.1, 16.9, and 14.2 kcal/mol and $\Delta S^{\ddagger}$ values of −24.3, −14.5, and −25.5 eu, respectively. The unusually low values of $\Delta H^{\ddagger}$ are interpreted in terms of ground-state destabilization due to steric repulsions that are relieved in going to the transition state by rotation about the C=N bond. The large negative $\Delta S^{\ddagger}$ values suggest solvent reorganization to stabilize the charge-separated character of the transition state. Geometry-optimized MNDO calculations are in agreement with conformation results from NOE experiments and predict a large dipole moment difference between *E* and *Z* isomers.

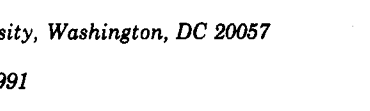
Interest in nitrone chemistry has increased markedly in recent years due to their applications in organic synthesis[2] and as spin trapping agents.[3] Although certain examples of cyclic alkoxynitrones have found use in the synthesis of spin labels,[4] reactions of acyclic *C*-alkoxynitrones have only recently been investigated and include cycloaddition,[5] electrophilic and nucleophilic substitutions,[6] hydrolysis,[6] redox reactions,[6] and radical additions.[7]

In the only reported mention of configuration assignment of an acyclic *C*-alkoxynitrone, Ashburn and Coates[5] concluded that *C*-ethoxy-*C*-phenyl-*N*-methylnitrone existed as a 5:2 mixture of *E*/*Z* isomers, assuming that the more upfield methyl was one shielded by phenyl in the *Z* configuration. An X-ray structure determination on a sulfur analogue supports this approach.[8] The configuration of one example of the recently reported, analogous *C*-vinylnitrones[9] was confirmed by NOE. We have shown for imidates that nuclear Overhauser effect difference spectroscopy can be used not only for configuration assignments but also for indicating preferred conformations.[10]

We now report configuration assignment and conformational preference for a series of *C*-methoxy-*N*-*tert*-butylnitrones by chemical shift data and NOE difference spectra. A more detailed study of the *C*-aryl nitrones revealed a striking solvent effect on configuration and an unusually facile *E* to *Z* isomerization in acetone.

Results

Nitrones **1a–d** were prepared as previously described by alkylation of the hydroxamic acids with methyl trifluoromethanesulfonate (triflate, or OTf^-) followed by deprotonation.[6]



1 a, R = C_6H_5
b, R = p-$CH_3OC_6H_4$
c, R = p-$O_2NC_6H_4$
d, R = H

Preferred Geometry. *C*-Alkoxy-*C*-arylnitrones. The parent nitrone **1a** in chloroform has ^{1}H chemical shifts in the first entry of Table I (deuterated solvents used throughout). When this solvent is evaporated and replaced with acetone, the shifts undergo slight changes due to a small solvent effect (second entry), but then these signals decrease with time as new signals (third entry) appear and grow in intensity until they are essentially the only signals present. From integrals the process involved is a simple isomerization. When the acetone is evaporated and replaced with chloroform, again there is a small solvent effect on chemical shifts (fourth entry), but the signals are replaced with time by the original ones, thereby demonstrating that the isomerization is reversible but with a striking solvent effect on isomer preference.

The preferred isomer in each solvent was assigned on the basis of chemical shift differences. In acetone, a more upfield *tert*-butyl signal (by 0.60 ppm) indicates the *Z* configuration in which these hydrogens are in the shielding cone of phenyl. This is in keeping with results for aldo- and ketonitrones,[11] *N*-*tert*-butyloxaziridines,[12] benzimidates,[10] and *C*-ethoxy-*C*-phenyl-*N*-methylnitrone.[5] In support of this assignment, the ortho hydrogens of this

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[1] Taken, in part, from the Ph.D. thesis of D. E. Gallis, present address: Environmental Resources Management, Inc., Exton, PA 19341.

[2] (a) Breuer, E. *Nitrones, Nitronates, and Nitroxides*; Breuer, E., Aurich, H. G., Nielsen, A., Eds.; Wiley: New York, 1989; pp 139–312. (b) Torssell, K. B. G. *Nitrile Oxides, Nitrones, and Nitronates in Organic Synthesis*; VCH Publishers: New York, 1988. (c) For a recent example, see: DeShong, P.; Li, W.; Kennington, J. W., Jr.; Ammon, H. L. *J. Org. Chem.* **1991**, *56*, 1364–1373.

[3] (a) Janzen, E. G. *Methods in Enzymology*; Academic Press: Orlando, FL, 1984; Vol. 105, pp 188–198. (b) Perkins, M. J. *Adv. Phys. Org. Chem.* **1980**, *17*, 1–64.

[4] Keana, J. F. W. *Chem. Rev.* **1978**, 37–64.

[5] Ashburn, S. P.; Coates, R. M. *J. Org. Chem.* **1985**, *50*, 3076–3081.

[6] Warshaw, J. A.; Gallis, D. E.; Acken, B. J.; Gonzalez, O. J.; Crist, D. R. *J. Org. Chem.* **1989**, *54*, 1736–1743.

[7] Acken, B. J.; Warshaw, J. A.; Gallis, D. E.; Crist, D. R. *J. Org. Chem.* **1989**, *54*, 1743–1745.

[8] Coates, R. M.; Firsan, S. J. *J. Org. Chem.* **1986**, *51*, 5198–5209.

[9] Bartoli, G.; Marcantoni, E.; Petrini, M.; Dalpozzo, R. *J. Org. Chem.* **1990**, *55*, 4456–4459.

[10] Gallis, D. E.; Crist, D. R. *Magn. Reson. Chem.* **1987**, 480–483.

[11] Bjorgo, J.; Boyd, D. R.; Neill, D. C.; Jennings, W. B. *J. Chem. Soc., Perkin Trans. 1* **1977**, 254–259.

[12] Gonzalez, O. J.; Gallis, D. E.; Crist, D. R. *J. Org. Chem.* **1986**, *51*, 3266–3270.

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Table I. ^1H Chemical Shifts of *C*-Methoxy-*C*-arylnitrones

structure		solvent	δ, ppm OCH$_3$	*N*-*t*-Bu	*o*-Ph	*m*-Ph	*p*-OCH$_3$
1a							
	(*E*)-sp^a	CDCl$_3$	3.64	1.63	7.91	7.41^b	
	(*E*)-sp	acetone-d_6	3.69	1.58	8.04	7.44^b	
	(*Z*)-sp^a	acetone-d_6	3.47	1.03	7.64	7.35^b	
	(*Z*)-sp	CDCl$_3$	3.49	1.03	7.61	7.31^b	
1b							
	(*E*)-sp^a	CDCl$_3$	3.64	1.63	7.96	6.93	3.85
	(*E*)-sp	acetone-d_6	3.68	1.51	8.04	6.99	3.87
	(*Z*)-sp^a	acetone-d_6	3.43	1.02	7.52	6.91	3.80
	(*Z*)-sp	CDCl$_3$	3.47	1.04	7.52	6.84	3.81
1c							
	(*E*)-sp^a	CDCl$_3$	3.76	1.67	8.17	8.32	
	(*E*)-sp	acetone-d_6	3.79	1.61	8.32	8.33	
	(*Z*)-sp^a	acetone-d_6	3.54	1.05	7.93	8.25	
	(*Z*)-sp	CDCl$_3$	3.53	1.03	7.81	8.18	

^{a}Preferred isomer in that solvent. ^{b}Also *p*-Ph hydrogens.

Table II. NOE Enhancements for *C*-Methoxy-*C*-arylnitrones^a

nitrone	^1H saturated	^1H observed, % (error) α-OCH_3	*o*-phenyl^b	other hydrogens
1a-*E*^{c}	*N*-*t*-Bu	2.5 (0.7)	0.0 (0.4)	
	α-OCH$_3$		4.5 (0.4)	
1a-*Z*^{d}	*N*-*t*-Bu	0.9 (0.1)	12.0 (0.1)	
	α-OCH$_3$		4.3 (0.1)	
				m-phenyl
1b-*E*^{c}	*N*-*t*-Bu	3.3 (0.1)	2.0 (0.1)	0.0 (0.1)
	α-OCH$_3$		5.9 (0.1)	0.0 (0.1)
	p-OCH$_3$	0.0 (0.1)	−2.1 (0.1)	14.4 (0.1)
1b-*Z*^{d}	*N*-*t*-Bu	1.5 (0.2)	9.6 (0.2)	0.0 (0.3)
	α-OCH$_3$		5.1 (0.2)	0.0 (0.3)
	p-OCH$_3$	0.0 (0.2)	0.0 (0.2)	14.9 (0.3)
1c-*E*^{c}	*N*-*t*-Bu	4.4 (0.3)	0.0 (0.2)	
	α-OCH$_3$		5.8 (0.2)	
1c-*Z*^{d}	*N*-*t*-Bu	0.0 (0.1)	11.0 (0.1)	
	α-OCH$_3$		4.2 (0.1)	

^{a}NOE data on samples deoxygenated prior to analysis at various temperatures: **1a-*E***, 7.0 °C; **1a-*Z***, 25 °C; **1b-*E***, −5 °C; **1b-*Z***, 7 °C; **1c-*E***, 2 °C; **1c-*Z***, 25 °C; **1d-*Z***, 0 °C. ^{b}With respect to the α carbon. ^{c}In CDCl$_3$. ^{d}In acetone-d_6.

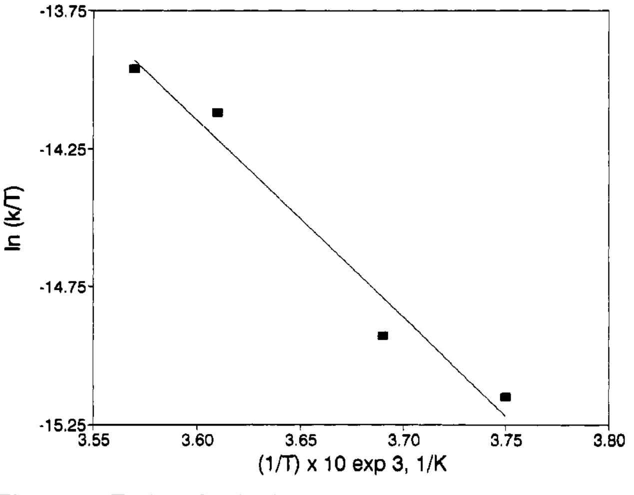
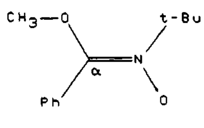


Figure 1. Eyring plot for *E* to *Z* isomerization of *C*-methoxy-*C*-phenyl-*N*-*tert*-butylnitrone (**1a**) in acetone-d_6.

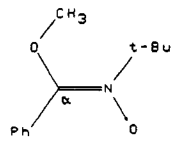
isomer are 0.30 ppm upfield from those of the *E* isomer, which exists in chloroform and whose ortho hydrogens are deshielded by oxygen of the *N*-oxide.[13]

Assignments of configurations were confirmed by NOE data in Table II. For the isomer in chloroform (**1a**–***E***) saturation of *N*-*tert*-butyl causes a 2.5% enhancement of the *O*-methoxy signal and, as expected for the *E* configuration, no enhancement for ortho hydrogens. For the isomer in acetone (**1a**–***Z***) saturation of *N*-*tert*-butyl gives a very large enhancement of 12.0% for ortho hydrogens (indicating that phenyl and *tert*-butyl are cis) but has little effect (<1%) on methoxy, as expected for the *Z* isomer. The magnitude of the ortho enhancement compares favorably to that of the related 3,3-bis(4-nitrophenyl)-2-*tert*-butyloxaziridine (14% on saturation of the *cis*-*N*-*tert*-butyl).[14]

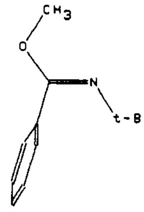
Two limiting conformations for **1a-*E*** are shown below, syn-periplanar (sp) with respect to methyl and phenyl about the C$_\alpha$–O bond or anti-periplanar (ap). Preferred conformations more sp than ap for both isomers are indicated by the NOE enhancement of ortho hydrogens on methoxy saturation. The values (4.5% for *E* and 4.3% for *Z*) are closer to the value of 3.9% observed for the sp



1a-*E* (sp)



1a-*E* (ap)



2-*E* (ap)

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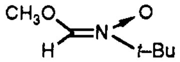
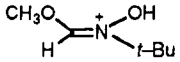
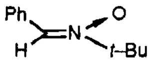
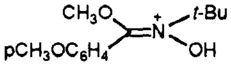
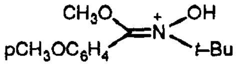
(13) (a) Koyano, K.; Suzuki, H. *Bull. Chem. Soc. Jpn.* **1969**, *42*, 3306–3309. (b) Grubbs, E. J.; Milligan, R. J.; Goodrow, M. H. *J. Org. Chem.* **1971**, *36*, 1780–1785. (c) Arumugam, N.; Manisankar, P.; Sivasubramanian, S.; Wilson, D. A. *Magn. Reson. Chem.* **1985**, *23*, 246–249.

(14) Boyd, D. R.; Jennings, W. B.; Wilson, V. E. *J. Chem. Res., Synop.* **1984**, 204–205.

Table III. NOE Data on Other Nitrones and Nitrone Salts

structure	^{1}H saturated	^{1}H observed, % (error)			
		α-OCH_3	*o*-phenyl[a]	*m*-phenyl[a]	α-*H*
 **1d-*Z***[b]	*t*-Bu α-OCH$_3$	0.0 (1.4)			24.7 (1.0) 5.5 (1.0)
 **4-*Z*-sp**[c]	*t*-Bu α-OCH$_3$	0.6 (0.1)			19.6 (0.1) 7.7 (0.1)
 **3-*Z***	*t*-Bu[b] *t*-Bu[d]		−1.5 (0.2) 0.0 (0.2)		11.2 (0.7) 20.9 (0.3)
 **7-*E*-sp**[c]	*t*-Bu α-OCH$_3$ *p*-OCH$_3$	1.3 (0.7) 0.0 (0.7)	0.0 (0.2) 3.5 (0.2) 0.0 (0.2)	0.0 (0.2) 0.0 (0.2) 10.7 (0.2)	
 **7-*Z*-Sp**[c]	*t*-Bu α-OCH$_3$ *p*-OCH$_3$	0.0 (0.2) 0.0 (0.2)	6.1 (0.4) 3.2 (0.4) 0.0 (0.4)	0.0 (0.2) 0.0 (0.2) 9.3 (0.2)	

[a] With respect to the α carbon. [b] In CDCl$_3$ at 0 °C. [c] As the triflate salt in CDCl$_3$ at 25 °C. [d] In acetone-d_6 at 25 °C.

Table IV. Kinetic Data on *E* to *Z* Isomerization of *C*-Alkoxy-*C*-arylnitrones[a]

nitrone	*T*, °K	$k \times 10^5$, s^{-1}	E_a, kcal/mol	$\Delta H^\ddagger$, kcal/mol	$\Delta S^\ddagger$, eu
1a	266.5	6.99 ± 0.06	14.7 ± 1.9	14.1 ± 1.9	−24.3 ± 7.3
	271.0	8.87 ± 0.23			
	277.0	20.4 ± 0.75			
	280.0	24.1 ± 0.46			
1b	268.0	5.58 ± 0.28	17.5 ± 0.3	16.9 ± 0.3	−14.5 ± 1.2
	272.0	9.25 ± 0.08			
	276.0	14.3 ± 0.30			
	280.0	23.1 ± 0.39			
1c	268.0	3.42 ± 0.08	14.7 ± 1.3	14.2 ± 1.4	−25.5 ± 7.6
	272.0	5.97 ± 0.12			
	276.0	7.76 ± 0.20			
	280.0	11.7 ± 0.19			

[a] In acetone-d_6 solvent.

conformer of the related (*Z*)-methyl *N*-*tert*-butylbenzimidate than that of 1.8% found for the ap conformer of the *E* isomer (structure **2-*E*** above).[10] In any case, *nearly the same* values for **1a-*E*** and **1a-*Z*** strongly suggest methoxy has a similar relationship with respect to phenyl in both isomers. Since this is surely an sp-like conformation for *E* (forced on methyl by *tert*-butyl), one can assume a similar conformation for the *Z* isomer.

Similar results were found for **1b** and **1c**, with chemical shift changes on exchange of solvents due to configuration isomerization (Table I). The chemical shifts are analogous to those for **1a** and lead to the conclusion that the exclusive isomer is *E* in chloroform and *Z* in acetone. The NOE data in Table II likewise indicate sp conformations for both.

The previous assumption that NOE enhancements in the phenyl region are due to ortho hydrogens was verified by saturation of the *p*-methoxy hydrogens of **1b** (see Table II). Enhancements of 14.4 and −2.1% occur in the phenyl region as expected for a linear three-spin system.[15] The large positive enhancement corresponds to adjacent hydrogens (meta with respect to C_α) and the smaller negative-relayed enhancement to ortho hydrogens. Furthermore, the absorptions giving this small negative effect are the same signals that experience a positive enhancement on α-methoxy saturation in chloroform or acetone and on *tert*-butyl saturation in acetone. It can therefore be assumed that the enhanced phenyl signals in **1a** and **1c** are likewise ortho hydrogens.

An interesting observation concerns the relative deshielding ability of the *N*-oxide on ortho hydrogens vs a nitro group on the benzene. The chemical shift of ortho hydrogens of **1c-*E*** in chloroform is at δ 8.17, since this is the signal with an NOE enhancement when α-methoxy is saturated. Since they are *upfield* from meta hydrogens, the nitro group in **1c** has a stronger deshielding effect on hydrogens adjacent to it than the *N*-oxide on ortho hydrogens of the *cis*-phenyl group. Aromatic hydrogens in *C*-(*p*-nitrophenyl)-*N*-phenylnitrone were assigned[16] assuming that N–O deshielding, which is larger for planar conjugated systems compared to nonplanar ones,[17,18] dominated.

MO Calculations. The semiempirical MNDO method[19] was applied to the *E* and *Z* isomers of **1a**. Geometries were optimized to give minimum heats of formation (see Experimental Section), which were 17.3 and 20.1 kcal/mol for the *E* and *Z* isomers, respectively. The minimum energy conformations for these isomers are in-

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(15) Noggle, J. H.; Shirmer, R. E. *The Nuclear Overhauser Effect*; Academic Press: London, 1971; pp 57–64.

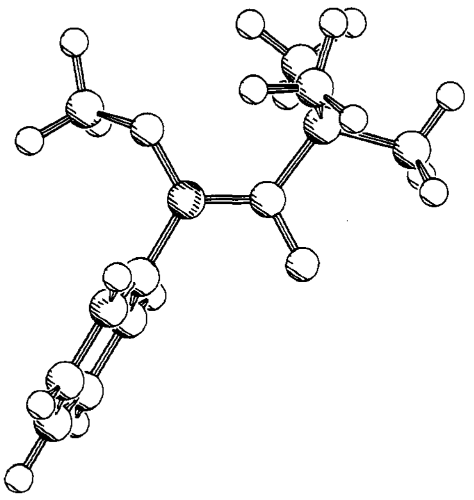
(16) Arumugam, N.; Manisankar, P.; Sivasubramanian, S.; Wilson, D. A. *Org. Magn. Reson.* **1984**, 592–596.

(17) Clack, D. W.; Khan, N.; Wilson, D. A. *J. Chem. Soc., Perkin Trans. 2* **1981**, 860–865.

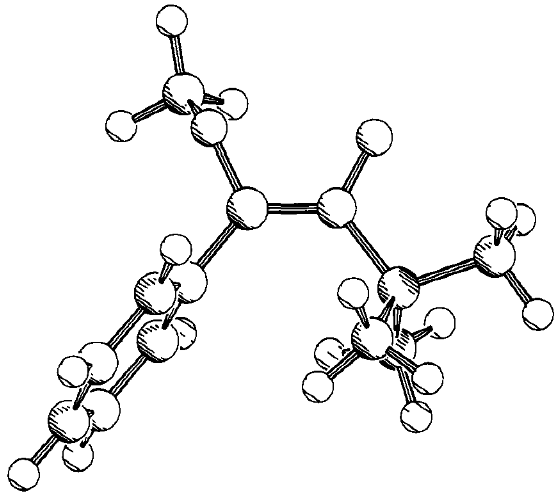
(18) Kerr, D. A.; Wilson, D. A. *J. Chem. Soc. C* **1970**, 1718–1725.

(19) (a) Dewar, M. J. S.; Thiel, W. *J. Am. Chem. Soc.* **1977**, *99*, 4899–4907. (b) Dewar, M. J. S.; Thiel, W. *J. Am. Chem. Soc.* **1977**, *99*, 4907–4917.

dicated in structures I below.



I-*E*

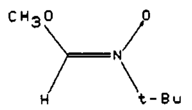


I-*Z*

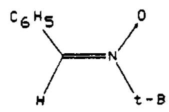
In I-*E* the *O*-methyl group is 49° from the limiting sp conformation and phenyl is nearly orthogonal (ϕ = 80°) to the plane of the nitrone group. In *Z* the absence of a *O*-methyl/*tert*-butyl repulsion allows a larger *O*-methyl twist angle (86°) but still on the side of sp rather than ap. In this isomer, *tert*-butyl forces phenyl to be orthogonal (ϕ = 88°),[20] in agreement with the upfield shift of *N*-*tert*-butyl hydrogens in **1a**-***Z***.

MNDO-calculated dipole moments for I-*E* and I-*Z* are 3.38 and 4.71 D, respectively. Geometry-optimized MNDO calculations on PBN[19] give values of 4.31 and 3.71 D for *E* and *Z* isomers, respectively.

Other Nitrones. In view of the striking solvent effect on configurational stability of **1a**, **1b**, and **1c** two additional nitrones were studied, α-alkoxynitrone **1d** and the widely used *C*-phenyl-*N*-*tert*-butylnitrone **3** (PBN). For **1d**, saturation of the *tert*-butyl signal gives a 24.7% enhancement of the α-hydrogen and none for the *O*-methyl signal (Table III). These data require the *Z* configuration for **1d**, even in chloroform. This is the same configurational preference observed for aldonitrones in general and shows that steric factors outweigh the less favorable dipole moment of this (*Z*)-*C*-methoxynitrone.



1d-*Z*



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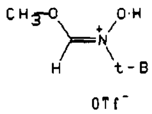
Despite the voluminous literature on PBN there has not been to our knowledge a direct determination of its configuration, which is generally assumed to be *Z*. Although chemical shift differences for **3** in chloroform and acetone are too slight for reliable configuration assignments, NOE data in Table III clearly show it is *Z* in both solvents. Thus, saturation of *N*-*tert*-butyl causes enhancement of the α-hydrogen with little or negative enhancement in the phenyl region, as expected for the *Z* configuration. With only a small dipole moment difference between *E* and *Z* isomers (0.60 D), the preferred configuration is determined by steric factors in this case.

Since no other stereochemical determination by NOE has been reported for salts of nitrones, this method was used to determine the configuration of **4**, which has no phenyl group and hence is not readily amenable to analysis by chemical shifts.



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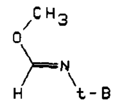

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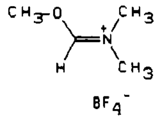

6

Saturation of *tert*-butyl of **4**, which occurs as a single isomer in chloroform, caused a 19.6% enhancement in the α-hydrogen and only 0.6% in *O*-methyl, showing clearly that the configuration must be *Z*. For comparison, irradiation of *tert*-butyl in formimidate **5**, shown to be *E* (ap),[10] gives a 16.6% enhancement of the α hydrogen. The methoxy conformation of **4** appears to be intermediate to sp and ap on the basis of the NOE of the α hydrogen on *O*-methyl saturation. Its value of 7.7% is intermediate to those of the ap **5** (2%)[10] and **6** (16%),[21] which is presumably sp due to *N*-methyl and *O*-methyl steric repulsions.

Another protonated nitrone, the hydrotriflate of *C*-arylnitrone **1b**, exists as a 3:1 *E*/*Z* mixture of isomers **7** in chloroform. Configurations were assigned by the chemical shift of *N*-*tert*-butyl, which is more upfield when *cis* to the aromatic ring (δ 1.69 for **7-*E*** and δ 1.35 for **7-*Z***). Phenyl and methoxy signals with larger integrals are associated with the *E* isomer. The assigned chemical shifts and configurations were confirmed by NOE data in Table III. Saturation of the δ 1.69 signal gives 0.0% *o*-phenyl and 1.3% *C*-methoxy enhancements, indicating a *tert*-butyl cis to *C*-methoxy as in the assigned *E* isomer. Also, saturation of the δ 1.35 signal gives 0.0% *C*-methoxy and 6.1% *o*-phenyl enhancements, demonstrating *tert*-butyl cis to phenyl as in the *Z* isomer.

Conformational aspects of the **7** isomers were revealed by NOE data in Table III. Saturation of (*E*)- and (*Z*)-*C*-methoxy signals yields nearly the same *o*-phenyl enhancements in both isomers. Given that the *C*-methoxy group cannot exist in an ap conformation in the *E* isomer, it follows that ap is also not favored in the *Z* isomer.

***E*/*Z* Isomerization.** Rates for the isomerization of the *E* to *Z* isomer were measured in acetone-d_6 for **1a**, **1b**, and **1c** at various temperatures. At long reaction time none

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[20] In agreement with this conformation for phenyl, CNDO/2 and INDO calculations for (*E*)-*C*-phenyl-*N*-methylnitrone (phenyl cis to the even less sterically demanding methyl) gave an energy that was ca. 30 kcal/mol larger when phenyl was coplanar rather than orthogonal to the C=N plane; see ref 26.

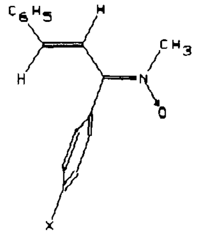
[21] Deslongchamps, P.; Dube, S.; Lebreux, C.; Patterson, D. R.; Taillefer, R. J. *Can. J. Chem.* **1975**, *53*, 2791-2807.

of the original signals are present. Values of the rate constants (Table IV) vary only within a factor of 2, as was the case for the *Z* to *E* isomerization of *C*-aryl-*C*-(β-styryl)-*N*-methylnitrones 8 with the same substituents.[17] Activation parameters are also given in Table IV, and a typical Eyring plot is given in Figure 1.

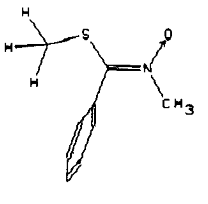
Discussion

Space-filling models of 1 support conclusions about preferred conformations based on NOE and MO considerations. The *E* isomer has serious steric interactions between *O*-methyl and *N*-*tert*-butyl groups in the ap conformer, which would cause methoxy to assume an sp conformation. Steric repulsions are also apparent between the *O*-methyl and *N*-oxide groups even in the *Z* isomer, making an anti-periplanar (ap) conformation unlikely in this isomer as well. Both isomers exhibit steric interactions between ortho hydrogens and methoxy as well as the nitrogen groups, thereby favoring phenyl orthogonal to the plane of the nitrone group.

These conformations, sp-like with orthogonal phenyl, are thus analogous to the sterically similar nitrones 8 whose spatial arrangements were assigned based on UV, NMR, and MO calculations.[17] An X-ray structure determination on an even closer analogue, nitrone 9, gave a phenyl twist angle of 65.6° and the *S*-methyl group 13.6° from an sp conformation.[8]

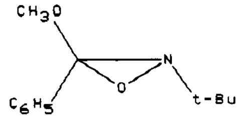


8

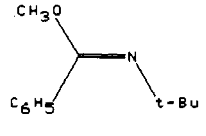


9

It might be pointed out that the *cis*-*tert*-butyl/orthogonal phenyl interaction in I-*Z* is also present in oxaziridine **10**-***E***, the preferred isomer in carbon tetrachloride, presumably due to the lower dipole moment of this isomer. It is also present in benzimidate **2**-***E***, which amounts to 40% of the *E*/*Z* mixture in chloroform at −58 °C. With regard to other interactions, the *N*-oxide oxygen may destabilize I-*E* by n–π repulsions[22] and I-*Z* by n–n repulsions. Although it is difficult to evaluate these factors, as well as the possibility of nonbonded attractions,[8,23] they may be comparable for the two isomers, as is the degree of phenyl conjugation. To the extent that a *tert*-butyl/phenyl steric interaction is similar to that of *tert*-butyl/*O*-methyl, the main difference between I-*E* and I-*Z* is their dipole moment.



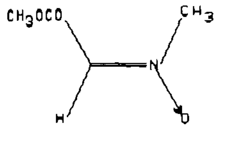
10-E



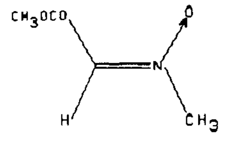
2-E

MNDO-calculated heats of formation, which refer, of course, to the gas phase, are relatively close for the two isomers, in agreement with the observation that the solvent can influence isomer preference so markedly. The lower energy isomer, by 2.8 kcal/mol, is for the less polar *E* configuration, which exists in the less polar chloroform.

The rather large calculated dipole moment difference of 1.33 D helps explain the striking solvent effect in which the exclusive isomer is *E* in chloroform and the more polar *Z* in the more polar acetone. Less pronounced solvent effects on isomer preference were reported for aldonitrones[24] and for nitrones 11.[25] Changing the solvent from chloroform to the more polar DMSO increased the relative amount of the more polar 11-***Z*** from 14% to 60%.



11-E



11-Z

Interestingly, the α-hydrogen of 11-***E*** in chloroform occurred at a lower field than 11-***Z*** due to deshielding by the *N*-oxide but at a higher field in DMSO. It was suggested[25] that the dipole of DMSO aligned with that of the *N*-oxide to cause an increased deshielding of this hydrogen in the *Z* isomer. A specific dipole–dipole interaction of the same sort may account for further stabilization of 1-***Z***.

It is clear that 1, with $\Delta H^{\ddagger}$ values <18 kcal/mol for *E* to *Z* conversion, undergo much more facile isomerizations compared with other aldo- and ketonitrones, which have typical $\Delta H^{\ddagger}$ values of 23–33 kcal/mol.[26,27] The unusually low 12 kcal/mol for $\Delta G^{\ddagger}$ reported[28] for *N*,*N*′-diphenyl-*p*-benzoquinonediamine *N*,*N*′-dioxide is due to special resonance effects.

The low value of $\Delta H^{\ddagger}$ in the present case probably represents the importance of ground-state destabilization by the steric and electronic interactions described above. The reaction coordinate for isomerization involves breaking the C=N π bond and rotating about the σ bond. From space-filling models it appears that there is relief of steric interactions in going to an orthogonal transition state.

From CNDO/2 and INDO calculations for planar $H_2C{=}N(O)H$ the electron density on C increased on going to an orthogonal transition state.[26] Geometry-optimized MINDO/3 calculations on this system showed that as C=N rotation occurred the carbon became pyramidal, reflecting the carbanion character of the α carbon.[29] Similarly, CNDO/2 calculations on the transition state for *C*-phenyl-*N*-methylnitrone[26] showed a preference for a carbanion-like geometry.[30] This buildup of negative charge may be the reason for the slightly larger $\Delta H^{\ddagger}$ for

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[22] (a) Bjørgo, J.; Boyd, D. R.; Watson, C. G.; Jennings, W. B.; Jerina, D. M. *J. Chem. Soc., Perkin Trans. 2* **1974**, 1081–1084. (b) For an alternative explanation to the imine results of ref 23, see: Kyba, E. P. *Tetrahedron Lett.* **1973**, 5117–5120. (c) Bakke, J. M.; Ronneberg, H.; Chadwick, D. J. *Magn. Reson. Chem.* **1987**, *25*, 251–254.

[23] Epiotis, N. D.; Bjorkquist, D.; Bjorkquist, L.; Sarkanen, S. *J. Am. Chem. Soc.* **1973**, *95*, 7558–7562.

[24] Bjørgo, J.; Boyd, D. R.; Neill, D. C.; Jennings, W. B. *J. Chem. Soc., Perkin Trans. 1* **1977**, 254–259.

[25] Inouye, Y.; Takaya, K.; Kakisawa, H. *Magn. Res. Chem.* **1985**, *23*, 101–102.

[26] Jennings, W. B.; Boyd, D. R.; Waring, L. C. *J. Chem. Soc., Perkin Trans. 2* **1976**, 610–613.

[27] (a) Koyano, K.; Tanaka, I. *J. Phys. Chem.* **1965**, *69*, 2545. (b) Dobashi, T. S.; Goodrow, M. H.; Grubbs, E. J. *J. Org. Chem.* **1973**, *38*, 4440–4443. (c) Ooi, N. S.; Wilson, D. A.; *J. Chem. Res. Synop.* **1980**, 394–395.

[28] Layer, R. W.; Carman, C. J. *Tetrahedron Lett.* **1968**, 1285–1286. $\Delta G^{\ddagger}$ is at the NMR coalescence temperature, which occurs between −40 °C and 31 °C.

[29] Jennings, W. B.; Worley, S. D. *Tetrahedron Lett.* **1977**, 1435–1438.

[30] Solvent effect data reported in ref 27c, however, suggest that the ground state is more polar.

1b in which a *p*-methoxy group destabilizes the transition state.

The values of $\Delta S^{\ddagger}$ for **1** are much more negative than those observed for other nitrones (+2 to −4 eu)[26,27b,c] and the near-zero value expected for unimolecular reactions,[26] especially given the highly ordered ground state in the present case. The major factor in the magnitude of this value is probably solvent ordering due to the localized charge buildup on C_α. More specifically, there may be alignment of the acetone dipole with an increased dipole of the transition state.[26]

It is interesting to note that certain examples of three classes of compounds, oxaziridine **10**,[12] imidate **2**,[10] and the nitrones **1**, undergo configurational isomerization at unusually enhanced rates. Significantly, all contained α-aryl, α-methoxy, and *N*-*tert*-butyl groups, but it is likely that they proceed by different mechanisms in each case: a ring opening for **10**, N inversion[31] for **2**, and bond rotation for **1**.

Conclusions

Unlike most nitrones, the present *C*-methoxy-*C*-aryl-*N*-*tert*-butylnitrones show a marked solvent effect on isomer preference. In chloroform they exist exclusively as the *E* isomers in conformations more syn- than anti-periplanar, as shown by ^{1}H NMR and NOE difference spectra. In the more polar acetone they existed exclusively as the more polar *Z* isomers. MNDO geometry-optimized structures are consistent with conformations based on NMR results. It appears that the several steric interactions balance out in the two isomers leaving their dipole moment difference as the main factor in determining isomer preference. The unusually low $\Delta H^{\ddagger}$ values reflect ground-state strain that is relieved on bond rotation in going to the transition state. Negative $\Delta S^{\ddagger}$ values are consistent with solvent reorganization accompanying buildup of charge in the transition state.

Experimental Section

Alkylation of hydroxamic acids with methyl triflate gave the nitrone hydrotriflates as previously described,[6] and deprotonation on silica gel preparative TLC plates gave the corresponding nitrones.[6] NMR spectra were run on a 300-MHz Bruker AM300 instrument and NOE difference spectra performed as described earlier.[10] Errors for % enhancements are based on three differences of reference to enhanced signals. Off-resonance and on-resonance saturating frequencies were alternated in 8–8 pulse cycles in order to minimize effects of spectrometer instabilities,[32] and each cycle was preceded by three dummy scans to ensure a steady-state condition. This procedure is comparable to four pulse/cycle procedures.[32,33]

MO Calculations. A MOPAC program was used for MNDO calculations on Digital VAX 11/750. The starting geometry for calculations of (*Z*)-*C*-phenyl-*C*,*N*-dimethylnitrone was taken by combining structural data of (*Z*)-*S*-methyl *N*-methylthiobenzimidate *N*-oxide,[8] acetaldehyde,[34] and benzene.[34] After energy minimization, the optimized values of this nitrone were used for the initial dimensions of **1a**. The phenyl twist angle was initially set to 90° (orthogonal), that of $H_3C{-}O{-}C_\alpha{-}C_{phenyl}$ to 0° (*syn*-periplanar), and that of O–N–C–O to 180° or 0° for *E* and *Z* isomers, respectively.

Kinetics. Chloroform solutions of the *E* isomers of **1a**, **1b**, and **1c** were evaporated to dryness under a stream of dry nitrogen at 0 °C, and acetone-d_6 (MSD Isotopes) was added to give dilute solutions (concentrations <1% or 0.05 M). Rates of isomerizations were monitored by ^{1}H NMR at reduced temperature (280–265 K). Temperature was regulated by a B-VT100 temperature control unit (Bruker), factory-calibrated to an accuracy of ±0.3 K for the range used. All spectra taken during a given kinetic run were phased with the same phasing parameters. Observations were made at approximately equal time intervals that were estimated to yield at least 10 data points over the first half life of the *E* to *Z* conversion. This conversion appears to proceed to completion, since at long time periods there was no detectable amount of *E* present. Least-squares regression analysis was applied to the integrated intensities of the *N*-*t*-Bu signals of the *E* isomer for a pseudo-first order treatment.

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Registry No. **1a**-***E***, 118891-54-6; **1a**-***Z***, 135733-53-8; **1b**-***E***, 118891-55-7; **1b**-***Z***, 135733-54-9; **1c**-***E***, 118891-56-8; **1c**-***Z***, 135733-55-0; **1d**-***Z***, 118891-58-0; **3**-***Z***, 52392-70-8; **4**-***Z*** triflate, 135733-56-1; **7**-***E*** triflate, 135733-57-2; **7**-***Z***, 135733-58-3.

Supplementary Material Available: MNDO-optimized geometry data for **1a**-***E*** and **1a**-***Z*** (2 pages). Ordering information is given on any current masthead page.

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(31) Moriarty, R. M.; Yeh, C.-L.; Ramey, K. C.; Whitehurst, P. W. *J. Am. Chem. Soc.* **1970**, *92*, 6360–6362.

(32) Eggert, H.; Nielsen, P. H. *Tetrahedron Lett.* **1981**, 4853–4854.

(33) DeShong, P.; Dicken, C. M.; Staib, R. R.; Freyer, A. J.; Weinreb, S. M. *J. Org. Chem.* **1982**, *47*, 4397–4403.

(34) *Handbook of Chemistry and Physics*, 53rd ed.; Weast, R. C., Ed. CRC Press: Boca Raton, 1972; p F-182.

Symmetry Breaking in Cyclodextrins: A Molecular Mechanics Investigation

Kenny B. Lipkowitz

Department of Chemistry, Indiana-Purdue University, 1125 East 38th Street, Indianapolis, Indiana 46205

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An analysis of the inherent features of cyclodextrins, void of water and crystal-lattice effects, has been undertaken with empirical force fields. It is found that these systems are not rigid and that symmetry breaking lowers the energies of these macrocycles. The highly symmetric structures portrayed in the literature are time-averaged views only.

Introduction

Cyclodextrins are cyclic oligomers of 1 → 4 linked α-D-glucose monomers. These molecules and their derivatives, as a class of compounds, have received considerable attention in this and more specialized journals for the past two decades.[1] The focus of these studies has been on the

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