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The amide bond rotation controlled by an unusual C–H···O hydrogen bonding that favors the 1,4-phenyl radical migration

Lilia Fuentes [a], Leticia Quintero [a], Alejandro Cordero-Vargas [b], Cesar Eustaquio [a], Joel L. Terán [a], Fernando Sartillo-Piscil [a,*]

[a] Centro de Investigación de la Facultad de Ciencias Químicas y Centro de Química del ICUAP, BUAP. 14 Sur Esq. San Claudio, San Manuel., 72570 Puebla, Mexico
[b] Instituto de Química, UNAM. Circuito Exterior s/n, Ciudad Universitaria., 04510 México, D. F., Mexico

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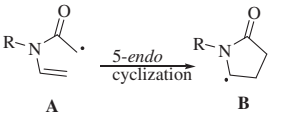
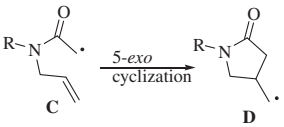
ABSTRACT

Experimental evidence in support of the presence of a weak C–H···O hydrogen bonding that favors 1,4-phenyl radical migration in a chiral amide is provided.

Among all the carbon-centered free radicals, the α-amide radicals represent one of the most useful reactive species that have found enormous application in synthetic chemistry.[1] Besides the high stability provided by the carbonyl group, another important feature of these radicals is that the C–N amide bond rotates at a moderate or slow rate, which is comparable or even slower than many radical reactions.[2] In this sense, researchers have taken advantages of this controlled dynamic behavior and have reported unexpected free radical reactions.[3] For example, Ishibashi and Ikeda have made possible what by ionic means appeared impossible to make: the 5-*endo* cyclization reaction of an α-amide radical (**A**) under either reductive or oxidative conditions to produce γ-lactam radical (**B**, eq. 1).[4] In a different way, the 5-*exo* cyclization of chiral α-amide radical (**C**) under reductive conditions to generate primary γ-lactam radical (**D**, eq. 2), represents a standard free radical transformation widely employed in organic synthesis, however, cyclization in stereoselective fashion have been proven to be uncommon (eq. 2).[5]



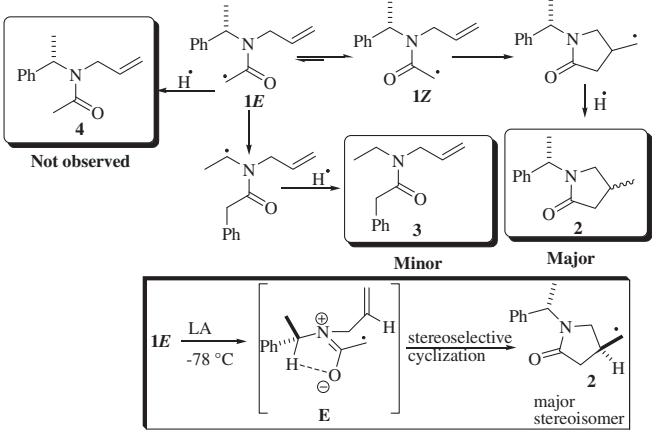
(1)



(2)

In the latter regard, preparation of 4-alkyl-pyrrolidinone **2** from radical rotamer **1*E***, and the rearranged product **3** from rotamer **1*Z***, were recently reported.[6] Although both radical transformations are well documented, the presence of the rearranged product **3** instead of the expected reduced product **4** represents an untypical outcome. In addition, the increase of stereoselectivity observed in the cyclization reaction at low temperatures in the presence of Lewis acid,[7] makes the α-amide radicals (**1*Z*** and **1*E***) an interesting model of study, especially because in both cases, the existence of a weak internal hydrogen bonding interaction (e.g., **E**) was postulated as a favorable interaction that controls the amide bond rotation and, therefore, favors both reactions (Scheme 1).

In spite of the C–H···O hydrogen bond interactions have been well-established in structural chemistry, it is not fully accepted that they are involved in chemical transformations, especially those in solution.[8] Questions concerning whether the C–H···O hydrogen bond interactions have biological significance or if these weak interactions are robust enough for leading chemical



Scheme 1. Free radical reactions of chiral α-amide radicals **1*Z*** and **1*E***.

* Corresponding author. Tel.: +52 222 2295500x7391; fax: +52 222 2295500.
E-mail address: fsarpis@siu.buap.mx (F. Sartillo-Piscil).

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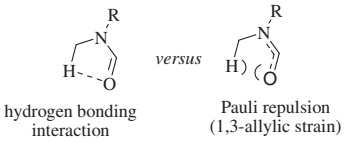
synthesis, are very difficult to be answered. One of the main problems here is to accept that the delocalization of an oxygen lone pair (n) into the C–H antibonding orbital (σ^*) can overcome Pauli repulsion between n orbital and the C–H σ bonding orbital (1,3-allylic strain, eq. 3).[9]

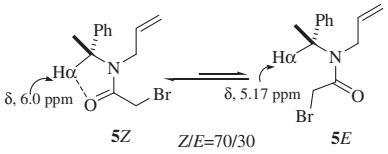


(3)

In this sense, this Letter attempts to provide further experimental evidences for the existence of unusual C–H···O hydrogen bonding, and determine whether this weak intramolecular interaction influences on the amide bond rotation and, therefore, interferes in the 1,4-phenyl radical migration of the chiral α-amide radical **1*Z*** (see Scheme 1).

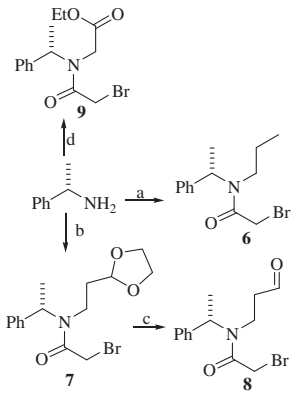
In previous work,[6] the chiral α-bromoamide **5** (precursor of the amide radicals **1*E*** and **1*Z***) was shown to exist as a mixture of rotamers *Z*/*E* (3:1) at room temperature, and after treatment with Bu_3SnH/AIBN afforded cyclization product **2** and rearranged product **3** in similar product distribution as that of the rotamer ratio. This observation led us to conclude that the presence of the *E*-rotamer is responsible for the rearranged product **3**.

It is important to note that, the structural assignment and ratio of *Z*/*E* rotamers for **5** were determined by ^{1}H NMR and computational calculations. The benzylic hydrogen atom (Hα) in **5** was used as a stereochemical marker that permitted to establish the orientation of the carbonyl group and, therefore, to establish the geometry of the *Z*/*E*-rotamers. In this sense, a quartet signal at 6.0 ppm was assigned to Hα for the *Z*-rotamer (due to its close proximity toward the oxygen atom of the carbonyl group), meanwhile a quartet signal at 5.17 ppm for *E*-rotamer (eq. 3).



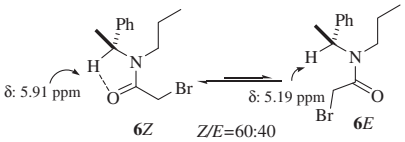
(4)

In order to demonstrate that the benzylic hydrogen atom (Hα) was the responsible for the higher *Z*-rotamer population, it was necessary to prepare other chiral amides (**6**–**9**) that would allow observation of the *Z*/*E* rotamer ratios under the same NMR criteria.

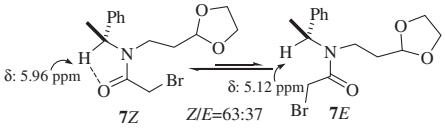


Scheme 2. Preparation of amides **6**–**9**. Reagents and conditions: (a) (i) PrI (1.2 equiv), NEt_3 (1.2 equiv), rt 3 h, 86%, (ii) bromoacethyl bromide (1.2 equiv), DMAP (1.2 equiv), 0 °C, 1 h, 60%; (b) (i) 2-(2-Bromoethyl)-[1.3]-dioxolane (1.0 equiv), K_2CO_3 (1.1 equiv), reflux 5 h, 84%, (ii) bromoacethyl bromide (2.7 equiv), K_2CO_3 (1.4 equiv), rt, 2 h, quantitative; (c) HCl 4.5 N, rt, 8 h, 97%; (d) (i) ethyl bromoacetate (1.2 equiv), NEt_3 (1.2 equiv), rt (ii) bromoacethyl bromide (1.2 equiv), NEt_3 (1.2 equiv), 0 °C, 2 h, 60%.

Thus, chiral amides **6**–**9** were prepared according to Scheme 2. It is important to mention that, to suppress the highly favorable 5-*exo* cyclization, the *N*-allyl substituent in **5** was switched (in all cases, **6**–**9**) to a substituent that is not a free radical acceptor.



(5)



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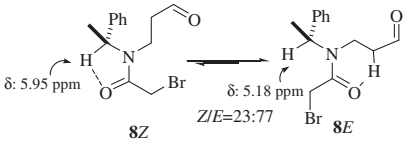
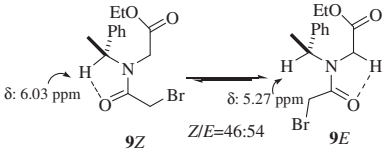


(7)



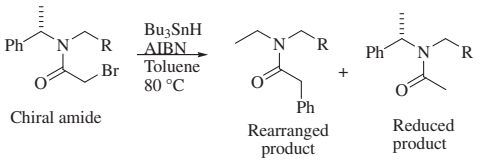
(8)

Chiral amides **6** and **7** were designed with the expectation to observe similar rotational behavior to that of amide **5**. On the other hand, due to the presence of an electron-withdrawing group (EWG) in amides **8** and **9**; we expected to invert the *Z*/*E* equilibrium by means of a stronger C–H···O hydrogen bond interaction. This was an attempt to show the presence of the unusual C–H···O hydrogen bond by attenuating this weak interaction with a stronger one, by forming a five-membered ring structure (**9*Z***, eq. 8), and a six-membered ring structure for amide **9** (**8*Z***, eq. 7).

The ^{1}H NMR spectra of amides **6** and **7** were very similar to amide **5**, exhibiting a pair of sharp well-resolved signals, wherein the Hα atoms in each rotamer resonances at the same frequencies to that in amide **5**, favoring in both cases the *Z*-rotamers (Eqs. 5 and 6). As anticipated, due to the electronic nature of the EWG, the rotamer ratios for the amides **8** and **9** were shifted toward the *E*-rotamer, showing now that the stronger hydrogen bonding is responsible for the major rotamer population (Eqs 7 and 8). Thus, these conformational behaviors provide significant evidence to the existence of the unusual C–H···O hydrogen bond interaction. This also suggests that it plays a key role in the rotational barrier of chiral amides bearing the chiral α-methylbenzylamine group, which it is a very important chiral auxiliary widely used in asymmetric synthesis.[10]

Having demonstrated the significant influence of the unusual C–H···O hydrogen bond interaction in the *Z*/*E*-rotamer ratios, we moved out to corroborate the initial hypothesis, which postulated that the weak interaction favors the formation of the rearranged product **3** (Scheme 1). Slow addition of Bu_3SnH and catalytic amounts of AIBN to amides **6**–**9** in toluene at 80 °C provided a mixture of expected rearranged/reduced products. As predicted, the product distribution varied as a function of the rotamer ratios. Higher amounts of reduced products were observed for amides **6** and **7** (*Z*-rotamer predominantly); while the rearranged product was predominant for amide **8** (where *E*-rotamer is favored). Unfortunately, amide **9** was not a suitable substrate, giving a complex mixture of side products (Scheme 3).

Because the free radical reactions are run at 80 °C, it was necessary to investigate whether the rotamer ratio changes at elevated temperature or keeps the same ratio. The amides **5** and **8** were selected for VTNMR studies in toluene-d_8 and demonstrated that the



Precursor	Rearrenged (%)[a]	Reduced (%)[a]
6, R = CH_2CH_3	**11** (25)	**12** (52)
7, R = CH_2-1,3-dioxolane	**13** (22)	**14** (55)
8, R = CO_2Et	**15** (48)	**16** (31)
9, R = CH_2COH	complex mixture of side-products	

a) Yields after purification

Scheme 3. Rearranged products versus reduction products of chiral amides **6–9.**

ratio of rotamers remains consistent at the reaction temperature (80 °C). Therefore, the proposal regarding the relationship between the rotamer ratio and products ratio seems to be correct. The VTNMR experiments allowed the determination of the C–N rotation barriers for **5** and **8**, wherein 15.8 kcal/mol was determined for **5** and 17.1 kcal/mol for **8**.[11] Although these numbers fall in the range for typical tertiary amides,[12] the energy difference of 1.3 kcal/mol between **5** and **8** might reflect the contribution of an additional C–H···O hydrogen bond interaction.

In summary, the results presented here provide experimental evidence of the existence of an unusual C–H···O hydrogen bond interaction in the chiral allylic amide **5** (and others), showing that this interaction is strong enough to overcome the Pauli repulsion between *n* orbital and the C–H σ bonding orbital (1,3-allylic strain) and therefore, favors the 1,4-phenyl radical migration. It is important to mention that, although there are various reports describing 1,4-aryl migration reactions in better yields,[13] this report represents the first example where phenyl-migration product is favored by a weak and unusual hydrogen bonding interaction. Further experimental and theoretical studies are currently underway.

Acknowledgments

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2011.05.016.

References and notes

1. (a) Porter, N. A.; Giese, B.; Curran, D. P. *Acc. Chem. Res.* **1991**, *24*, 296–304; (b) Curran, D. P.; Porter, N. A.; Giese, B. *Stereochemisty of Radical Reactions: Concepts, Guidelines, and Synthetic Applications*; VCH: Weinheim, 1995.
2. (a) Musa, O. M.; Choi, S.-Y.; Horner, J. H.; Newcomb, M. *J. Org. Chem.* **1998**, *63*, 786–793; (b) Musa, O. M.; Horner, J. H.; Newcomb, M. *J. Org. Chem.* **1999**, *64*, 1022–1025.
3. (a) Curran, D. P.; Guthrie, D. B.; Geib, S. J. *J. Am. Chem. Soc.* **2008**, *130*, 8437–8445; (b) Guthrie, D. B.; Geib, S. J.; Curran, D. P. *J. Am. Chem. Soc.* **2009**, *131*, 15492–15500; (c) Guthrie, D. B.; Geib, S. J.; Curran, D. P. *J. Am. Chem. Soc.* **2011**, *133*, 115–122.
4. (a) Sato, T.; Nakamura, N.; Ikeda, K.; Okada, M.; Ishibashi, H.; Ikeda, M. *J. Chem. Soc., Perkin Trans. 1* **1992**, 2399–2407; (b) Sato, T.; Chono, N.; Ishibashi, H.; Ikeda, M. *J. Chem. Soc., Perkin Trans. 1* **1995**, 1115–1120; (c) Ikeda, M.; Ohtani, S.; Okada, M.; Minakuchi, E.; Sato, T.; Ishibashi, H. *Heterocycles* **1998**, *47*, 181–186; (d) Ikeda, M.; Ohtani, S.; Yamamoto, T.; Sato, T.; Ishibashi, H. *J. Chem. Soc., Perkin Trans. 1* **1998**, 1763–1768; (e) Ishibashi, H.; Matsukida, H.; Toyao, A.; Tamura, O.; Takeda, Y. *Synlett* **2000**, 1497–1499; (f) Ishibashi, H.; Kodama, K.; Higuchi, M.; Muraoka, O.; Tanabe, G.; Takeda, Y. *Tetrahedron* **2001**, *57*, 7629–7637.
5. (a) Bellesia, F.; Danieli, C.; De Buyck, L.; Galeazzi, R.; Ghelfi, F.; Mucci, A.; Orena, M.; Pagnoni, U. M.; Parsons, A. F.; Roncaglia, F. *Tetrahedron* **2006**, *62*, 746–757; (b) Cardillo, B.; Galeazzi, R.; Mobbili, G.; Orena, M.; Rossetti, M. *Heterocycles* **1994**, *38*, 2663–2676; (c) Ishibashi, H.; Fuke, Y.; Yamashita, T.; Ikeda, M. *Tetrahedron: Asymmetry* **1996**, *7*, 2531–2538; (c) Saito, M.; Matsuo, J.-I.; Ishibashi, H. *Tetrahedron* **2007**, *63*, 4863–4865.
6. Rodríguez, V.; Sánchez, M.; Quintero, L.; Sartillo-Piscil, F. *Tetrahedron* **2004**, *60*, 10809–10815.
7. Rodríguez, V.; Quintero, L.; Sartillo-Piscil, F. *Tetrahedron Lett.* **2007**, *48*, 4305–4308.
8. (a) Desiraju, G. R. *Acc. Chem. Res.* **1996**, *29*, 441–449; (b) Steiner, T. *Chem. Commun.* **1997**, 727–734.
9. Massimi, M. *Pauli's Exclusion Principle: The Origin and Validation of a Scientific Principle*; Cambridge University Press: Cambridge, U.K., 2005; (b) Jakobsche, C. E.; Choudhary, A.; Miller, S. J.; Raines, R. T. *J. Am. Chem. Soc.* **2010**, *132*, 6651–6653; (c) Hosoya, M.; Otani, Y.; Kawahata, M.; Yamaguichi, K.; Ohwada, T. *J. Am. Chem. Soc.* **2010**, *132*, 14780–14789.
10. Juaristi, E.; León-Romo, J. L.; Reyes, A.; Escalante, J. *Tetrahedron: Asymmetry* **1999**, *10*, 2441–2495.
11. The rate constants *k* for the present dynamic process were calculated at the coalescence temperature (*Tc*) employing the Gutowsky-Holm equation ($k_c = \pi\Delta\upsilon/2^{-1/2}$). Assuming the transmission coefficient to be unity, the free energies of activation ($\Delta G^{\neq}$) were calculated according to the Eyring equation ($\Delta G^{\neq} = RTc[\ln Tc - \ln k_c + 23.76]$); See reference: Modarresi-Alam, A. R.; Najafi, P.; Rostamizadeh, M.; Keykha, H.; Bijanzadeh, H.-R.; Kleinpeter, E. *J. Org. Chem.* **2007**, *72*, 2208–2211.
12. Wunderlich, M. D.; Leung, L. K.; Sandberg, J. A.; Meyer, K. D.; Yoder, C. H. *J. Am. Chem. Soc.* **1978**, *100*, 1500–1503.
13. Studer, A.; Bossart, M. *Tetrahedron* **2001**, *57*, 9649–9667. And references cited herein.