Supporting Information: Photochemical and Single Electron Transfer Generation of 2′-Deoxycytidin-N4-yl Radical From Oxime Esters

Haihui Peng[a,c,#], Son Vu[a,#], Parker Retes[b], Samuel Ward[b], Anil Kumar[b], Michael D. Sevilla[*b], Amitava Adhikary[*b] and Marc M. Greenberg[*a]

[a]Department of Chemistry, Johns Hopkins University, 3400 N. Charles St., Baltimore, MD 21218, USA

[b]Department of Chemistry, 146 Library Drive, Oakland University, Rochester, MI 48309, USA

[c]Current address: State Key Laboratory of Organometallic Chemistry, Shanghai Institute of Organic Chemistry, Chinese Academy of Sciences, 345 Lingling Road, Shanghai 200032, China

#The authors contributed equally to this manuscript.

[*]Corresponding author: Michael D. Sevilla

Phone: 248-370-2328   Fax: 248370-2321   E-mail: sevilla@oakland.edu

[*]Corresponding author: Amitava Adhikary

Phone: 248-370-2094   Fax: 248370-2321   E-mail: adhikary@oakland.edu

[*]Corresponding author: Marc M. Greenberg

Phone: 410-516-8095   Fax: 410-516-8420   E-mail: mgreenberg@jhu.edu

Contents:

Figure S1. ^{1}H NMR spectrum of **3** (DMSO-d$_6$, 400 MHz).

Figure S2. ^{1}H NMR spectrum of **2a** (MeOH-d$_4$, 400 MHz).

Figure S3. ^{1}H (Acetone-d$_6$, 400 MHz) and ^{13}C{^{1}H} (DMSO-d$_6$, 101 MHz) NMR spectra of **2b**.

Figure S4. ^{1}H (MeOH-d$_4$, 400 MHz) (* = hydroxylamine impurity) and ^{13}C{^{1}H} (MeOH-d$_4$, 101 MHz) NMR spectra of **2c** (MeOH-d$_4$).

Figure S5. ^{1}H (MeOH-d$_4$, 400 MHz) and ^{13}C{^{1}H} (Acetone-d$_6$, 101 MHz) spectra of **2d**.

Figure S6. ^{1}H (MeOH-d$_4$, 400 MHz) and ^{13}C{^{1}H} (Acetone-d$_6$, 101 MHz) NMR spectra of **2e**.

Figure S7. ^{31}P (162 MHz, D$_2$O) NMR spectrum of **5**.

Level: Uωb97xd/6-31++g** opt scrf=pcm freq thermodynamic values

Summary for Bond Dissociation Enthalpies   ωb97xd/6-31++g**   G4 (kcal/mol)
  Aminyl   BDEnthalpy (N4-H) cis   = (2) + (4) - (1) =   108.6 kcal/mol   107.43
  Aminyl   BDEnthalpy (N4-H) trans = (3) + (4) - (1) =   106.9 kcal/mol   106.11
  Iminyl   BDEnthalpy (N3-H)   = (3) + (4) - (1) =   104.55 kcal/mol   102.73

Summary for Bond Dissociation Free Energies   ωb97xd/6-31++g**   G4 (kcal/mol)
  Aminyl   BD   Enthalpy (N4-H) cis   = (2) + (4) - (1) =   100.81 kcal/mol   98.84
  Aminyl   BD Enthalpy (N4-H) trans   = (3) + (4) - (1) =   99.19 kcal/mol   97.59
  Iminyl   BD Enthalpy (N3-H)   = (3) + (4) - (1) =   96.24 kcal/mol   93.70

Full Data

1. Neutral (0, 1)   Parent   1-methylcytosine

Sum of electronic and thermal Enthalpies=   -434.016374

Sum of electronic and thermal Free Energies=   -434.058614

  G4   Enthalpy   =   -434.040571 A.U.

  G4   Free Energy   =   -434.081919 A.U.

2. Radical (0, 2) cis 1-methylcytosine(N4-H) radical

Sum of electronic and thermal Enthalpies=   -433.343650

Sum of electronic and thermal Free Energies=   -433.385292

  G4   Enthalpy =   -433.370294 A.U.

  G4   Free Energy =   -433.412320 A.U.

3. Radical (0, 2) trans 1-methylcytosine(N4-H) radical

   Sum of electronic and thermal Enthalpies=   -433.346326

   Sum of electronic and thermal Free Energies=   -433.387881

   G4   Enthalpy =   -433.372405 A.U.

   G4   Free Energy =   -433.414313 A.U.

(3)

4. Hydrogen atom (0, 2)   TE = -0.502011584125 A.U.

   Sum of electronic and thermal Enthalpies=   -0.499651

   Sum of electronic and thermal Free Energies=   -0.512666

   G4   Enthalpy   =   -0.499077 A.U.

   G4   Free Energy   =   -0.512092 A.U

5. Radical (0, 2)   Iminyl radical

   Sum of electronic and thermal Enthalpies=   -433.350119

   Sum of electronic and thermal Free Energies=   -433.392504

   G4   Enthalpy   =   -433.377783 A.U.

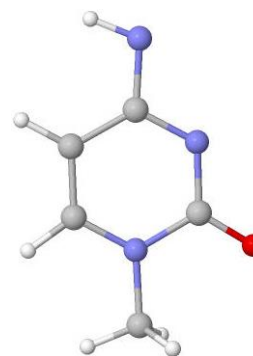   G4   Free Energy   =   -433.420508 A.U.

(4)

Figure S8. DFT and G4 calculations of 1-Methyl cytosine bond dissociation enthalpies (ΔH) and free energies (ΔG).

Uωb97xd/6-31++G** opt total energies   scrf=pcm scf=yqc (the sugar moiety was substituted by -CH₃)

Dissociation path   (1) favored   B+C –A   = -34.0 kcal/mol

(5)

(4)

(6)

2d anion radical

(-1, 2) A

-779.857381838 a.u.

dC•

(0, 2) B

-433.474316502 A.U.

$(CH_3)_3C-C(=O)-O^-$

(-1, 1) C

-346.486844955 A.U.

B + C =   -779.961161457 A.U.

Dissociation path (2)   unfavored   D+E –A   = 14.3 kcal/mol

(5)

(7)

(8)

2d anion radical

(-1, 2) A

-779.857381838 a.u.

dC⁻

(-1, 1) D

-433.610791210 A.U.

$(CH_3)_3C-C(=O)-O•$

(0, 2) E

-346.273450470 A.U.

D + E =   -779.88424168 A.U.

Stability Path1 is more stable than path 2 by 48.27 kcal/mol

Estimated E_0 for cytosine-iminyl radical $(0,2)/(-1, 1)$

$E_0 = -0.73$ V vs SHE (4.44 V)

-----similar calculations were done for **2e**--------------------------

Dissociation path **(1)** **favored** B+C −A = -34.9 kcal/mol

2e anion radical

(-1, 2) A

-853.672187468 A.U.

dC•

(0, 2) B

-433.474316502 A.U.

Ph-C(=O)-O⁻

(-1, 1) C

-420.253496978 A.U.

B + C = -853.72781348 A.U.

Dissociation path **(2)** **unfavored** D+E −A = 21.5 kcal/mol

2e anion radical

(-1, 2) A

-853.672187468 A.U.

dC⁻

(-1, 1) D

-433.610791210 A.U.

Ph-C(=O)-O•

(0, 2) E

-420.027062439 A.U.

D + E = -853.637853649 A.U.

Path 1 is 56.45 kcal/mol more stable than path 2.

Figure S9. DFT calculations of radical anion fragmentation. Calculations were carried out on the 1-methylcytosine analogues of **2d** and **2e**. All calculations are for total energies and do not include the thermodynamic factors. They are therefore reasonable estimates.

(1) TE = -434.153256553 A.U.   No negative frequency

Charge =   0.   Multiplicity =   1

N	-1.11496	0.43286	0.00000
C	-0.26472	1.49153	0.00000
H	-0.72275	2.47358	-0.00000
C	1.07995	1.31984	0.00000
H	1.75467	2.16477	-0.00000
C	1.54909	-0.03128	0.00000
N	2.87211	-0.28168	-0.00000
H	3.19708	-1.23546	-0.00000
H	3.54957	0.46250	-0.00000
N	0.72538	-1.07341	0.00000
C	-0.62129	-0.88329	0.00001
O	-1.43312	-1.81727	-0.00000
C	-2.56244	0.62226	-0.00000
H	-2.99944	0.16173	-0.88750
H	-2.99944	0.16174	0.88749
H	-2.77602	1.69062	-0.00001

(2) TE = -433.466200652 A.U.   No negative frequency

Charge =   0 Multiplicity = 2

N	-1.04522	0.45483	-0.00000
C	-0.17769	1.48973	0.00000
H	-0.60999	2.48291	0.00000
C	1.16877	1.27024	-0.00000
H	1.86803	2.09533	0.00000
C	1.59979	-0.08897	-0.00000
N	2.91971	-0.43530	0.00000
H	3.48730	0.41759	0.00001
N	0.74403	-1.11483	-0.00000
C	-0.60255	-0.88602	-0.00001
O	-1.44172	-1.78706	0.00001
C	-2.48903	0.67833	0.00000
H	-2.92755	0.21915	-0.88693
H	-2.92754	0.21914	0.88693
H	-2.68180	1.74957	0.00001

(3) TE = -433.468866332 A.U. No negative frequency

Charge = 0 Multiplicity = 2

N	-1.05263	0.43839	-0.00000
C	-0.21969	1.50052	0.00000
H	-0.68398	2.47910	0.00001
C	1.13453	1.32309	-0.00000
H	1.82029	2.15803	0.00000
C	1.60201	-0.01935	-0.00000
N	2.94838	-0.22170	0.00000
H	3.10118	-1.23623	0.00000
N	0.78188	-1.07589	-0.00000
C	-0.56991	-0.89180	-0.00002
O	-1.38295	-1.81632	0.00001
C	-2.50287	0.61673	0.00000
H	-2.92640	0.14376	-0.88689
H	-2.92640	0.14374	0.88689
H	-2.72908	1.68139	0.00001

(4) TE = -433.474316502 A.U. No negative frequency

Charge = 0 Multiplicity = 2

N	-1.03708	0.45249	0.00000
C	-0.13868	1.49878	0.00000
H	-0.58259	2.48665	-0.00000
C	1.19497	1.32566	0.00000
H	1.87068	2.16843	0.00000
C	1.73073	-0.02683	-0.00000
N	2.97938	-0.30533	-0.00000
N	0.76331	-1.03089	0.00000
C	-0.60396	-0.85592	0.00000
O	-1.37359	-1.80892	-0.00000
C	-2.48043	0.68402	-0.00000
H	-2.93276	0.24267	-0.88959
H	-2.93276	0.24267	0.88959
H	-2.65647	1.75847	-0.00000
H	1.06757	-1.99568	-0.00000

(5) TE = -779.857381838 A.U.

Charge = -1 Multiplicity = 2

N	3.55351	0.65783	0.00001
C	2.44535	1.47075	0.00001
H	2.63638	2.54202	0.00001

C	1.18130	1.00841	0.00001
H	0.35652	1.72511	0.00001
C	0.96762	-0.41555	0.00002
N	-0.14331	-1.08557	0.00002
N	2.12498	-1.18344	0.00003
C	3.41812	-0.71622	-0.00002
O	4.38101	-1.47530	-0.00003
C	4.90854	1.20470	-0.00002
H	5.44790	0.87505	0.88935
H	5.44778	0.87527	-0.88954
H	4.83934	2.29140	0.00012
H	2.03084	-2.19138	0.00000
O	-1.21198	-0.15805	-0.00000
C	-2.43742	-0.71685	-0.00002
O	-2.63417	-1.91231	-0.00001
C	-3.52063	0.36465	-0.00001
C	-3.36910	1.24002	1.25871
C	-3.36897	1.24021	-1.25857
C	-4.89182	-0.31894	-0.00013
H	-3.39229	0.63531	2.17172
H	-2.43626	1.81634	1.23646
H	-4.20124	1.95060	1.30095
H	-3.39204	0.63563	-2.17168
H	-4.20112	1.95078	-1.30081
H	-2.43615	1.81655	-1.23614
H	-5.67397	0.44620	-0.00011
H	-5.02435	-0.94619	-0.88618
H	-5.02444	-0.94633	0.88581

(6) TE = -346.486844955 A.U.

Charge = -1 Multiplicity = 1
O	1.62504	1.12003	-0.03710
C	1.04322	0.00004	-0.04537
O	1.62501	-1.11997	-0.03714
C	-0.51632	0.00002	-0.00850
C	-0.93445	-0.00083	1.47436
C	-1.08516	1.25077	-0.68942
C	-1.08508	-1.25003	-0.69079
H	-0.55386	-0.88936	1.98933
H	-0.55385	0.88711	1.99037

H	-2.02785	-0.00086	1.56055
H	-0.79648	1.29079	-1.74584
H	-2.18083	1.24205	-0.63888
H	-0.72192	2.16115	-0.20676
H	-2.18075	-1.24136	-0.64037
H	-0.79628	-1.28896	-1.74722
H	-0.72191	-2.16089	-0.20900

(7) TE = -433.610791210 A.U.

Charge = -1 Multiplicity = 1

N	-1.05388	0.44804	-0.00000
C	-0.14118	1.50015	-0.00000
H	-0.59257	2.48608	0.00000
C	1.19001	1.32663	-0.00000
H	1.83978	2.19406	0.00000
C	1.82621	-0.01271	0.00000
N	3.03236	-0.33250	0.00000
N	0.73329	-1.02819	-0.00000
C	-0.61309	-0.86212	-0.00000
O	-1.41828	-1.80697	0.00000
C	-2.48866	0.69218	0.00000
H	-2.95697	0.25996	-0.88764
H	-2.95697	0.25996	0.88764
H	-2.65724	1.76894	0.00000
H	1.04800	-1.98953	0.00000

(8) TE = -346.273450470 A.U.

Charge = 0   Multiplicity = 2

O	1.68091	1.02714	-0.02280
C	0.94887	0.00002	-0.03395
O	1.68091	-1.02710	-0.02277
C	-0.55618	0.00001	-0.01120
C	-0.97340	-0.00068	1.47703
C	-1.07158	1.26729	-0.70597
C	-1.07155	-1.26666	-0.70713
H	-0.60291	-0.89050	1.99364
H	-0.60285	0.88863	1.99448
H	-2.06560	-0.00066	1.53277
H	-0.78545	1.28750	-1.76146

H	-2.16351	1.28526	-0.64680
H	-0.69120	2.17241	-0.22408
H	-2.16346	-1.28479	-0.64787
H	-0.78550	-1.28584	-1.76267
H	-0.69104	-2.17220	-0.22614

(9) TE = -853.672187468 A.U.

Charge = -1   Multiplicity = 2

N	-3.99383	-0.84692	0.00454
C	-2.81367	-1.56089	0.02495
H	-2.92811	-2.63792	0.04138
C	-1.59997	-0.97842	0.02450
H	-0.69807	-1.57035	0.04055
C	-1.51572	0.46534	0.00183
N	-0.46965	1.22160	-0.00493
N	-2.74929	1.12176	-0.01458
C	-3.98679	0.53505	-0.01500
O	-5.02220	1.19549	-0.03146
C	-5.29174	-1.51618	0.00602
H	-5.86239	-1.23526	0.89291
H	-5.85896	-1.24342	-0.88542
H	-5.12475	-2.59214	0.01108
H	-2.74790	2.13329	-0.02976
O	0.67499	0.43107	0.01264
C	1.88592	1.15514	0.01131
O	1.88585	2.40595	0.02089
C	3.00457	0.28591	0.00169
C	4.33260	0.83955	0.00692
C	2.90618	-1.15105	-0.01269
C	5.44834	0.02572	-0.00158
H	4.44537	1.91960	0.01767
C	4.03916	-1.94217	-0.02092
H	1.92708	-1.61878	-0.01762
C	5.33309	-1.38066	-0.01556
H	6.43586	0.48285	0.00270
H	3.92507	-3.02431	-0.03196
H	6.21544	-2.01285	-0.02211

(10)   TE = -420.253496978 A.U.

Charge = -1   Multiplicity = 1

O	-2.37748	1.12274	0.03202

C	-1.80729	0.00000	-0.00002
O	-2.37733	-1.12278	-0.03204
C	-0.27572	0.00003	0.00004
C	0.43695	1.20312	-0.01236
C	0.43693	-1.20308	0.01241
C	1.83104	1.20607	-0.01364
H	-0.11658	2.13623	-0.02153
C	1.83101	-1.20607	0.01361
H	-0.11665	-2.13617	0.02148
C	2.53235	-0.00001	0.00002
H	2.37092	2.14844	-0.02513
H	2.37087	-2.14845	0.02495
H	3.61830	-0.00003	-0.00004

(11) TE = -420.027062439 A.U.
Charge = 0 Multiplicity = 2

O	-2.51889	0.00825	1.04177
C	-1.79293	0.00020	0.06670
O	-2.07451	-0.00954	-1.18456
C	-0.28579	-0.00011	0.01319
C	0.40659	1.22644	-0.01909
C	0.40717	-1.22648	-0.01180
C	1.79079	1.21815	0.03142
H	-0.14373	2.16029	-0.05525
C	1.79144	-1.21734	0.03854
H	-0.14275	-2.16076	-0.04271
C	2.48109	0.00059	0.05949
H	2.33842	2.15377	0.03736
H	2.33951	-2.15265	0.04986
H	3.56568	0.00093	0.08240

Figure S10. ωb97xd/6-31++G** optimized cartesian coordinates of various species (Figures S8, S9 and in the main manuscript) are considered in this study. They are numbered as (**1**), (**2**), etc.

Complete reference of ref. no. 68 in the main manuscript. Frisch, M. J.; Trucks, G. W.; Schlegel, H. B.; Scuseria, G. E.; Robb, M. A.; Cheeseman, J. R.; Scalmani, G.; Barone, V.; Petersson, G. A.; Nakatsuji, H.; Li, X.; Caricato, M.; Marenich, A. V.; Bloino, J.; Janesko, B. G.; Gomperts, R.; Mennucci, B.; Hratchian, H. P.; Ortiz, J. V.; Izmaylov, A. F.; Sonnenberg, J. L.; Williams-Young, D.; Ding, F.; Lipparini, F.; Egidi, F.; Goings, J.; Peng, B.; Petrone, A.; Henderson, T.; Ranasinghe, D.; Zakrzewski, V. G.; Gao, J.; Rega, N.; Zheng, G.; Liang, W.; Hada, M.; Ehara, M.; Toyota, K.; Fukuda, R.; Hasegawa, J.; Ishida, M.; Nakajima, T.; Honda, Y.; Kitao, O.; Nakai, H.; Vreven, T.; Throssell, K.; Montgomery, J. A.; Peralta, J. E.; Ogliaro, F.; Bearpark, M. J.; Heyd, J. J.; Brothers, E. N.; Kudin, K. N.; Staroverov, V. N.; Keith, T. A.; Kobayashi, R.; Normand, J.; Raghavachari, K.; Rendell, A. P.; Burant, J. C.; Iyengar, S. S.; Tomasi, J.; Cossi, M.; Millam, J. M.; Klene, M.; Adamo, C.; Cammi, R.; Ochterski, J. W.; Martin, R. L.; Morokuma, K.; Farkas, O.; Foresman, J. B.; Fox, D. J. Gaussian 16, Revision A.03; Gaussian.Com; Gaussian, Inc., Wallingford CT, 2016.