



Ab initio study of the mechanisms of reactions of NF₃ with aliphatic and benzylic substrates

Randolph K. Belter ^{a,*}, Cheri A. McFerrin ^b

^a Y-Not Chemical Consulting, Zachary, LA 70791, USA

^b Dept. of Chemistry, Louisiana State University, Baton Rouge, LA 70803, USA

ARTICLE INFO

Article history:

Received 22 September 2011

Received in revised form 10 December 2011

Accepted 12 December 2011

Available online 20 December 2011

Keywords:

Nitrogen trifluoride

Ab initio

Gaussian

Alkyl substitution

Aromatic substitution

Radical abstraction

Difluoroalkylamines

ABSTRACT

At temperatures around 400 °C, nitrogen trifluoride (NF₃) readily reacts with alkanes and benzene as well as ethers to produce stable N,N-difluoroamines. Difluoroamination of benzylic substrates results in initial N,N-difluoroamines that undergo eliminations or rearrangements. Toluene and ethylbenzene produce benzonitrile. Cumene produces α -methylstyrene. Diphenylmethane produces benzanimide. Little or no direct fluorination or radical dimerization is observed. This study uses *ab initio* calculations to help understand the reasons for such diverse reaction pathways.

© 2011 Elsevier B.V. All rights reserved.

1. Introduction

1.1. Organic reactions of nitrogen trifluoride

We have shown experimentally that nitrogen trifluoride (NF₃) can be reacted in a controlled manner with benzylic substrates in a 400 °C vapor phase reactor [1]. Each substrate tested underwent N,N-difluoroamination at the benzylic position. In every case, the initial N,N-difluoroamine was unstable and converted to another functionality. Specifically, toluene produced benzonitrile via HF elimination. Ethylbenzene also produced benzonitrile, but via Beckmann rearrangement. Cumene produced α -methylstyrene via HNF₂ elimination. Diphenylmethane produced benzanimide, again via Beckmann rearrangement. Additionally, we have shown that alkanes, cycloalkanes, ethers, cyclic ethers and benzene also react with NF₃ at high temperature to produce STABLE difluoroamines [2]. Little direct fluorination or radical dimerization was observed. We have now used *ab initio* calculations to help understand the stability/instability of difluoroaminoorganics and the selectivity toward the various decomposition routes. For each

case below, the first reaction (Rxn 1) is the thermal dissociation of NF₃ to F[•] and \bullet NF₂.

2. Results and discussion

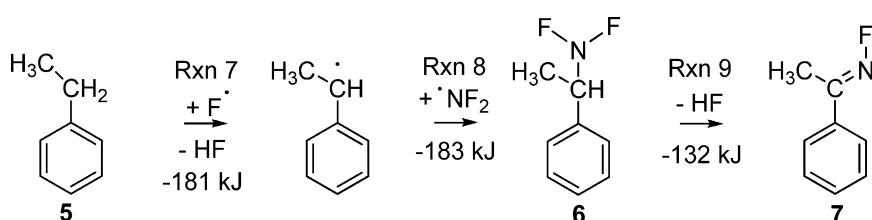
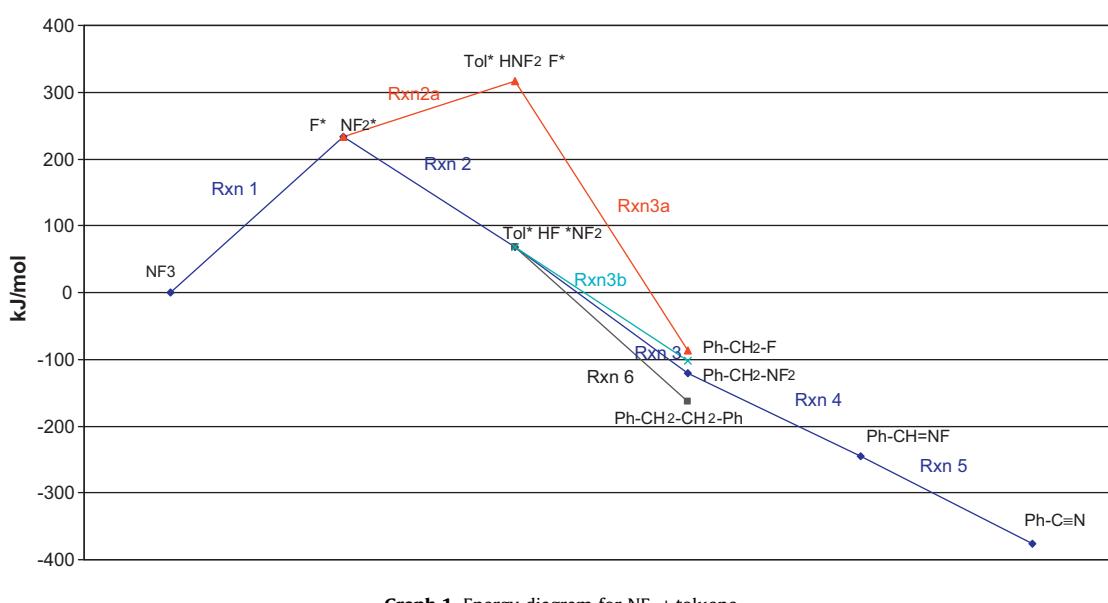
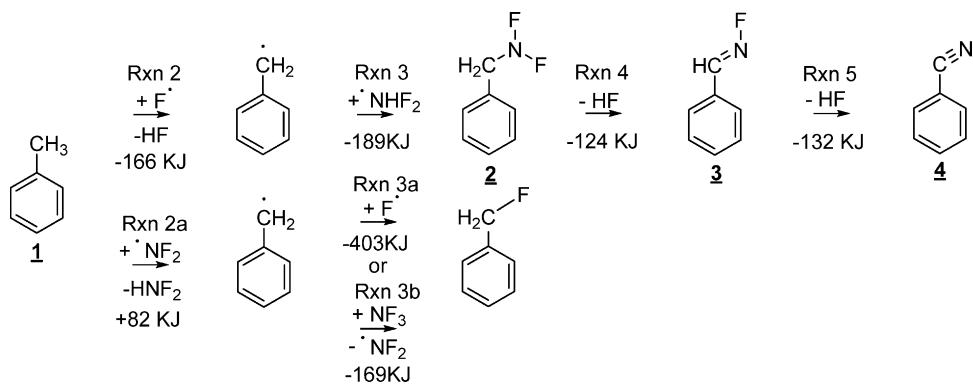
2.1. Reaction course for α -difluoroaminotoluene decomposition to benzonitrile

We have concluded previously that toluene, **1**, reacts with NF₃ at 400 °C to produce transient α -difluoroaminotoluene, **2**. However, **2** converts to benzonitrile, **3** under the high temperature conditions under which it is generated. **Scheme 1** shows the logical routes to each potential product and the associated energetics. However, the lack of α -fluorotoluenes or dimers in the product composition is puzzling. Our calculations show that abstraction of the α -hydrogen by fluoride radical is favored by a factor of greater than 2100:1 over abstraction by \bullet NF₂ (Rxn 2a), so the direct route to α -fluorotoluenes is non-viable. An alternative mechanistic step, where toluene radical abstracts fluorine from NF₃ (Rxn 3b), could generate α -fluorotoluene in a radical chain reaction and is disfavored overall by only 20 kJ/mol. However the energetics of α -hydrogen abstraction (+82 kJ/mol) by \bullet NF₂ preclude any propagation.

Interestingly, the dimerization of toluene radical is the most favorable reaction of Tol[•] of all (**Graph 1**, Rxn 6). However, evidently either Tol[•] is generated in low concentration or is so intimately associated with \bullet NF₂ that essentially no dimer is being produced.

* Corresponding author. Tel.: +1 225 658 8792.

E-mail addresses: randolphbelter@gmail.com (R.K. Belter), cmcferr1@lsu.edu (C.A. McFerrin).



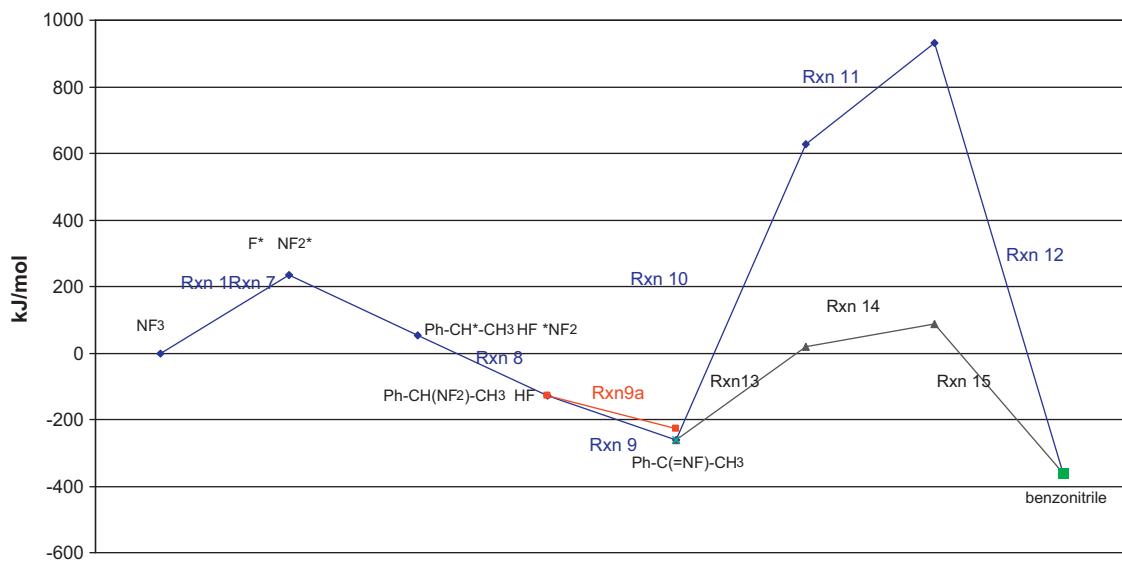
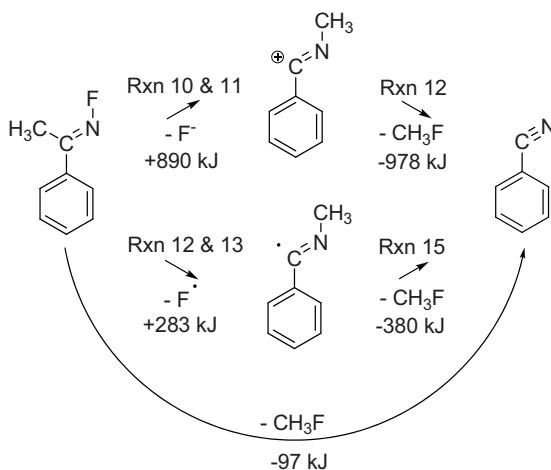
2.2. Reaction course for α -difluoroaminoethylbenzene decomposition to benzonitrile

In our initial study, the high temperature reaction of ethylbenzene with NF_3 had a surprising result. The only product was benzonitrile, the result of an apparent Beckmann rearrangement. In Scheme 2, the reaction of ethylbenzene, 5, with NF_3 progresses predictably from reagents through radicals to α -difluoroaminoethylbenzene, 6. Compound 6 eliminates HF to the fluoroimine, 7, which is necessary for the Beckmann rearrangement.

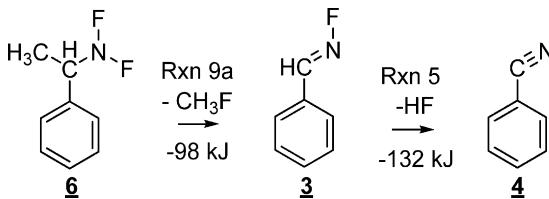
The classic Beckmann rearrangement occurs through cationic intermediates and we used Gaussian to evaluate the energetics of such a process. Scheme 3 shows that the generation of an initial cation followed by the formal shift (Rxns 10 & 11) is unfavorable by +890 kJ/mol. Immediately, we evaluated the possibility of a radical

Beckmann rearrangement. The initial formation of a radical, followed by the formal rearrangement (Rxns 13 & 14) is a much more modest +283 kJ/mol. If a rearrangement is truly occurring, the radical mechanism is much more favorable than the cationic alternative (see Graph 2).

One mechanism that cannot be ignored is the direct elimination of CH_3F from the difluoroamine 6 as a way to convert to benzonitrile and the accompanying -98 kJ/mol energy stabilization (Rxn 9a, Graph 2). Sequential loss of HF would be immediate with a further -132 kJ/mol stabilization (Scheme 4). Alternatively, an initial loss of HF from 6, then elimination of CH_3F effectively exchanges the two steps with an almost exact exchange of the energy values. Either way, all steps are exothermic, even if counterintuitive. We expect that a syn CH_3/F relationship is required for elimination.

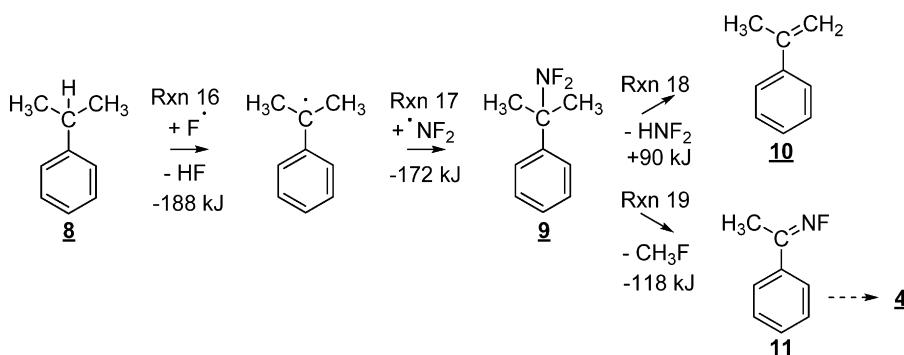
Graph 2. Energy diagram for $\text{NF}_3 + \text{ethylbenzene}$.

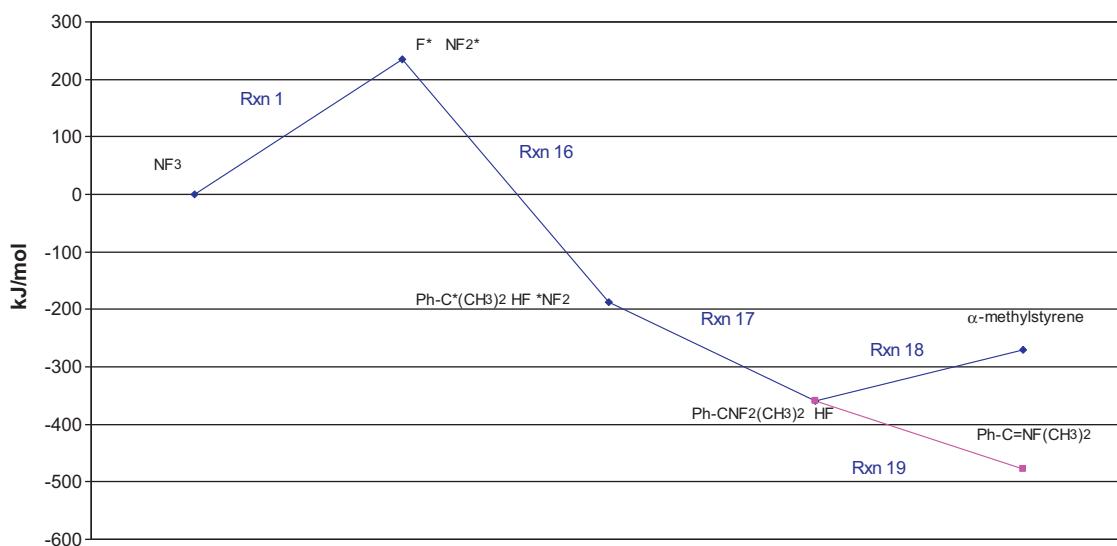
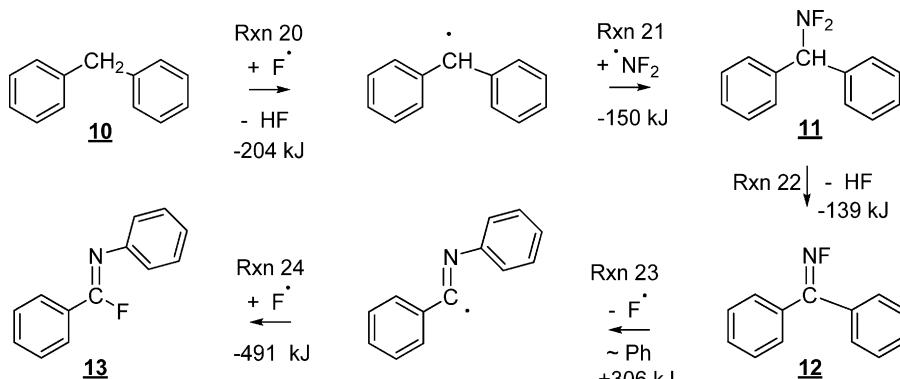
Scheme 3. Beckmann rearrangement of ethylbenzene intermediate.



Scheme 4. Alternative elimination sequence.

of HF to a fluoroimine is impossible. Instead, the apparent elimination of HNF_2 is occurring. We used Gaussian calculations to evaluate whether the apparent reaction could be the actual reaction. Generation of an α -cumene radical and combination with $\cdot\text{NF}_2$ to generate **9** is straightforward and energetically favorable (Graph 3). However, a direct elimination of H-NF_2 is unfavorable to $+90 \text{ kJ/mol}$ (in the previous case of ethylbenzene, such an elimination would be unfavorable to $+101 \text{ kJ/mol}$ and yet it is superceded by a Beckmann rearrangement that is unfavorable to at least $+283 \text{ kJ/mol}$ because of favorable formation of the pre-Beckmann fluoroimine, **7**). Small amounts of polystyrene observed from the ethylbenzene reaction may attest to some H-NF_2 elimination). At -118 kJ/mol , it is energetically more “logical” for elimination of CH_3F to occur to generate **7** (and subsequently **4**). As no such products (or hydrolysis products) were observed, then the other “logical” alternative is for α -difluoroaminocumene to be

Scheme 5. Formation of α -methylstyrene from cumene.

Graph 3. Energy diagram for $\text{NF}_3 + \text{cumene}$.

Scheme 6. Reaction sequence for diphenylmethane.

an isolable, stable product. Clearly, under our conditions, that is not the case. In fact, difluoroamine **9**, generated by photochemical methods, was observed to eliminate HNF_2 to generate α -methylstyrene simply upon distillation [3]. The combined experimental results thus show that elimination of $\text{CH}_3\text{-F}$ does not occur in this case of cumene + NF_3 . This reflects back on the discussion of the case of ethylbenzene + NF_3 in Section 2.3 indicating that a direct $\text{CH}_3\text{-F}$ elimination mechanism is not likely and that the Beckmann rearrangement is truly the operating mechanism.

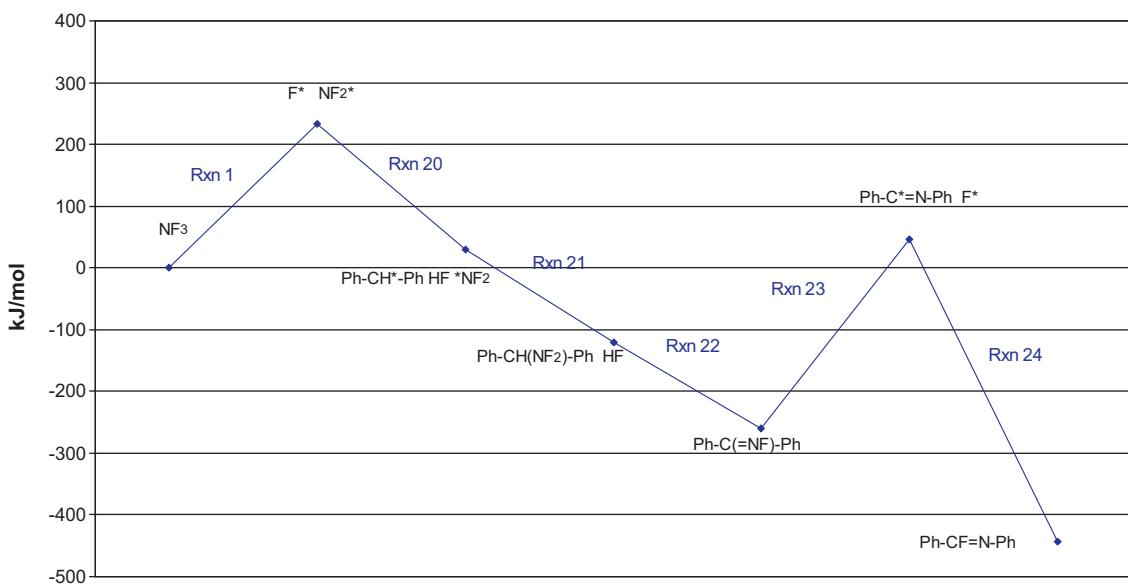
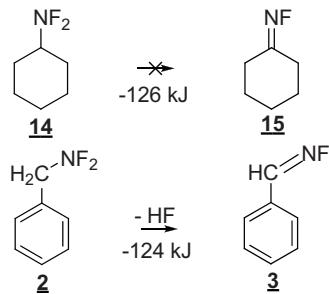
2.4. Reaction course for Beckmann rearrangement of α -difluoroaminodiphenylmethane

Diphenylmethane, **10**, reacted with NF_3 at 400–410 °C to produce benzalide ($\text{Ph}-(\text{C}=\text{O})-\text{NH}-\text{Ph}$) and related compounds via difluoroamine **11** (Scheme 6). Once again, a Beckmann rearrangement is occurring, though this time with no real mechanistic alternatives (because of no α or β -protons). Having established the radical nature of the Beckmann rearrangement with the rearrangement of α -difluoroaminoethylbenzene, we calculated the energetics of a radical Beckmann rearrangement for α -fluoroiminodiphenylbenzene, **12**. The reaction sequence faces a modest energy barrier as did the ethylbenzene case. Fluoroimine **13** is, of course, hydrolyzed by aqueous conditions to the final product benzalide.

2.5. Stability vs. instability of difluoroamino compounds

In the above examples of the products vapor phase high temperature NF_3 reactions, each initial difluoroamino product has been unstable and was not isolable under the reaction conditions. In almost every case of instability, the decomposition reaction is dependent on an initial elimination of HF to form a fluoroimine. However, simple and cyclic alkanes, diethylether and THF all produce thermally stable difluoroamino products [2]. It would seem that the difference in stability between α -difluoroaminotoluene, **2**, and difluoroaminocyclohexane, **14**, for example, is the relative acidity of the α -proton next to the NF_2 group. The benzylic position of toluene has a pK_a of 35 while cyclohexane has a pK_a of 45 [4], a differentiation of 10 units. The electron withdrawing nature of the $-\text{NF}_2$ group would be expected to increase the acidity for both difluoroaminocyclohexane and α -difluoroiminotoluene. In an attempt to determine the threshold at which elimination occurs, we used Gaussian calculations to determine the extent of that increase. For a review of methods for determining acidity constants see Ref. [5] (Graph 4).

The pK for the elimination of HF from difluoroaminotoluene and difluoroaminocyclohexane were determined from the equation $K = e^{-\Delta G^\circ/RT}$. ΔG° was determined from the difference of the free energies, i.e. $G_{\text{transition state}} - G_{\text{reactant}}$. The transition state was located after performing a 2 dimensional scan which stretched the α hydrogen distance and the fluorine distance of a syn oriented

Graph 4. Energy diagram for $\text{NF}_3 + \text{diphenylmethane}$.

Scheme 7. Elimination of HF from difluoroamino compounds.

pair. The resulting grid of energies was used to isolate a reactant, product, and transition state structure for a Gaussian 09 QST3 calculation. IRC calculations were performed in order to confirm that the transition state connects to the appropriate reactant and product. IRC calculations follow the transition state vector to reactants and products [6].

After all our calculations, we were surprised to find that the room temperature pK's of difluoroaminotoluene and of difluoroaminocyclohexane were extremely close, 31.8 and 32.6. At the reaction temperatures of 400 °C, they are effectively equivalent. Based on activation energies to the respective transition states, we see no reason why difluoroaminocyclohexane should be stable whereas difluoroaminotoluene is not. Furthermore, the $\Delta E_{\text{reaction}}$ for elimination of difluoroaminocyclohexane to its imine is -126.0 kJ/mol whereas the $\Delta E_{\text{reaction}}$ for elimination of difluoroaminotoluene is -123.9 kJ/mol . Energetically, neither is particularly more stable than the other and, if anything, difluoroaminocyclohexane should be the unstable compound and difluoroaminotoluene should be the stable one. Under delicate conditions both α -difluoroaminotoluene, **2**, and difluoroaminocyclohexane, **14**, were prepared in small quantities by photoreaction of $\text{F}_2\text{N}-\text{NF}_2$ [3]. Interestingly, in a 2005 paper on the reaction of azides with BrF_3 to generate nitriles, the authors postulate a mechanism where the difluoroaminoalkanes $\text{R}-\text{CH}_2-\text{NF}_2$ are unstable intermediates under mild conditions [7].

We must concede that our Gaussian calculations have not provided any compelling reason for the relative stability of alkyl difluoroamino compounds over benzylic difluoroamino compounds (Scheme 7).

3. Conclusion

At 400 °C, NF_3 reacts with simple alkanes to generate stable N,N -difluoroalkylamines. Benzylic substrates generate N,N -difluorobenzylamines which are unstable and not isolated. Gaussian calculations show a room temperature pK difference of only 0.8 units for the α -protons of α -difluoroaminotoluene and difluoroaminocyclohexane which does not account for the former being much more likely to eliminate HF than the latter.

The benzylic compounds α -difluoroaminotoluene, α -difluoroaminoethylbenzene, α -difluoroaminocumene and α -difluoroamino-diphenylmethane all decompose by differing mechanisms. Our Gaussian calculations have shown that benzonitrile is the logical decomposition product of α -difluoroaminotoluene. Our calculations have shown that benzonitrile is also the logical decomposition product of α -difluoroaminoethylbenzene and that the requisite Beckmann rearrangement is most likely radical in nature. Our Gaussian calculations, however, do not show α -methylstyrene to be the energetically logical decomposition product of α -difluoroaminocumene. The decomposition of α -difluoroaminodiphenylmethane mimics that of α -difluoroaminoethylbenzene and most likely occur as a radical Beckmann rearrangement.

4. Computational procedures

Ab initio calculations were performed using the Gaussian 09 suite of programs [3]. Calculations were performed using the B3LYP/6-31G(d,p) model chemistry. In this work, we were interested in the relative ΔE_{rxn} for the progression of a series of intermediates. Stationary points were characterized as a local minimum structure (no imaginary frequencies) by analytical evaluation of their Hessians. When more than one isomer of a particular species existed, the more stable isomer was used in the calculations. The energies are unscaled and zero point corrected. All energies are given in kJ/mol. Reaction energies were determined as $\Delta E_{\text{rxn}} = \Delta E_{\text{prods}} - \Delta E_{\text{reacts}}$.

References

- [1] R.K. Belter, *J. Fluorine Chem.* 132 (2011) 318.
- [2] R.K. Belter, *J. Fluorine Chem.* 132 (2011) 961.
- [3] C. Gotzmer Jr., K.F. Mueller, M.J. Czesla, *J. Org. Chem.* 38 (1973) 2964.
- [4] J. March, *Advanced Organic Chemistry*, 2nd ed., McGraw-Hill, 1977 277.
- [5] R.F. Cookson, *Chem. Rev.* 74 (1974) 5.
- [6] M.J. Frisch, G.W. Trucks, H.B. Schlegel, G.E. Scuseria, M.A. Robb, J.R. Cheeseman, G. Scalmani, V. Barone, B. Mennucci, G.A. Petersson, H. Nakatsuji, M. Caricato, X. Li, H.P. Hratchian, A.F. Izmaylov, J. Bloino, G. Zheng, J.L. Sonnenberg, M. Hada, M. Ehara, K. Toyota, R. Fukuda, J. Hasegawa, M. Ishida, T. Nakajima, Y. Honda, O. Kitao, H. Nakai, T. Vreven, J.A. Montgomery Jr., J.E. Peralta, F. Ogliaro, M. Bearpark, J.J. Heyd, E. Brothers, K.N. Kudin, V.N. Staroverov, R. Kobayashi, J. Normand, K. Raghavachari, A. Rendell, J.C. Burant, S.S. Iyengar, J. Tomasi, M. Cossi, N. Rega, N.J. Millam, M. Klene, J.E. Knox, J.B. Cross, V. Bakken, C. Adamo, J. Jaramillo, R. Gomperts, R.E. Stratmann, O. Yazyev, A.J. Austin, R. Cammi, C. Pomelli, J.W. Ochterski, R.L. Martin, K. Morokuma, V.G. Zakrzewski, G.A. Voth, P. Salvador, J.J. Dannenberg, S. Dapprich, A.D. Daniels, Ö. Farkas, J.B. Foresman, J.V. Ortiz, J. Cioslowski, D.J. Fox, Gaussian 09, Revision A.1, Gaussian, Inc., Wallingford, CT, 2009
- [7] R. Sasson, S. Rozen, *Org. Lett.* 7 (2005) 2177.