

Biomolecular Condensates Power Nitrogen Cycling via Concurrent Redox Activities

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ABSTRACT: The role of the inherent chemical activities of biomolecular condensates in metabolism remains underexplored. We discovered that biomolecular condensates, the constituents of which do not possess any intrinsic enzymatic activities, can modulate the nitrogen cycle composed of nitrate (NO_3^-), ammonia (NH_3), and nitric oxide ($\text{NO}\cdot$). By developing a single-condensate-based mass spectrometry technique, we observed condensate-dependent interconversion between NO_3^- and NH_4^+ with externally supplied nitrogen sources. Surprisingly, through mass-spectrometry-based protein analysis and fluorogenic reaction assays, we found that the autoxidation of the arginine residue on the disordered protein could also directly contribute to the released $\text{NO}\cdot$, an important signaling factor in biological systems. This work expands our understanding about the intrinsic reactivity of biomolecular condensates, providing insight into its fundamental impact on nitrogen metabolism as a nitrogen supplier and regulator.

Biomolecular condensates organize spatiotemporal cellular biochemistry.^{1–4} Previous studies have been largely

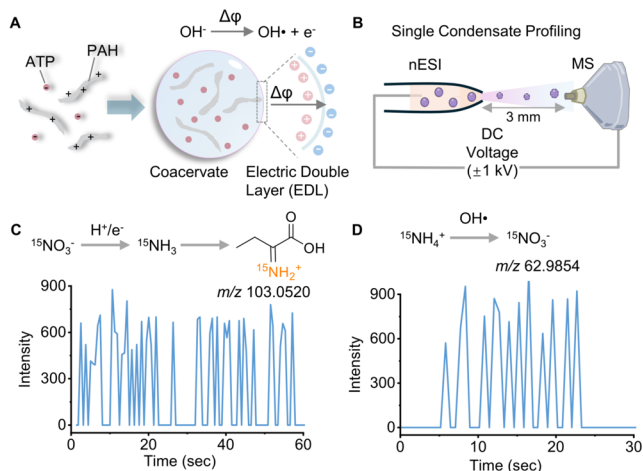


Figure 1. Mass spectrometric characterization of individual coacervates. (A) Scheme of the PAH-ATP coacervate formation, its electric double layer, and interfacial electric field-induced hydroxyl radical generation. (B) Nanoelectrospray ionization (nESI)-mass spectrometry setup for characterizing the molecular profiles of coacervates. (C) Extracted ion chromatogram of ion at m/z 103.0520 in the positive mode, which represents the imine structure formed by alpha-ketobutyric acid and ^{15}N -labeled NH_3 observed from 25 individual condensate droplets. (D) Extracted ion chromatogram of the ion at m/z 62.9854 in the negative mode, which represents the ^{15}N -labeled nitrate anion observed from 11 individual condensate droplets after feeding ^{15}N in the coacervate suspension.

focusing on how condensation could affect the functions of biomolecular constituents through selective partitioning effects.^{2,4} Recent reports demonstrate that condensate formation results in the reorganization of ions between the

dilute and the dense phases,^{5–7} which encode an electric potential across the liquid–liquid interface.^{8–10} These electrochemical properties of condensates encode inherent electrochemical functions of condensates,⁸ including redox reactions and aldol reactions.^{9,11,38,39}

A key chemical driving force for this inherent condensate function is the formation of reactive oxygen species and solvated electrons through water oxidation mediated by interfacial electric field.^{12–15} This is similar to the diverse chemical functions observed in confined microdroplet or solid–liquid interfaces.^{16–18} For example, water microdroplets dispersed in air or organic phases can initiate reactive oxygen species-dependent single-electron transfer-based oxidation and reduction reactions that are thermodynamically unfavorable in the bulk solution.^{19–22} Recently, beyond generating reactive oxygen species, several nitrogen fixation pathways—such as dinitrogen reduction to ammonia, ammonia oxidation to nitrate, urea synthesis from dinitrogen and carbon dioxide—have been discovered in microdroplet systems.^{23–25,33–37}

Given the property similarities between microdroplet and condensates and the central role of nitrogen cycle in chemical homeostasis and metabolite synthesis in biology,²⁶ we herein explored the role of condensates in modulating the nitrogen cycle.

Single-Condensate Characterization of Nitrate/Ammonia Conversion

We first constructed a model condensate based on the complex coacervate formation between adenosine triphosphate (ATP)

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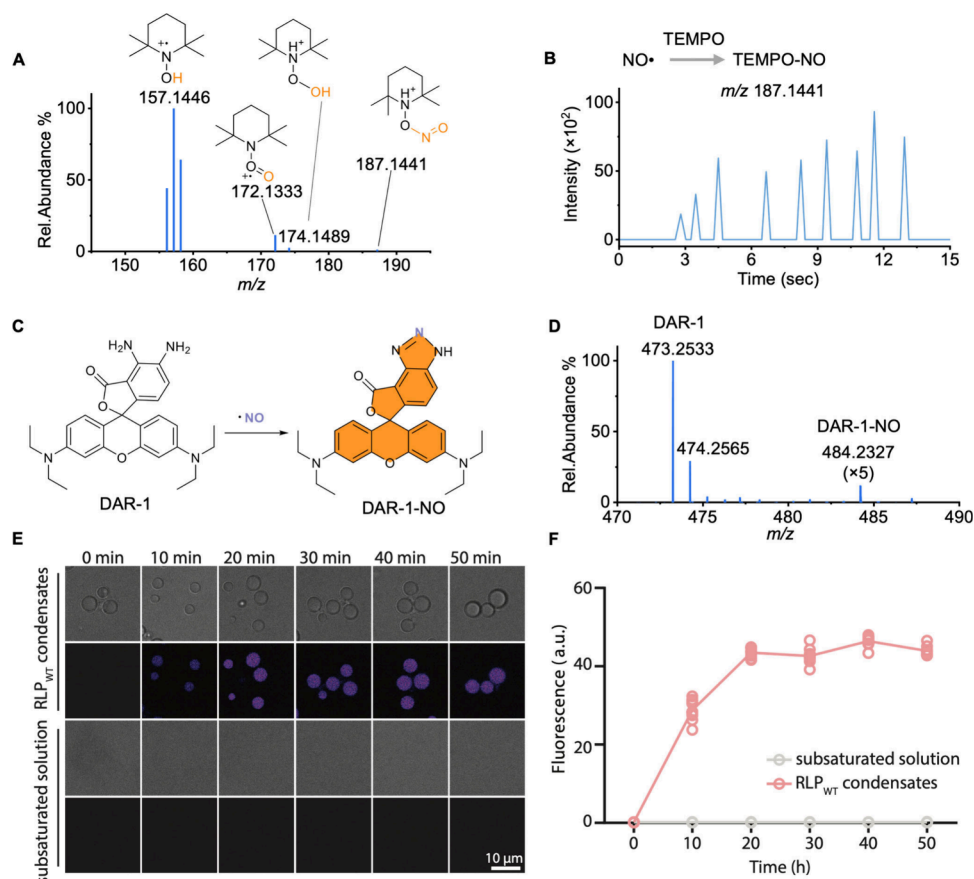


Figure 2. Characterization of nitric oxide generation in biomolecular condensates. (A) Mass spectrum of radicals that were captured by TEMPO including hydrogen radical ($\text{H}\cdot$), atomic oxygen ($\text{O}\cdot$), hydroxyl radical ($\text{OH}\cdot$), and nitric oxide ($\text{NO}\cdot$). (B) Extracted ion current of m/z 187.1441 representing the TEMPO-NO. (C) Scheme of the principle for the $\text{NO}\cdot$ capturing by the fluorescent probe DAR-1. (D) High-resolution mass spectrum showing the presence of $\text{NO}\cdot$ denoted by the ion at m/z 484.2327. (E) Fluorescent microscopic images showing the $\text{NO}\cdot$ generation within a single RLP condensate formation and aging process. The emission wavelength was at 586 nm. (F) Temporal changes of the DAR-1-NO fluorescent intensity shows the generation and depletion of $\text{NO}\cdot$ during a RLP condensate period (replicates $n = 3$).

and poly(allylamine) hydrochloride (PAH). Because of the asymmetric distribution of positive and negative charges across dense phase and dilute phase, an electric double layer (EDL) is formed at the condensates interface (Figure 1A), making the coacervate electrochemically active. The experimental coacervation ratio was adopted from a recent ATP-PAH coacervate study showcasing the high-redox activity for this composition,¹³ in which hydroxyl radicals and solvated electrons were detected.

To investigate condensate-dependent reactions, we designed a single-condensate profiling platform utilizing nano-electrospray ionization mass spectrometry (nESI-MS), as described in more detail in the Supporting Information. Our approach excludes any possible interference from the dilute phase (Figure 1B). This strategy precisely characterizes the individual compositions of condensates and allows us to evaluate the variations within the whole condensate population (Figures S1 and S2).

We first applied an ^{15}N isotope-labeled nitrogen species to confirm the occurrence of the nitrogen cycle, specifically, nitrate reduction into ammonia and ammonia oxidation into nitrate. For the reduction reaction, $\text{Na}^{15}\text{NO}_3$ was incubated with ATP-PAH coacervate for 2 h before loading the sample in the nESI emitter. We observed the reduction product $^{15}\text{NH}_3$ in the form of imine (m/z 103.0520) trapped by 2-ketobutyric acid. The extracted ion chromatogram at m/z 103.0520 of 22

individual condensates shows a clear difference with the sample containing only $\text{Na}^{15}\text{NO}_3$ (Figure 1C). Conversely, by feeding the ATP-PAH condensates with $^{15}\text{NH}_4\text{Cl}$, we observed its oxidation product $^{15}\text{NO}_3$ represented by m/z 62.9854 (Figure 1D), confirming the oxidative ability of the coacervate to drive the nitrogen cycle. These observations show that condensate can drive both reductive and oxidative transformations of nitrogen-containing species, contingent on the available reactants.

To verify the concurrent reduction and oxidation abilities of condensates, we introduced into the ATP-PAH condensate system the redox-active spin probe 2,2,6,6-tetramethylpiperidine-1-oxyl (TEMPO),²⁷ which can be either oxidized or reduced. The results are presented in Figure 2A and the Supporting Information, which confirm the coexistence of both oxidizing and reductive sources from the condensate system, which aligns with the interfacial field-dependent generation of hydroxyl radicals.^{9,13,16,21,22}

Condensate-Dependent Generation of Nitric Oxide Radical

Next, we explored whether condensates formed by intrinsically disordered proteins, which serve as the primary driver of condensate formation in living systems, could also mediate the nitrogen cycle. To this end, we employed the condensate formed by a resilin-like polypeptide (RLP), which has been

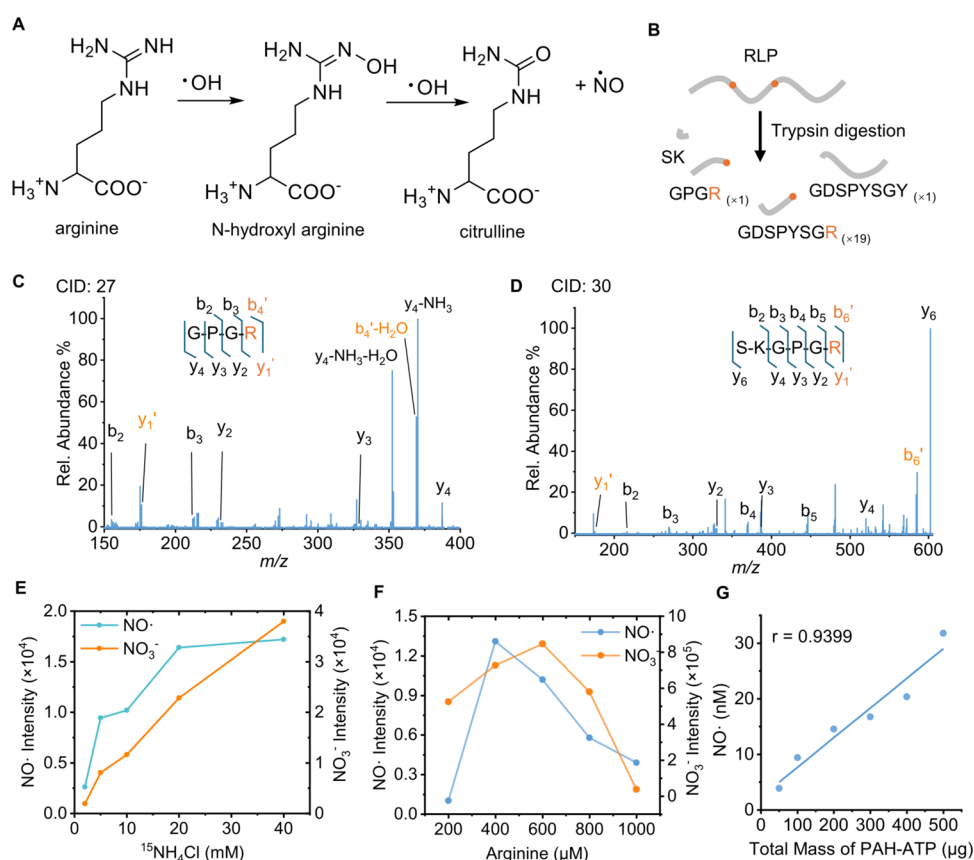


Figure 3. Investigation of the nitrogen source responsible for $\text{NO}\cdot$ and NO_3^- release. (A) Nitric oxide release from arginine through a two-step oxidation. (B) Bottom-up peptide mass fingerprinting by using trypsin digestion strategy. (C–D) Sequencing of GPGR and SKGPR to identify arginine (R) as the oxidation site by MS/MS experiments. (E) The $\text{NO}\cdot$ and NO_3^- intensities increase after gradual addition of $^{15}\text{NH}_4\text{Cl}$ into the RLP condensate solution. (F) Changes in the $\text{NO}\cdot$ and NO_3^- intensities with the addition of arginine. (G) Dependency of $\text{NO}\cdot$ generation on the total mass of PAH-ATP condensates (1:1 mass ratio). Condensates can be formed across mass ranges from 50 to 500 μg in a 100 μL solution biomolecular condensates.

shown to be electrochemically active and could drive redox reactions.⁹ The RLP consists of 20 repeats of [Gly-Arg-Gly-Asp-Ser-Pro-Tyr-Ser]₂₀. We reasoned that because (i) the oxidation capacity originates from the formation of hydroxyl radical and (ii) arginine (Arg, R) serves as a primary precursor for generating nitric oxide ($\text{NO}\cdot$) in biology, the condensate itself might sustain the production of $\text{NO}\cdot$. $\text{NO}\cdot$ is the key redox intermediate in the nitrogen cycle and an important signaling factor mediating cellular activities.²⁸ With the TEMPO assay using HR-MS, we discovered the presence of nitric oxide ($\text{NO}\cdot$) in the condensate solution, as determined by the existence of TEMPO- NO species at m/z 187.1441 ($[\text{M} + \text{H}]^+$, Figure 2A). The time-resolved ion intensity of this adduct (Figure 2B) also shows the generation of $\text{NO}\cdot$ at the single condensate level, providing unambiguous evidence that the condensate microenvironment facilitates the radical-mediated interconversion of nitrogen species. Using a fluorogenic $\text{NO}\cdot$ probe, DAR-1, we further confirmed the condensate-dependent chemical activation of the probe through mass spectrometry (Figure 2C–2D). With confocal microscopy, compared to subsaturated solution, in which no condensate forms, we found that the activation of the probe is condensate dependent (Figure 2E–2F). These observations collectively confirm the capability of the condensate system in generating radicals.

Origin of Nitric Oxide from Protein Side Chains

To evaluate the mechanism of nitric oxide ($\text{NO}\cdot$) generation, we next evaluated the oxidation of arginine by condensates. Arginine could undergo a two-step oxidation by reacting with the hydroxyl radical to form *N*-hydroxyl-arginine, which in turn converts to citrulline and $\text{NO}\cdot$ (Figure 3A). To evaluate this from the protein side chain, we performed tryptic digestion of the RLP condensates followed by MS/MS sequencing (Figure 3B). We focused on the arginine-containing fragments GPGR and GDSYSGR. We detected a modified peptide species where the Arg residue was oxidatively transformed (denoted as R'). The proposed mechanism involves the OH-mediated attack on the guanidino group of arginine, releasing NO and yielding a modified side chain. The tandem mass spectra (MS/MS) provided structural proof: Figure 3C shows the fragmentation of the unmodified GPGR peptide, while Figure 3D reveals the distinct fragmentation pattern of the oxidized species containing oxidized Arg, confirming that the protein itself could directly contribute to the nitrogen cycle.

It is worth noting that only the arginine closest to the positive N-terminus was found to be oxidized. We speculated it is attributed to the location close to the positive N-terminal that is distributed across the interface.²⁹ Thus, it has a higher chance of being exposed to the reactive environment. In comparison, the arginine in the middle peptide chain is located within the interior region and is excluded from the interfacial

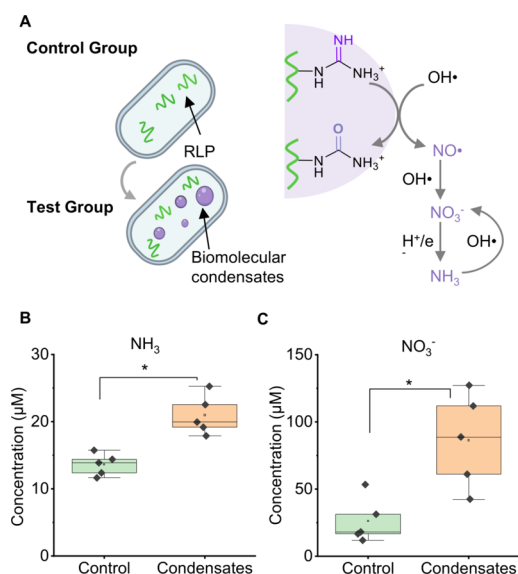


Figure 4. *in vivo* production of the extra ammonia and nitrate in cells. (A) *E. coli* cell lines with or without MG1655 stress-induced condensates formation. The scheme on the right shows that the ammonia and nitrate originated from the guanidine group on the arginine residue in RLP. (B–C) Box plots of the ammonia and nitrate levels in control and condensate groups. Data point represents mean \pm SD with $n = 5$ biological replicates. Statistical analysis was performed using a two-tailed t test. * $p < 0.05$.

effects (Figure S3). We also compared the NO· production ability among three amino acids, arginine, lysine, and histidine under the same OH· exposure level using Fenton chemistry.^{40,41} The NO· level generated from arginine is around three times higher than those from histidine and lysine (Figure S4). This result suggests the unique role of arginine on mediating NO· production by condensates.

Further, we tested the generality of this feature on transforming arginine using the PAH-ATP condensate system. We first varied the concentration of isotopically labeled ammonium chloride (¹⁵NH₄Cl) and soluble arginine. Figure 3E shows that while external ammonium correlates with nitrate/NO· production, the addition of exogenous arginine (Figure 3F) exhibits a biphasic effect, peaking at 400 µM before inhibiting the reaction, likely caused by saturation of the interfacial sites or radical scavenging effects. Notably, we observed a strong linear correlation between the total mass of condensate and the concentration of generated NO· (Figure 3G). This density dependence strongly implies that the scaffold material is not inert but actively participates in the reaction.

Verification of Condensate-Mediated Nitrogen Cycle in Living Cells

Finally, we evaluated whether the capability to mediate the nitrogen cycle is valid in living cells. A comparative study was conducted between the cell with or without RLP condensates in *E. coli* based on our previously established protocol^{29,30} (Figure 4A). We quantified the concentrations of nitrate and ammonia in cell lysates suspensions.³¹ The formation of condensates resulted in significant upregulation of nitrogen cycling. Specifically, the intracellular levels of ammonia (NH₃), represented by the *N*-isopropyl amine after reductive amination with acetone, were significantly higher in the condensate-forming group compared to the control ($p =$

0.0012, $n = 5$, Figure 4B). Similarly, the production of nitrate (NO₃⁻) was markedly enhanced in the cells with condensates ($p = 0.0306$, $n = 5$, Figure 4C).

These results support a model in which phase separation spatially confines the arginine-rich protein materials and the reaction substrates. The high local density of arginine residues within the condensate, coupled with the generation of interfacial radicals (OH·) and solvated electrons, creates an efficient "microreactor", facilitating the rapid oxidation of arginine to NO· and subsequently to NO₃⁻, while also supporting the reductive return to ammonia. Thus, the phase separation of arginine-rich proteins, which are prevalent in intrinsically disordered proteins,³² serves as a fundamental regulatory mechanism, switching the nitrogen cycle from a basal level to a high-flux state in response to condensate formation. This work discovered the potential impact of condensates on metabolism regulation by producing ammonia and nitric oxide, respectively. The ammonia recycled from nitrates can be a supplementary nitrogen source for building essential biomolecules such as amino acids, nucleotides, and vitamins.

In summary, we discovered that biomolecular condensates assembled from nonenzymatic components can directly catalyze redox interconversions among nitrogen species, including ammonia and nitrate. The nonenzymatic production of NO· can be directly driven by the protein side chain chemistry using arginine as the feedstock. Given the prevalence of arginine in phase separation—driving intrinsically disordered proteins—and the universality of condensate mesoscale electrochemical environments, condensate-mediated modulation of the nitrogen cycle is likely a general feature of cell biology. This emerging aspect of condensate functions motivates a deeper exploration of condensates as active participants in cellular nitrogen cycling rather than passive sites of metabolite storage or enzyme clustering. Understanding this potential role may open up a new dimension in the study of redox regulation and biochemical energy flow inside cells.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at <https://pubs.acs.org/doi/10.1021/jacs.5c22593>.

Detailed description can be accessed in the Supporting Information including reagents and materials; coacervate preparation; induction of RLP expression in *E. coli* model cells; RLP purification protocol; preparation of RLP condensates; *in situ* characterization of nitric oxide generation by fluorescent microscopy; post-treatment of condensate protein before proteomic analysis; oxidation site identification of RLP backbones by nESI-MS. (PDF)

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Notes

The authors declare no competing financial interest.

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